Journal of Theoretical Biology 368 (2015) 27–36

Contents lists available at ScienceDirect

Journal of Theoretical Biology

journal homepage: www.elsevier.com/locate/yjtbi

# Characterization of the endemic equilibrium and response to mutant injection in a multi-strain disease model

Tomás Aquino [a,b], Diogo Bolster [a], Ana Nunes [b,*]

[a] Department of Civil & Environmental Engineering and Earth Sciences, University of Notre Dame, 46556 IN, USA
[b] Centro de Física da Matéria Condensada and Departamento de Física, Faculdade de Ciências da Universidade de Lisboa, P-1649-003 Lisboa Codex, Portugal

## HIGHLIGHTS

- This work deals with multi-strain systems competing through cross-immunity in an SIR type framework with vital dynamics.
- We explore this system using a deterministic model that postulates strain immunity cross-correlations, together with stochastic simulations.
- We study in particular the multi-strain equilibrium, and how diversity may develop from a single founding strain.
- We show how strain prevalence is reduced because of overall cross-immunity.
- We find that the build up of diversity from a single founding strain is extremely unlikely for different choices of the population's immune response.

## ARTICLE INFO

*Article history:*
Received 3 April 2014
Received in revised form
17 November 2014
Accepted 3 December 2014
Available online 12 December 2014

*Keywords:*
Mathematical epidemiology
Strain cross-immunity
Strain competition and evolution

## ABSTRACT

We explore a model of an antigenically diverse infection whose otherwise identical strains compete through cross-immunity. We assume that individuals may produce upon infection different numbers of antibody types, each of which matches the antigenic configuration of a particular epitope, and that one matching antibody type grants total immunity against a challenging strain. In order to reduce the number of equations involved in the analytic description of the dynamics, we follow the strategy proposed by Kryazhimskiy et al. (2007) and apply a low-order closure reminiscent of a pair approximation. Using this approximation, we go beyond the numerical studies of Kryazhimskiy et al. (2007) and explore the analytic properties of the ensuing model in the absence of mutation. We characterize its endemic equilibrium, comparing with the results of agent based simulations of the full model to assess the performance of the closure assumption. We show that a particular choice of immune response leads to a degenerate endemic equilibrium, where different strain prevalences may exist, breaking the symmetry of the model. Finally we study the behavior of the system under the injection of mutant strains. We find that the build up of diversity from a single founding strain is extremely unlikely for different choices of the population's immune response.



## 1. Introduction

Many human pathogens exhibit antigenic diversity, with several strains that elicit different immune responses coexisting in the population or within individual hosts at a given time, or replacing one another over time (Cobey and Koelle, 2008; Lukehart et al., 2009). Infectious diseases of this class still defy effective control, and improving our understanding of their dynamics is of great practical importance. Modeling multi-strain infections is in itself a theoretical challenge, because typical compartmental models of mathematical epidemiology keep track of the infection histories of the hosts (Castillo-Chavez et al., 1989; Andreasen et al., 1997). This results in a number of variables that increases exponentially with the number of strains, making the problem intractable even for a relatively modest number of strains competing through cross-immunity. Ferguson and co-workers (Abu-Raddad and Ferguson, 2005a,b; Abu-Raddad et al., 2005) characterized the symmetric equilibrium of a fixed, arbitrary number of strains with identical epidemiological parameters, but it has proven very difficult to go beyond the description of equilibrium properties in this framework.

Two strategies have been proposed to reduce the complexity of the problem using reasonable simplifying assumptions. Gog and co-workers (Gog and Grenfell, 2002; Gog and Swinton, 2002)

* Corresponding author.
*E-mail address:* anunes@ptmat.fc.ul.pt (A. Nunes).

http://dx.doi.org/10.1016/j.jtbi.2014.12.001
0022-5193/

introduced the idea of a status based approach, where different compartments in the population are associated with current immunity profiles rather than with the individuals' infection history. In this approach, each host is either susceptible or immune to any given strain $i$ (polarized immunity). Partial immunity conferred by infection with another strain $j$ translates into a fraction of those infected by $j$ becoming immune to $i$, rather than all the infected becoming partially immune. They showed that this approach, combined with the assumption of 'reduced infectivity', results in a drastic reduction of the number of variables needed to describe the system. Reduced infectivity means that an immune host exposed to a given strain will not transmit that strain, but will develop an immune response just as a susceptible infected with that strain would. By contrast with 'reduced susceptibility', whereby immunity prevents infection and there is no change in the host's immune repertoire, under reduced infectivity immunity prevents further transmission but does not prevent infection. While this assumption may be difficult to sustain from the biological point of view, it makes the scaling of the number of variables of the system with the number of strains linear, instead of exponential, allowing for the exploration of large sets of competing strains.

The second approach, put forward in Kryazhimskiy et al. (2007), is also status based. It takes as dynamic variables the fraction of the population that is immune to and the fraction that is infected with each strain. The equations that determine the time evolution of the fraction of immune individuals involve, apart from the cross-immunity properties of the set of strains, the fraction of the population that is immune to pairs of strains. In order to close the system, time evolution equations for these must be derived, which in turn involve the fraction of the population that is immune to strain triplets, and so on. In much the same way as is usually done for spatially extended systems, this process can be truncated at a given order via a moment closure, i.e., an ansatz that expresses n-tuplets in terms of the lower order variables. This elegant idea works without the disputable reduced infectivity assumption. It allows for the reduction of the number of variables that describe the system, which becomes polynomial in the number of strains, the actual order depending on the order of the closure. Although this approach is explored in Kryazhimskiy et al. (2007) only through numerical simulations, it is amenable to analytic treatment, as shown below.

A benchmark for a successful theoretical model is its ability to reproduce the antigenic drift and shift typical of influenza A when pathogen mutation is included. Both Gog and Grenfell (2002) and Kryazhimskiy et al. (2007) offer applications to influenza A and show that in strain spaces of dimensions 1 and 2 the models do indeed recover the essential qualitative features of influenza evolution, namely the steady strain replacement over the years combined with limited diversity at any given time. In higher dimensional strain spaces, however, extinction or explosive diversity is the generic outcomes of the simplest models (Girvan et al., 2002; Tria et al., 2005; Ballesteros et al., 2009; Koelle et al., 2009). Theoretical proposals relying on specific assumptions regarding strain cross-immunity were shown to generate patterns of antigenic evolution compatible with influenza A (Ferguson et al., 2003; Koelle et al., 2006, 2009; Bedford et al., 2012). However, their actual implementation as computational models involves a combination of features and is too complex to provide a generally accepted modeling framework for multi-strain infection dynamics. Indeed, agent-based simulations give us the insight of virtual experiments but, even with modern computational facilities, they can be too time consuming to enable a full exploration of parameter space. Additionally, they are not amenable to analytic treatment. In recent years, along with other contributions in agent-based modeling frameworks (Cobey and Pascual, 2011; Buckee et al., 2011; Zinder et al., 2013), the effort to deal with multi-strain dynamics in a deterministic setting has been continued (Adams et al., 2007; Adams and Sasaki, 2009; Minayev and Ferguson, 2009a,b; Koelle et al., 2010; Kucharski and Gog, 2012).

In this paper we add to this effort, using the approach of Kryazhimskiy et al. (2007) as a starting point, so as to avoid the large number of degrees of freedom that comes with infection-history-based rate equation models, together with the following assumptions about the host's immune response. We model each strain as a set of integers that represent different configurations of the pathogen's antigenic sites or epitopes and we stipulate an immune response in the host population with some degree of heterogeneity. Different hosts may build antibodies to different numbers and different sets of antigenic sites, and all antigenic sites are equally likely to be targeted. Together with the assumption that a single matching antibody provides lifelong immunity to a strain, this immune response scheme completely determines the cross-immunity structure of the strain set.

In Section 2 we set up the mathematical model, and in Section 3 we add to the results of Abu-Raddad and Ferguson (2005a,b), Abu-Raddad et al. (2005), and Kryazhimskiy et al. (2007) a fully analytic study of the multi-strain endemic equilibrium. We find the symmetric endemic equilibria of the model for arbitrary cross-immunity structure, and show that a simple closure assumption of first order may introduce spurious equilibria, which are not found in simulations of the full system. We further show that if we take strain cross-immunity to be proportional to the fraction of shared epitopes then the endemic equilibrium becomes degenerate and different strain prevalences may coexist in equilibrium, breaking the symmetry of the model. A quantitative comparative assessment of different closure assumptions and of the reduction approach of Gog and Swinton (2002) was given in Kryazhimskiy et al. (2007) for four strains with a particular cross-immunity structure. Our results show that, under certain conditions, the simplest moment closure can fail even qualitatively. In Section 4 we consider a single founding strain in endemic equilibrium and investigate the possible outcomes, coexistence, substitution or extinction, of an immunity evading mutation, following the system until a new equilibrium is reached. To deal with extinction and mutation in a description based on continuous variables that represent population densities, we define a cut-off, the inverse of the effective population size, such that if densities become lower than this cut-off they are taken to be zero. A related study was presented in Adams et al. (2007) and Adams and Sasaki (2009), where the fate of the mutant strain was assessed only from the initial value of the time derivative of the corresponding density of infected. For populations as large as $10^8$, we find that extinction is overwhelmingly likely, followed by strain substitution, and that coexistence requires infectiousness to be very small or cross-immunity to be very large.

## 2. Model

In this model we assume a simple setup where each viral strain is characterized by a certain number of epitopes, each of which is in one of a number of possible configurations. All epitopes have equal roles, and the infectious properties of viral strains are all identical; their effectiveness at infecting a host is fully determined by the host's immune history. Upon infection with a strain, the host will produce a certain number of antibodies, each of which matches the antigen configuration at a particular epitope. In general, the immune system builds a polyclonal response upon infection with a strain, that is, it will produce antibodies that respond to all or a large fraction of the virus's epitopes. However, there is evidence of variation in the individual immune responses to identical strains and it has been proposed that children's immune system may have a

monoclonal response (Nakajima et al., 2000; Sato et al., 2012), meaning that with each infection a child will build an antibody for only one of the epitopes. In the proposed framework, we model different responses by a probability that an individual will produce a certain number of antibodies. With these assumptions in mind, let us derive the rate equation formulation of the model for multi-strain competition in a well mixed population. A list of the different symbols and their meaning is given for reference in Table 1 at the end of this section.

A given strain is characterized by a set of $n_e$ integers in $\{1,\ldots,n_c\}$, each representing a different configuration of the antigen at a certain epitope. This comprises a total of $N_s = n_c^{n_e}$ strains in the system, since there are $n_c$ configurations for each of the $n_e$ epitopes. At any particular time, an individual may be infected with at most a single strain; they are said to be susceptible if are not infected with any strain. The assumption of no co-infections (no infection by more than one strain) is arguable, but can be defended in two ways: (i) a sick individual tends to stay at home, and thus isolate himself from contact with new infections, and (ii) upon infection the immune system is highly active and responds more effectively to secondary infections.

Additionally, each individual in the population has an immune history made up of $n_e$ sets of integers, representing antibodies against specific configurations of the antigens at each of the $n_e$ epitopes. To make the model amenable to the analytical treatment that will be presented in Section 2.2, we further assume that having one matching antibody for any of the epitope configurations is enough to grant total immunity against a strain. In formal terms, we say an individual with immune history $A=\{A_1,\ldots,A_{n_e}\}$ is immune to a strain $i=\{i_1,\ldots,i_{n_e}\}$ if $\exists j : i_j \in A_j$, and in this case we write $i \in A$. Otherwise, we write $i \notin A$.

Consider now the formalization of immunity acquisition. Take an individual with immune history $A$ as discussed above. Upon infection with strain $i$, the immune repertoire becomes $B=\{B_1,\ldots,B_j\}$, where for each $j$ we have either $B_j=A_j$, if an antibody was not produced for epitope $j$, or $B_j = A_j \cup \{i_j\}$, if an antibody was produced for that epitope. For each infection, consider that the number of antibodies produced follows a distribution $p_{\{1\le\alpha\le n_e\}}$, where $p_\alpha$ represents the probability of $\alpha$ antibodies being produced. Furthermore, we will assume from now on that antibodies for each epitope have the same probability of being produced, leaving aside the possibility of epitope immunodominance (Cobey and Pascual, 2011), which for a given $p_{\{\alpha\}}$ would reduce the diversity of immune responses.

**Table 1**
List of the main symbols and their meaning.

| | |
|---|---|
| $n_e$ | Number of epitopes |
| $n_c$ | Number of epitope configurations |
| $N_s$ | Total number of strains |
| $p_{\{1\le\alpha\le n_e\}}$ | Probability distribution for the number of antibody types produced upon infection |
| $S$ | Fraction of susceptible individuals |
| $I$ | Fraction of infected individuals |
| $I^k$ | Fraction of individuals infected with strain $k$ |
| $\mu$ | Birth rate per individual |
| $\mu I^k$ | Rate of recovery from strain $k$ per individual |
| $\beta S I^k$ | Rate of infection with strain $k$ per individual |
| $\xi_k$ | Fraction of healthy individuals immune to strain $k$ |
| $\eta_k^j$ | Fraction of infected with strain $j$ that are immune to strain $k$ |
| $(\sigma_{ik})$ | Cross-immunity matrix |
| $\sigma_{ik}^{(\alpha)}$ | Cross-immunity matrix when exactly $\alpha$ antibody types are always produced |
| $\Lambda$ | Set of circulating strains |
| $\overline{\sigma}$ | Average pairwise cross-immunity |
| $\tilde{\sigma}\overline{\sigma}$ | Average pairwise squared cross-immunity |

Let us now define the processes that describe the dynamics. We assume that the population is at demographic equilibrium, that is, the rate of birth of individuals equals the rate of death. An important assumption made at this point is that all individuals have the same death rate, meaning we do not consider an age structure or a disease-related death. Finally, we consider a well mixed population, or in other words pairwise interactions occur with the same probability between any two individuals in appropriate states. Let $I^k$ be the fraction of individuals infected with strain $k$ and $S$ be the fraction of susceptible (not infected) individuals. The following processes are then present:

1. *Birth–death*: At rate $\mu$, each individual becomes naïve (immune repertoire $A=\varnothing$) and susceptible.
2. *Infection*: At rate $\beta S$, each individual infected with strain $k$ tries to infect a susceptible. The susceptible becomes infected if it is not immune to $k$. The overall rate of attempted infection per individual in the population is $\beta I^k S$.
3. *Recovery*: At rate $\gamma$, each infected individual becomes susceptible. The overall rate per individual is $\gamma I$.
4. *Acquiring immunity*: Infected individuals are immune to all strains. Upon recovery, an individual adds $\alpha$ antibodies corresponding to the infecting strain. The number $\alpha > 1$ follows the prescribed distribution $p_{\{\alpha\}}$. Each possible antibody is produced with the same probability.
5. *Mutation*: At rate $m$, each strain present in the population changes a random antigen to a random new one, if the infected individual is not immune to the new strain. We say that the old strain mutated to the new one. The overall rate of attempted mutation per individual is $mI$.

### 2.1. Immune history description

This model is a generalization of the simple classical Susceptible–Infected–Recovered (SIR) model to a system with multiple circulating strains. To develop equations for our system, we need to set up classes corresponding to each immune history, representing different immunity profiles in the population due to contact with different diseases. We also need to specify how these classes evolve into one another, that is, how immunity is acquired upon infection. As we will see, this characterizes the cross-immunity profile, that is, the way strains confer immunity to each other. Finally, we must specify the structure of "strain space" by defining what strains are allowed to mutate into one another.

Let $S_A$ be the fraction of individuals not infected with any strain, generically referred to as "healthy" or "susceptibles", with immune history $A$, and $I_A^i$ be the fraction of individuals infected with strain $i$ with immune history $A$. Let $C(A,k,B)$ denote the probability that upon infection with strain $k$ the immune history of an individual changes from $B$ to $A$. Define also $M_i$ as the mutational neighborhood of $i$, i.e., the set of strains to which $i$ may mutate (here corresponding to strains that are related by changing the configuration of a single epitope).

Then the dynamics presented above may be described in a rate equation formalism as

$$\begin{cases} \dot{S}_A = \mu(\delta_{A,\varnothing} - S_A) + \gamma\sum_k I_A^k - \sum_k (1-\delta_{k,A})\beta I^k S_A, & \text{(a)} \\ \dot{I}_A^j = \sum_B\sum_k C(A,k,B)(1-\delta_{j,B})\left(\delta_{jk}\beta I^k S_B + m_{jk} I_B^k\right) + & \\ \quad -(m+\gamma+\mu) I_A^j, & \text{(b)} \end{cases} \tag{1}$$

where $m_{jk} = \delta_{j,M_k} m/|M_k|$. Here and throughout, $|\cdot|$ applied to a set denotes the cardinality, or number of elements. We use the Kronecker Delta symbol in a generalized manner: if both $i$ and $j$

are strains, then $\delta_{ij}=1$ if $i=j$, and zero otherwise. Similarly, if both A and B are immune history sets, $\delta_{A,B}$ equals one if $A=B$, and zero otherwise. Finally, if $i$ is a strain and A is an immune history or mutational neighborhood, $\delta_{i,A}=1$ if $i\in A$, and zero otherwise.

The first set of equations describes the time evolution of the fraction of susceptibles with immune history $A$. The first term describes death of susceptibles with any immune history and birth of naïve (immune history $A=\varnothing$) susceptibles. The second term represents the increase of susceptibles with immune history $A$ due to recovery of individuals infected with any strain and immune history $A$. The last term represents the decrease of susceptibles with immune history $A$ due to infection with each strain $k$; the $\delta_{k,A}$ accounts for the fact that susceptibles immune to $k$ (that is, for which $k\in A$) cannot be infected by strain $k$.

The second set of equations describes the time evolution of the fraction of individuals infected with strain $j$ and immune history $A$. The first term has two components, corresponding to each of the terms in the final parenthesis. The first term in the parenthesis accounts for infection with strain $j$ of susceptibles with immune history $B$. The second accounts for mutation of the strain $k$ infecting individuals with immune history $B$ to strain $j$. Both these terms are multiplied by $C(A,k,B)$ and summed over all $B$ and $k$; this accounts for acquiring of immunity that leads from history $B$ to history $A$. The Kronecker Delta $\delta_{jk}$ is introduced simply for notational compactness and ensures that only strain $j$ contributes to that term. The $1-\delta_{j,B}$ factor deals with the fact that individuals immune to $j$ cannot be infected by that strain, whether through contact or through mutation. Finally, the last term in this equation accounts for the decrease in individuals infected with strain $j$ due to mutation, recovery, and natural death.

There are $2^{N_s}(N_s+1)$ equations in this description. However, they imply one conservation condition that arises from demographic equilibrium and says that the total number of individuals in the population is constant:

$$\sum_A\sum_k I_A^k+\sum_A S_A=I+S=1. \tag{2}$$

Thus, we have $2^{N_s}(N_s+1)-1$ independent equations.

### 2.2. Strain-level description

As mentioned above, this type of rate-equation formalism rapidly leads to a very large number of equations. This is because we must keep track of all possible immune histories; if there are $N_s$ strains circulating, there are $2^{N_s}$ different immune histories, corresponding to an individual having or not having an antibody corresponding to each particular epitope configuration. Correspondingly we find on the order of $2^{N_s}$ equations, as we saw above. This leads to two main complications: (i) it is difficult to deal with the enormous number of ensuing equations, either analytically or even numerically, and (ii) the very large number of different immune histories in relation to the population size means that we subdivide the population into a large number of classes which correspondingly have very small numbers of elements. This can make stochastic effects important, putting into question the deterministic rate equation formalism for reasonable population sizes. Note that the rate equation formalism implicitly considers the limit of infinite population sizes by considering fractions of individuals as continuous variables.

To simplify system (1), we make use of the general strategy outlined in Kryazhimskiy et al. (2007) which requires that (i) immunity is not lost from an infection process, (ii) each strain confers total immunity to itself, and (iii) acquiring of immunity is independent of previous history. All these are satisfied by the model described here: (i) is trivial, and (ii) and (iii) are a consequence of the fact that in this model at least one antibody is produced upon infection and one antibody is enough to grant immunity. Adapting the technique of Kryazhimskiy et al. (2007) to this model, we define the immunity variables:

$$\xi_i=\sum_{A:i}S_A,\quad \eta_i^j=\sum_{A:i}I_A^j, \tag{3}$$

where $A:i$ is shorthand for $A:i\in A$. The physical meaning of these variables should be clear: $\xi_i$ represents the fraction of healthy individuals immune to strain $i$, and $\eta_i^j$ represent the fraction of infected with strain $j$ that are immune to strain $i$. Note that, because we have chosen to account for immunity updating at the time of infection, being infected with strain $i$ requires being immune to it, and so $\eta_i^j$ represents the fraction of individuals infected with strain $i$. The idea here is to describe the system in terms of a set of variables that allows for reasonable approximations. Although it is easier to write the equations for the system in the form given by (1), taking the point of view of the single strain as opposed to generic immune history will lead to natural approximations on the way strains interact through cross-immunity.

Define $C_i(k,B)=\sum_{A:i}C(A,k,B)$, the probability of ending up with immunity to strain $i$ upon infection with strain $k$. In the model described above we have, for $i\notin B$, $C_i(k,B)\equiv\sigma_{ik}\equiv\sum_{\alpha=1}^{n_e}p_\alpha\sigma_{ik}^{(\alpha)}$, where $\sigma_{ik}^{(\alpha)}$ corresponds to the production of exactly $\alpha$ antibodies, which happens with probability $p_\alpha$. Simple combinatorial arguments tell us that

$$\sigma_{ik}^{(\alpha)}=\sigma_{ki}^{(\alpha)}=\begin{cases}1, & |i\cap k|>n_e-\alpha,\\ 1-\dfrac{(n_e-|i\cap k|)!}{(n_e-|i\cap k|-\alpha)!}\dfrac{(n_e-\alpha)!}{n_e!}, & |i\cap k|\le n_e-\alpha.\end{cases} \tag{4}$$

Here, $i\cap k$ denotes the set of matching antigens between strains $i$ and $k$. We find that $\sigma_{ik}$ is independent of previous immune history $B$. On the other hand, $C_i(k,B)=1$ if $i\in B$, that is, immunity is not lost upon infection. The matrix $(\sigma_{ik})$ is central to the model and encodes the cross-immunity granted by each strain to every other.

Expressions (4) become particularly simple for $\alpha=1$ and for $\alpha=n_e$. For $\alpha=1$, (4) reads

$$\sigma_{ik}^{(1)}=\sigma_{ki}^{(1)}=\frac{|i\cap k|}{n_e}, \tag{5}$$

meaning that cross-immunity of two strains is simply given by their fraction of identical epitopes. For $\alpha=n_e$,

$$\sigma_{ik}^{(n_e)}=\sigma_{ki}^{(n_e)}=\begin{cases}1, & |i\cap k|>0,\\ 0, & |i\cap k|=0,\end{cases} \tag{6}$$

which simply states that each strain confers total cross-immunity to any other strain so long as it shares at least one antigen with it, and there is no cross-immunity between completely different strains.

Appropriately summing over immune histories in Eqs (1), we find

$$\begin{cases}\dot\xi_i=\sum_k\left[\gamma\eta_i^k-\beta\eta_k^k(\xi_i-\xi_{ik})\right]-\mu\xi_i, & \text{(a)}\\ \dot\eta_i^j=\beta\eta_j^j\left[\xi_i-\xi_{ij}+\sigma_{ij}(1-I-\xi_i-\xi_j+\xi_{ij})\right]+\\ \quad+\sum_k m_{jk}\left[\eta_i^k-\eta_{ij}^k+\sigma_{ij}(I^k-\eta_i^k-\eta_j^k+\eta_{ij}^k)\right]+-(m+\gamma+\mu)\eta_i^j. & \text{(b)}\end{cases} \tag{7}$$

Here, $\xi_{ij}$ and $\eta_{ij}^k$ are the so-called second-order variables and denote fractions of the population that are immune to $i$ and $j$ simultaneously, while being respectively healthy or infected with strain $k$. Note that this description would be exact if we knew the time evolution of these variables. However, describing their evolution requires introducing further equations, which will depend on further variables describing simultaneous immunity to higher numbers of multiple strains. This in turn will require the introduction of equa-

tions for higher order terms. Thus, to make the problem tractable, we must truncate the system at some order by specifying a so-called closure relation, a heuristic description of a higher-order variable describing simultaneous immunity in terms of lower-order variables. Here we adopt a closure of order one, that is, we close the system by providing descriptions for the second order variables. The main strength of this approach is that it becomes easier to make assumptions based on physical ideas about the structure of the cross-immunity interactions between strains, leading to a significant simplification of the original system. We introduce a particular closure below. With a closure of this order, there are a total of $N_s(N_s+1)$ equations in this description. This can still be a large number, but represents a considerable reduction from exponential to quadratic in the number of strains.

We note that a simple and reasonable closure for $\xi_{ij}$ is Kryazhimskiy et al. (2007)

$$\xi_{ij} = (1-\sigma_{ij})\xi_i\xi_j + \sigma_{ij}\min(\xi_i,\xi_j). \tag{8}$$

For each pair $i,j$ of strains, this expression interpolates between the $\sigma_{ij}=0$ scenario, where the probability of being immune to $i$ and $j$ is independent, and the $\sigma_{ij}=1$ scenario, where infection by $i$ guarantees immunity to $j$.

In order to bring Eqs. (7) to closed form when $m\neq 0$, a similar assumption should be made to express $\eta_{ij}^k$ in terms of $\eta_i^k$ and $\eta_j^k$. However, since we will side step (7) when dealing with mutations, this additional closure assumption will be left unspecified. The set (7) of ordinary differential equations (ODEs) with $m=0$ together with the closure assumption (8) describes the behavior of our model in the absence of mutations and will be called from now on the ODE model.

## 3. Endemic equilibrium

Let us now look at the endemic equilibrium of Eqs. (7) in the absence of mutations.

### 3.1. Deriving an equation for equilibrium

Eqs. (7b) for $i=j$, that is, for the total fractions of infected with each strain, tell us that, for all $j$

$$\eta_j^j\left[R_0(1-I-\xi_j)-1\right]=0, \tag{9}$$

where $R_0=\beta/(\gamma+\mu)$. Now let $\Lambda=\{j:\eta_j^j\neq 0\}$. Then we have $I=\sum_{j\in\Lambda}\eta_j^j$, and for all circulating strains $j\in\Lambda$ we find

$$\xi_j=\xi=1-I-R_0^{-1}. \tag{10}$$

This shows that the existence of an endemic equilibrium requires $R_0>1$, which is directly analogous to results from classical SIR models. Because all strains in this model are equivalent as they have the same $\beta$ and $\gamma$, the equilibrium also forces all immunity variables $\xi_j$ corresponding to the circulating strains to take the same value.

In equilibrium, defining $\eta_i=\sum_j\eta_i^j$, Eqs. (7a) for $i\in\Lambda$ can be written as

$$-\gamma\eta_i-\beta\sum_{j\in\Lambda}\eta_j^j\xi_{ij}+\beta I\xi+\mu\xi=0. \tag{11}$$

Summing over all $j$ in Eqs. (7b) leads to

$$\eta_i=R_0\left[\xi I+\sum_{j\in\Lambda}\eta_j^j\left[-\xi_{ij}+\sigma_{ij}(1-I-2\xi+\xi_{ij})\right]\right]. \tag{12}$$

Substituting this result into Eq. (11) and using (10) for $I$, we find

$$\sum_{j\in\Lambda}C_{ij}\eta_j^j=\frac{\mu}{\gamma}\xi(1-\xi), \tag{13}$$

where

$$C_{ij}=\xi_{ij}\left[\sigma_{ij}+\frac{\mu}{\gamma}\right]+\sigma_{ij}\left(R_0^{-1}-\xi\right). \tag{14}$$

Eq. (13) is a linear system of $\tilde{N}_S$ equations in $\tilde{N}_S$ variables, where $\tilde{N}_S=|\Lambda|$ is the number of circulating strains. Because for a given closure $\xi_{ij}=f(\xi_i,\xi_j,\sigma_{ij})$, $\xi_{ij}$ becomes a function of $\xi$ and $\sigma_{ij}$ for $i,j\in\Lambda$; the solution of Eq. (13) gives the individual prevalences as a function of $\xi$, which can in turn be found by substitution into Eq. (10). For a certain solution for the $\eta_j^j$, the crossed $\eta_i^j$ can be found through the equilibrium of Eq. (7b):

$$\eta_i^j=R_0\eta_j^j\left[\xi_i-\xi_{ij}+\sigma_{ij}(1-I-\xi_i-\xi_j+\xi_{ij})\right]. \tag{15}$$

In particular, note that for all $i$ we have $j\notin\Lambda\Rightarrow\eta_i^j=0$.

### 3.2. Symmetric equilibrium

Let $\delta_j:=\eta_j^j-I/|\Lambda|$. Note that as a consequence $\sum_{j\in\Lambda}\delta_j=0$. Substituting into Eq. (13), we find

$$\sum_{j\in\Lambda}C_{ij}\delta_j+\frac{I}{|\Lambda|}\sum_{j\in\Lambda}C_{ij}=\frac{\mu}{\gamma}\xi(1-\xi). \tag{16}$$

For a symmetric equilibrium to exist, $(\delta_j)_{j\in\Lambda}=0$ must be a solution. In that case, we must have

$$\sum_{j\in\Lambda}C_{ij}=\frac{|\Lambda|}{I}\frac{\mu}{\gamma}\xi(1-\xi). \tag{17}$$

In particular, $\sum_{j\in\Lambda}C_{ij}$ must be independent of $i$. Conversely, if $\sum_{j\in\Lambda}C_{ij}$ is independent of $i$ then Eq. (17) together with Eq. (10) becomes an equation for the total infective density $I$ whose form will depend on the closure assumption. Given a solution $I$ of this equation, the individual prevalences are then $\eta_j^j=I/|\Lambda|$ for all $j$. Assuming that there is at least one solution $I$ in the interval $(0,1]$, we conclude that the system has symmetric equilibria if and only if $\sum_{j\in\Lambda}C_{ij}$ is independent of $i$. Since by construction the lines of $(\sigma_{ij})$ are permutations of each other (all strains are equivalent), and since we have found that $C_{ij}$ depends on $i$ and $j$ only through $\sigma_{ij}$, this condition is always fulfilled when $\Lambda$ coincides with the set of all strains.

Let us then study Eq. (17) for the total prevalence in a symmetric equilibrium with all strains present. Define $\overline{\sigma}=\sum_{i\in\Lambda}\sigma_{ij}/|\Lambda|$, for any $j$. This is well defined because, since the lines of the matrix $(\sigma_{ij})$ are permutations of each other, this quantity is independent of $j$. For the same reason, we may define the $j$-independent (equilibrium) quantities $\overline{s}=\sum_{i\in\Lambda}\xi_{ij}/|\Lambda|$ and $\tilde{s}=\sum_{i\in\Lambda}\sigma_{ij}\xi_{ij}/|\Lambda|$. With these definitions, by summing over all $i$ in Eq. (13) we obtain an equation for the total infected density $I$:

$$I\left[\overline{\sigma}\left(R_0^{-1}-\xi\right)+\frac{\mu}{\gamma}\overline{s}+\tilde{s}\right]=\frac{\mu}{\gamma}\xi(1-\xi), \tag{18}$$

where $\xi$, $\overline{s}$ and $\tilde{s}$ are to be understood as functions of $I$ due to the equilibrium constraints (Eq. (10)).

To proceed, we must now settle for a specific closure relation. Let us consider the one defined by Eq. (8). Using (10) for $\xi$, some algebra leads to an explicit cubic equation for $I$ depending only on system parameters:

$$\begin{aligned}P_3(I)=&R_0\left[\overline{\sigma}(1-\tilde{\sigma})+\frac{\mu}{\gamma}(1-\overline{\sigma})\right]I^3\\&+(2-R_0)\left[\overline{\sigma}(1-\tilde{\sigma})+\frac{\mu}{\gamma}(1-\overline{\sigma})\right]I^2\\&+\left\{\overline{\sigma}\left[R_0^{-1}(1-\tilde{\sigma})+\tilde{\sigma}\right]+\frac{\mu}{\gamma}\left[R_0^{-1}(1-\overline{\sigma})+\overline{\sigma}\right]\right\}I+\\&-\frac{\mu}{\gamma}\left(1-R_0^{-1}\right)=0,\end{aligned} \tag{19}$$

where $\tilde{\sigma}:=\sum_{i\in|\Lambda|}\sigma_{ij}^2/(|\Lambda|\overline{\sigma})$.

For $R_0 > 1$, Eq. (19) always has a solution in $(0,1)$ which for $\mu/\gamma \ll 1$ is approximately given by

$$I \approx \frac{\mu}{\gamma}\frac{R_0 - 1}{\bar{\sigma}[1+\tilde{\sigma}(R_0-1)]}. \tag{20}$$

This should be compared with $I = (\mu/\gamma)(R_0 - 1)$ for the prevalence of each strain of the classical SIR model in the same approximation, and shows how strain cross-immunity reduces overall prevalence.

In general, the polynomial $P_3$ satisfies $P_3(0) < 0$, $P_3(1) > 0$ and so it has either one root or three roots in $(0,1)$. For $R_0 < 2$, it is easy to check that there is only one root in $(0,1)$. For $R_0$ large enough, however, an additional pair of roots may exist for certain choices of $(\sigma_{ij})$. These two roots correspond to a stable and an unstable equilibrium for the total density of infected, and they are 'unphysical', in the sense that they have no correspondence with the SIR model and are a consequence of the closure assumption equation (8). It can be seen that they are associated with cross immunity profiles which have values of $\sigma_{ij}$ well away from the values 0 and 1 for which the closure is exact. Moreover, the mechanism behind the high prevalence additional equilibrium is as follows: the susceptibility to reinfection is overestimated because cross-immunity is underestimated, and so the infection of individuals who have been infected previously by other strains is overestimated.

### 3.3. Agent-based model

In order to check that this additional stable equilibrium is indeed an artifact of the closure assumption, we set up a fully stochastic agent-based model that directly implements the immune-history-based model as described by steps 1–5 of Section 2 (retaining the assumption that any antibody against a strain confers total immunity). Taking parameter values for which the ODE model predicted a low prevalence equilibrium with $I \approx 4.3 \times 10^{-4}$ and $\xi \approx 0.93$, and a high prevalence equilibrium with $I \approx 0.66$, $\xi \approx 0.27$, we performed simulations from initial configurations close to each of the predicted equilibria. The implementation of the initial configuration was made maximally random given those values as follows. First, a fraction $I/N_s$ of the population was infected with each of the possible strains. We considered a fully monoclonal population ($\sigma_{ij} = \sigma_{ij}^{(1)}$), which means that each infected agent carried exactly one antibody against the infecting strain. Then, we added a random antibody to the immune history of each agent, with uniform probability for each antibody, until the fraction immune to one arbitrary strain attained the equilibrium value for $\xi$. Assignment of a previously existing antibody was ignored. With this procedure, the resulting immunity to any strain is close to the equilibrium value.

Simulations started off in this way for the values of $I$ and $\xi$ associated with the high prevalence equilibrium are shown in Fig. 1, right panel. In contrast, simulations started off for the low-prevalence values of $I$ and $\xi$ exhibit only fluctuations due to finite size effects, as one would expect in a stochastic realization of a true mean field equilibrium, see Fig. 1, left panel.

### 3.4. Degeneracy of the symmetric equilibrium and coexistence of non-symmetric equilibria

We will now show how certain cross immunity profiles, which arise under common assumptions, can give rise to unexpected properties for the endemic equilibrium of a multi-strain system.

To see the relation between the properties of the cross-immunity matrix and equilibrium, assume that a symmetric equilibrium does exist. In particular, as we have just seen, this is always the case when all strains are circulating. Then, the equilibrium is degenerate if and only if

$$\sum_{j \in \Lambda} C_{ij}\delta_j = 0 \tag{21}$$

admits a nontrivial solution for $(\delta_j)_{j\in\Lambda}$ such that $\sum_{j\in\Lambda}\delta_j = 0$. Since by hypothesis the sum $\sum_{j\in\Lambda}C_{ij}$ must be independent of $i$ and the matrix $(C_{ij})$ is symmetric, the line sum $\sum_{i\in\Lambda}C_{ij}$ is independent of $j$, and therefore any nontrivial solution $(\delta_j)_{j\in\Lambda}$ of Eq. (21) fulfills $\sum_{j\in\Lambda}\delta_j = 0$. Since the sum of the components of any eigenvector associated with the zero eigenvalue of $(C_{ij})$ is null, any nontrivial element of the kernel of $(C_{ij})$ corresponds to a non-symmetric endemic equilibrium.

In general, $(C_{ij})$ is non-degenerate, but for some particular choices several properties of the cross-immunity matrix $(\sigma_{ij})$ contrive to produce a $(C_{ij})$ with a high dimensional kernel, as we will see shortly.

Consider first the case when all strains are circulating. For most parameter choices, the matrix $(\sigma_{ij})$ is non-degenerate. However, as discussed in Section 2.2, a simple and natural choice for modeling cross-immunity is to take $\sigma_{ij} = \sigma_{ij}^{(1)}$, which corresponds to measuring the cross-immunity between two strains by the number of overlapping antibodies. The resulting cross-immunity matrices are directly related to the Hamming distance matrix, and this can be used to compute their spectrum (Gopalapillai, 2009), which turns out to be highly degenerate and also quite simple: it has a positive

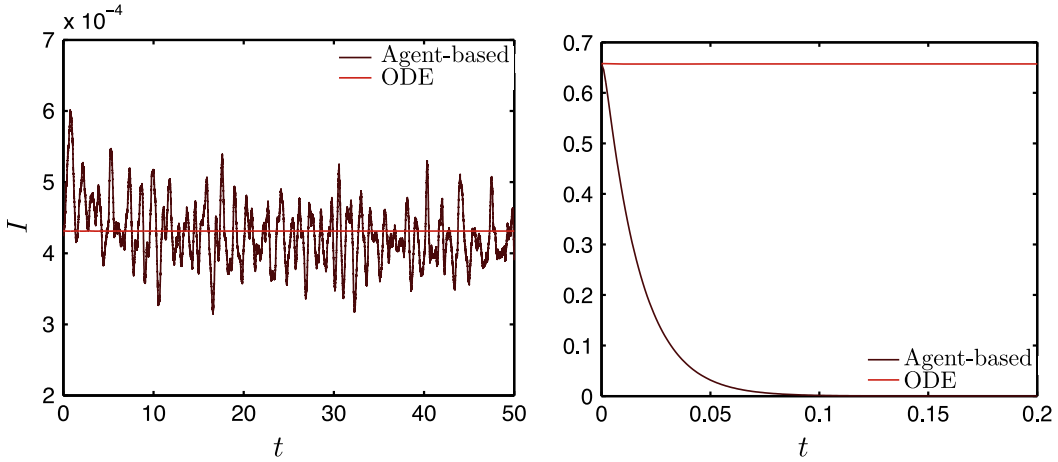


**Fig. 1.** Comparison of agent-based simulations with integration of the ODE model for the evolution of the total prevalence with all strains circulating starting from (left) initial conditions close to the high prevalence equilibrium, and (right) initial conditions close to the low prevalence equilibrium. Parameters are $n_e = 3$, $n_c = 2$, $\sigma_{ij} = \sigma_{ij}^{(1)}$, $R_0 = 15$, $\gamma = 90\ \text{year}^{-1}$ and $\mu = 70\ \text{year}^{-1}$. The agent-based simulations use $5 \times 10^6$ agents and are averaged over 30 runs.

(Perron–Frobenius) non-degenerate real eigenvalue, another positive eigenvalue with multiplicity $n_e(n_c-1)$, and a zero eigenvalue with multiplicity $n_c^{n_e}-n_e(n_c-1)-1$. The matrix $(\sigma_{ij}^2)$ also has a positive (Perron–Frobenius) non-degenerate real eigenvalue, and, for $n_e \geq 3$ and $n_c \geq n_e-1$, analysis of several particular cases reveals that it is also degenerate, with another two positive eigenvalues of multiplicities $n_e(n_c-1)$ and $n_e(n_e-1)(n_c-1)^2/2$, and a zero eigenvalue of multiplicity $n_c^{n_e}-n_e(n_c-1)(1+(n_e-1)(n_c-1)/2)-1$. Also for this particular choice of $\sigma_{ij}=\sigma_{ij}^{(1)}$, the analysis of numerous examples indicates that the eigenvectors of $(\sigma_{ij}^2)$ are also eigenvectors of $(\sigma_{ij})$ and that, moreover, all eigenvectors of $(\sigma_{ij}^2)$ associated with the zero eigenvalue are also eigenvectors of $(\sigma_{ij})$ associated with the same eigenvalue.

With closure assumption (8), this implies the degeneracy of the homogeneous system (21). Indeed, we can then write $C_{ij}=\tilde{C}_{ij}+b_0=b_2(\sigma_{ij}^2)+b_1(\sigma_{ij})+b_0$, where $b_n$, $n=0,1,2$, are functions of $\xi$ and of the system's parameters. Eq. (21) is equivalent to $\sum_{j=1}^{N_s}\tilde{C}_{ij}\delta_j=0$ because $\sum_{j=1}^{N_s}\delta_j=0$. The properties of $(\sigma_{ij})$ and of $(\sigma_{ij}^2)$ stated above imply that $(\tilde{C}_{ij})$ is degenerate with a zero eigenvalue with multiplicity $n_c^{n_e}-n_e(n_c-1)(1+(n_e-1)(n_c-1)/2)-1$. Therefore the equilibrium value for the overall prevalence $I$ corresponds in the $\eta_j^i$ simplex to a hyperplane of equilibria, given by the solution space of Eq. (21). The preceding argument holds only for the trivial distribution $p_1=1$, $p_{\{2\leq\alpha\leq n_e\}}=0$, and depends on the closure assumption (8) and on the presence of all strains.

In Fig. 2 we illustrate this degeneracy effect for 8 strains, with $n_e=3$ and $n_c=2$. The plot shows orbits with different initial conditions converging to equilibria where, despite the symmetry of the system with respect to strain permutation, different strains have different prevalences. In this case, the dimension of the hyperplane of equilibria is 1. In the presence of mutations, the system may drift within this hyperplane of equilibria.

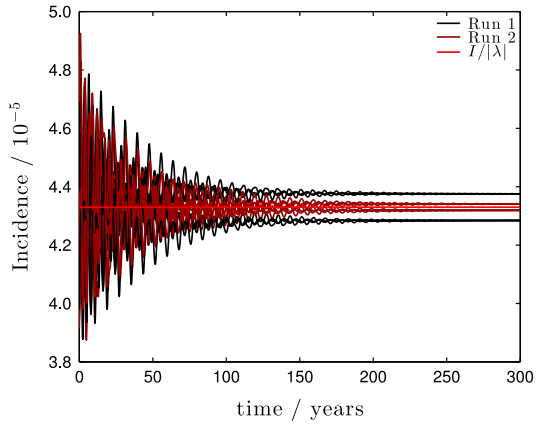


**Fig. 2.** Illustration of the degeneracy of the symmetric equilibrium of the ODE model. The incidence of each strain is shown for two runs with different initial incidences close to equilibrium. Parameters are $n_e=3$, $n_c=2$, $\sigma_{ij}=\sigma_{ij}^{(1)}$, $R_0=5$, $\gamma=90\ \text{year}^{-1}$ and $\mu=70\ \text{year}^{-1}$. The equilibrium value of $I/|\lambda|$ is also shown. It was obtained from Eq. (19) and was verified to agree with that found for both runs.

To illustrate the behavior of the degeneracy of the cross-immunity matrix when an arbitrary subset of the possible strains is circulating, Fig. 3 shows a measure of the number of zero eigenvalues of $(\sigma_{ij})$ and $(\sigma_{ij}^2)$ with $i$ and $j$ in each of the possible subsets. For each possible number of strains $N_d$ considered to not be circulating, let $C_{N_d}$ be the set of all possible combinations of circulating strains. Then the total number of zero eigenvalues for all possible combinations in $C_{N_d}$ is shown normalized by $|C_{N_d}|$. Three simple choices of cross-immunity profiles are shown for different choices of $n_e$ and $n_c$. We see that degeneracy is overall rare, although it is particularly high for the $\sigma_{ij}^{(1)}$ case mentioned above when most strains are circulating.

Closures involving higher powers of $\sigma_{ij}$ will typically lift the degeneracy. Writing $\xi_{ij}$ as a Taylor expansion in powers of $\sigma_{ij}$, we have, in equilibrium

$$\xi_{ij}=\sum_{n=0}^{N}a_n(\xi)\sigma_{ij}^n. \tag{22}$$

The highest power $N$ can in principle be infinity, but is typically small. Substituting in the definition of $C_{ij}$ we have

$$C_{ij}=\sum_{n=0}^{N+1}b_n(\xi)\sigma_{ij}^n, \tag{23}$$

where

$$b_n(\xi)=a_{n-1}(\xi)+\frac{\mu}{\gamma}a_n(\xi)+\delta_{n1}(R_0^{-1}-\xi), \tag{24}$$

with the convention that $a_{N+1}=a_{-1}=0$. Using Eq. (21), we find the condition for equilibrium:

$$\sum_{n=1}^{N+1}b_n(\xi)\sum_{j\in\Lambda}\sigma_{ij}^n\delta_j=0, \tag{25}$$

where again we have used the fact that $\sum_{j\in\Lambda}\delta_j=0$ to drop the zeroth-power terms. The properties that relate the spectra and eigenspaces of $(\sigma_{ij}^2)$ and $(\sigma_{ij})$ for $\sigma_{ij}=\sigma_{ij}^{(1)}$ do not seem to carry over to higher powers, and so for $N\geq 2$ the system (25) becomes non-degenerate even for the simplest cross-immunity profile $\sigma_{ij}^{(1)}$.

A common approach in the literature is to study the properties of equilibrium for simple models such as the one presented here (Abu-Raddad and Ferguson, 2005a,b; Abu-Raddad et al., 2005; Cobey and Pascual, 2011), and the particular cross-immunity profile associated with degeneracy is often chosen (Zinder et al., 2013). As such, we believe it is important to keep in mind that

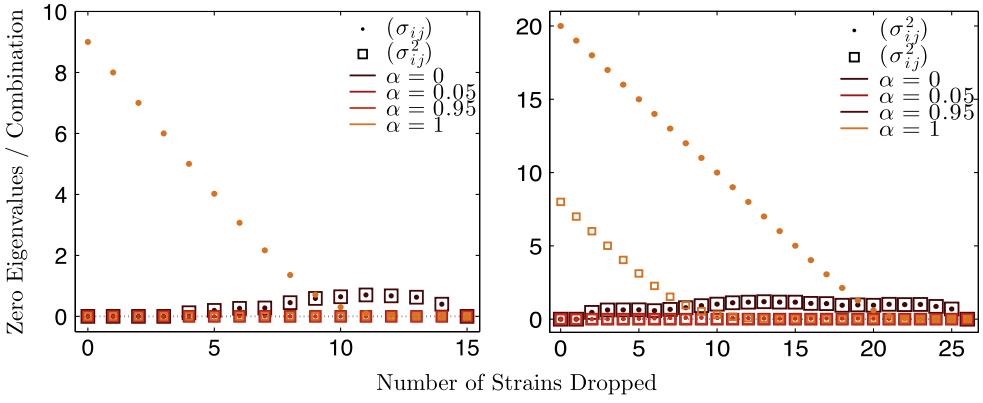


**Fig. 3.** Illustration of the degeneracy of $(\sigma_{ij})$ (dots) and $(\sigma_{ij}^2)$ (squares) for $\sigma_{ij}=\alpha\sigma_{ij}^{(1)}+(1-\alpha)\sigma_{ij}^{(n_e)}$, for different values of $\alpha$ and two choices of $n_e$ and $n_c$ (see main text for details): (left) $n_e=2$, $n_c=4$; (right) $n_e=n_c=3$.

simple models with reasonable assumptions may lead to the presence of degeneracy; this degeneracy should be treated as unphysical, since, as can be seen from the discussion presented here, assuming other forms of cross-immunity, or most importantly increasing the order of the closure or assuming not all possible strains are circulating, will in general lift the degeneracy.

## 4. Injection of mutant strains

In this section we explore the behavior of our multi-strain model from an evolutionary perspective. Instead of assuming the presence of a certain number of coexisting strains, as one is led to the analysis of the equilibria of Eq. (7) in the absence of mutations, we shall investigate how diversity may develop from a single founding strain. We consider Eq. (7) for two strains, the founding strain 1 and strain 2 in its mutational neighborhood. We also invoke the closure assumption (8). For a particular choice of the distribution $p_\alpha$, $\alpha=1,\ldots,n_e$, we assume this system to be in equilibrium with strain 2 absent, with the corresponding single strain equilibrium values $\xi_i$ and $\eta_i^j$, $i$, $j=1$, 2, when a mutation occurs. To represent a mutation event in the ODEs framework we use, we introduce an implicit population size $N$ and use the initial conditions $\eta_1^1(0)=\eta_1^1-1/N$, $\eta_2^2(0)=\eta_1^2(0)=1/N$, with the remaining variables unchanged at their single strain equilibrium values.

In contrast with other models where invasion of escape mutants may be conditioned, mutant strain 2 is always a successful invader. It will always undergo a period of exponential growth, because immunity in the population is below its equilibrium value. More precisely, it can be seen from Eq. (7) that the initial rate of this exponential growth of $\eta_2^2(\tau)$, in terms of nondimensional time, $\tau=t/(\gamma+\mu)$, is $g=R_0(\xi_1(\gamma+\mu)/\gamma-\xi_2-\eta_1^1)\approx R_0(\xi_1-\xi_2)$, where the approximation holds for $\mu\ll\gamma$. This growth factor is always positive. In Fig. 4 we show a plot of $g$ as a function of $R_0$ and the single non-trivial cross-immunity parameter $\sigma$ using the approximation:

$$g(R_0,\sigma)=(1-\sigma)(R_0-1)\frac{\sigma(R_0-1)+R_0}{\sigma(1-\sigma)(R_0-1)+R_0}, \tag{26}$$

which holds for $\mu\ll\gamma$.

We are interested in monitoring the behavior of the system beyond this initial phase of exponential growth, and check if any of the variables $\eta_1^1$ and $\eta_2^2$ ever goes below $1/N$, the value that corresponds to a single individual in a population of size $N$ and therefore to extinction of the corresponding strain.

Even for a population size as large as $10^8$, the most common outcome of mutation implemented in this way is extinction of the founding strain, followed by extinction of strain 2. The reservoir of susceptibility to strain 2 in the initial population fuels a huge epidemic of 2, causing first the extinction of strain 1 and then that

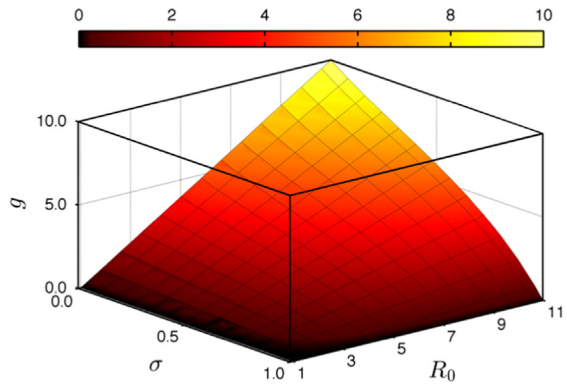


**Fig. 4.** Plot of the approximate initial growth factor $g$ of the invading strain as a function of $\sigma$ and $R_0$.

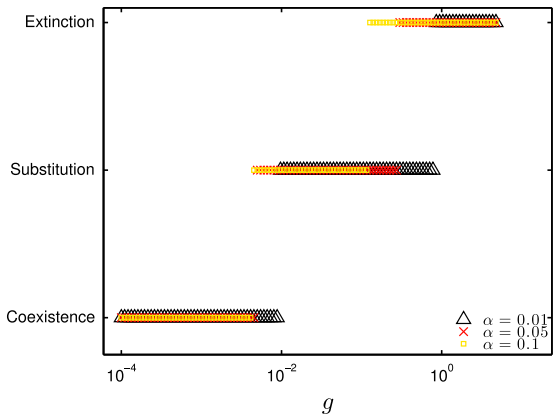


**Fig. 5.** Illustration of the different possible outcomes of an invading mutation occurring at the single strain equilibrium, as a function of the initial growth factor $g$ of the invading strain, for different values of $\alpha$. Note the qualitatively similar behavior regardless of the value of $\alpha$, whose specific value appears only to set the precise transition value of $g$ between different outcomes. Here, population size is $10^8$.

of strain 2 because of a depletion of susceptibles, whose time scale for reposition is much slower.

This phenomenon is determined mainly by the rate $g$. Different outcomes can be engineered by fine-tuning parameter $g$ through the choice either of $R_0$ or $\sigma$. For small values of $g$, corresponding to $R_0$ close to one or to almost total cross-immunity, we may observe strain substitution, or even strain coexistence, after mutation (see Fig. 5). However, for these values of $g$ invasion by strain 2 becomes so slow that stochastic extinction events prevent these outcomes from being observed in agent-based simulations and most likely in real systems.

Note that relaxing the assumption that the original strain has reached equilibrium when the mutant is injected further favors extinction. A more detailed discussion of the implications of these results is presented in Section 5.

## 5. Discussion and conclusions

This work deals with multi-strain systems competing through cross-immunity in an SIR type framework with vital dynamics. Each strain is characterized by a particular configuration, out of $n_c$ possibilities, of each of its $n_e$ epitopes, and all $N_s=n_c^{n_e}$ strains have the same epidemiological parameters. The immune response of the population is heterogeneous, in the sense that the number of epitopes to which antibodies are produced upon infection may vary in the population. It is homogeneous in the sense that any immune repertoire with at least one matching antibody confers full protection against a challenging strain.

In the spirit of Kryazhimskiy et al. (2007), we built a reduced deterministic model via a closure assumption that postulates the form of strain immunity cross-correlations. For this reduced model with an arbitrary cross-immunity structure, we studied the properties of the endemic equilibrium in the presence of the whole set of strains and of arbitrary subsets of this set. We obtain two results that highlight a word of caution against possible unphysical consequences of seemingly reasonable assumptions made in the scope of analytic models.

First, we find, in a region of parameter space, a high prevalence endemic equilibrium in addition to the SIR low prevalence equilibrium. Comparison with agent-based simulations show that this additional equilibrium is an artifact of the closure assumption. Second, we obtain conditions for the endemic equilibrium to be symmetric, reflecting the symmetry of the full system with regard to strain permutation. We then find that for a particular choice of

the immune response profile of the population this symmetry is broken, and there exists a manifold of non-symmetric endemic equilibria. This too can be seen as a spurious feature of the closure assumption, since higher order closures will in general lift the degeneracy.

The main goal is to explore the consequences of the basic assumptions made about the cross-immunity competition mechanisms in the presence of mutations. In particular, we investigated if the former are compatible with the build up of antigenic diversity from a single founding strain. Although the reduced deterministic model developed here may include the representation of mutations, it is well known that this treatment of discrete mutation events is too unrealistic. Here we adopted a mixed approach in which a cut-off value for the fraction of the population in each class stands for an implicit population size, and mutations are implemented by an instantaneous change in the values of these variables translating the switch of an individual infected with a given strain to an individual infected with a mutant.

Extensive numerical integrations of the model show that, except in a small region of parameter space that allows strain substitution or strain coexistence starting from a founding strain, a mutation event leads to disease extinction. These results are confirmed by agent-based simulations, which show furthermore that, due to stochastic extinctions, the regimes of strain substitution and addition are not observed in reasonably sized populations. This is in contrast with the development of limited and even explosive diversity reported in the literature for similar models (Ferguson et al., 2003; Koelle et al., 2006; Minayev and Ferguson, 2009a,b). The motivation for these models is to find the conditions that reproduce the characteristic phylogenetic pattern of influenza A, and extinctions are avoided either by working with continuous density variables and very low, perhaps unphysical, cut-offs (Minayev and Ferguson, 2009a,b), or by including immigration of infectives (Ferguson et al., 2003; Koelle et al., 2006). The qualitative features of influenza A evolution are obtained when this is combined with assumptions on strain space structure (Ferguson et al., 2003; Koelle et al., 2006) or on immune response (Ferguson et al., 2003; Minayev and Ferguson, 2009a,b).

Apart from underlying SIR type dynamics with the same epidemiological parameters for all strains, the only ingredient of the model that was kept unchanged in our study is the hypothesis that, across the whole population, a single matching antibody confers immunity to a challenging strain. Given that the agent-based simulations are free of the limitations of the reduced deterministic model and validate its predictions, our results taken together strongly suggest that the build up of antigenic diversity from a single founding strain by invasion of mutants competing through cross-immunity is incompatible with that assumption, in the framework of uniform SIR dynamics and unstructured strain space. This conclusion is in agreement with the results of a study based purely on simulations in which strain diversity is achieved by modifying that hypothesis (Parisi et al., 2013).

It is interesting to compare the results above with the fate of an antigenically identical mutant that competes through increased infectiousness. In that case, strain substitution is easily observed (results not shown), in agreement with the predictions of deterministic models for antigenically similar pathogens (Cortez, 2013) . The model we develop here thus reveals a mechanism acting at the population level that would favor a serologically monotypic virus evolving towards increased infectiousness. For example, the virus of measles, a highly contagious disease, exists as a single serotype, despite having in vitro mutation rates similar to other viruses such as influenza that exhibit large antigenic diversity. The measles virus also seems to conform to the hypothesis of immunity being conferred by a single matching anti-body. It has been shown that successful escape mutants may require changes in all the epitopes of its hemagglutinin protein targeted by human antibodies, and that this plays a role in keeping measles serologically monotypic (Lech et al., 2013).

We speculate that the model developed here adequately describes the evolutionary epidemiology of a virus like measles, and that rapidly evolving, diverse pathogens such as influenza are associated with a weaker antibody protection in some hosts.

## Acknowledgments

Two of the authors (T.A. and A.N.) gratefully acknowledge the support of Fundação Calouste Gulbenkian through its Programa Estímulo à Investigação 2011, and of Fundação para a Ciência e a Tecnologia through Grants PTDC/SAU-EPI/112179/2009 and PEst-OE/FIS/ UI0261/2011.

## References

Abu-Raddad, L.J., Ferguson, N.M., 2005a. Characterizing the symmetric equilibrium of multi-strain host-pathogen systems in the presence of cross immunity. J. Math. Biol. 50, 531–558.
Abu-Raddad, L.J., Ferguson, N.M., 2005b. The impact of cross-immunity, mutation and stochastic extinction on pathogen diversity. Proc. R. Soc. Lond. B 271, 2431–2438.
Abu-Raddad, L.J., van der Ventesl, B.I.S., Ferguson, N.M., 2005. Interactions of multiple strain pathogen diseases in the presence of coinfection. Phys. Rev. Lett. 100, 168102.
Adams, B., Sasaki, A., 2007. Cross-immunity, invasion and coexistence of pathogen strains in epidemiological models with one-dimensional antigenic space. Math. Biosci. 210, 680–699.
Adams, B., Sasaki, A., 2009. Antigenic distance and cross-immunity, invasibility and coexistence of pathogen strains in an epidemiological model with discrete antigenic space. Theor. Pop. Biol. 76, 157–167.
Andreasen, V., Lin, J., Levin, S.A., 1997. The dynamics of cocirculating strains conferring partial cross-immunity. J. Math. Biol. 35, 825–842.
Ballesteros, S., Vergu, E., Cazelles, B., 2009. Influenza A gradual and epochal evolution: insights from simple models. PLoS One 4, e7426.
Bedford, T., Rambuat, A., Pascual, M., 2012. Canalization of the evolutionary trajectory of the human influenza virus. BMC Biol. 10, 38.
Buckee, C.O., Recker, M., Watkins, E.R., Gupta, S., 2011. Role of stochastic processes in maintaining discrete strain structure in antigenically diverse pathogen populations. Proc. Natl. Acad. Sci. 108, 15504–15509.
Castillo-Chavez, C., Hethcote, H.W., Andreasen, V., Levin, S.A., Liu, W.M., 1989. Epidemiological models with age structure, proportionate mixing, and cross-immunity. J. Math. Biol. 27, 233–258.
Cobey, S., Koelle, K., 2008. Capturing escape in infectious disease dynamics. Trends Ecol. Evol. 23, 572–577.
Cobey, S., Pascual, M., 2011. Consequences of host heterogeneity, epitope immunodominance, and immune breadth for strain competition. J. Theor. Biol. 270, 80–87.
Cortez, M.H., 2013. When does pathogen evolution maximize the basic reproductive number in well-mixed hostpathogen systems? J. Math. Biol. 67, 1533–1585.
Ferguson, N.M., Galvani, A.P., Bush, R.M., 2003. Ecological and immunological determinants of influenza evolution. Nature 422, 428–433.
Girvan, M., Callaway, D.S., Newman, M.E.J., Strogatz, S.H., 2002. Simple model of epidemics with pathogen mutation. Phys. Rev. E 65, 031915.
Gog, J.R., Grenfell, B.T., 2002. Dynamics and selection of many-strain pathogens. Proc. Natl. Acad. Sci. 99, 17209–17214.
Gog, J.R., Swinton, J., 2002. A status-based approach to multiple strain dynamics. J. Math. Biol. 44, 169–184.
Gopalapillai, I., 2009. Distance spectrum of graph compositions. Ars Math. Contemp. 2 (1).
Koelle, K., Cobey, S., Grenfell, B., Pascual, M., 2006. Epochal evolution shapes the phylodynamics of interpandemic influenza A (H3N2) in humans. Science 314, 1898–1903.
Koelle, K., Kamradt, M., Pascual, M., 2009. Understanding the dynamics of rapidly evolving pathogens through modeling the tempo of antigenic change: influenza as a case study. Epidemics 1, 129–137.
Koelle, K., Khatri, P., Kamradt, M., Kepler, T., 2010. A two-tiered model for simulating the ecological and evolutionary dynamics of rapidly evolving viruses, with an application to influenza. J. R. Soc. Interface 7, 1257–1274.
Kryazhimskiy, S., Dieckmann, U., Levin, S.A., Dushoff, J., 2007. On state-space reduction in multi-strain pathogen models, with an application to antigenic drift in influenza A. PLoS Comput. Biol. 3, e159.
Kucharski, A., Gog, J., 2012. Age profile of immunity to influenza: effect of original antigenic sin. Theor. Pop. Biol. 81, 102–112.
Lech, P.J., Tobin, G.J., Bushnell, R., Gutschenritter, E., Pham, L.D., Nace, R., Verhoeyen, E., Cosset, F.L., Muller, C.P., Russell, S.J., Nara, P.L., 2013. Epitope dampening monotypic measles virus hemagglutinin glycoprotein results in resistance to cocktail of monoclonal antibodies. PLoS One 8, e52306.

Lukehart, S.A., Deitsch, K.W., Stringer, J.R., 2009. Common strategies for antigenic variation by bacterial, fungal and protozoan pathogens. Nat. Rev. Microbiol. 7, 493–503.
Minayev, P., Ferguson, N., 2009a. Improving the realism of deterministic multi-strain models: implications for modelling influenza A. J. R. Soc. Interface 6, 509–518.
Minayev, P., Ferguson, N., 2009b. Incorporating demographic stochasticity into multi-strain epidemic models: application to influenza A. J. R. Soc. Interface 6, 989–996.
Nakajima, S., Nobusawa, E., Nakajima, K., 2000. Variation in response among individuals to antigenic sites on the HA protein of human influenza virus may be responsible for the emergence of drift strains in the human population. Virology 274, 220–231.
Parisi, A., Lopes, J.S., Nunes, A., Gomes, M.G.M., 2013. Heterogeneity in antibody range and the antigenic drift of influenza A viruses. Ecol. Complex. 14, 157–165.
Sato, K., Morishita, T., Nobusawa, E., Tonegawa, K., Sakae, K., Nakajima, S., Nakajima, K., 2012. Amino-acid change on the antigenic region B1 of H3 haemagglutinin may be a trigger for the emergence of drift strain of influenza A virus. Epidemiol. Infect. 132, 399–406.
Tria, F., Lässig, M., Peliti, L., Franz, S., 2005. A minimal stochastic model for influenza evolution. J. Stat. Mech.: Theory Exp. 2005, P07008.
Zinder, D., Bedford, T., Gupta, S., Pascual, M., 2013. The roles of competition and mutation in shaping antigenic and genetic diversity in influenza. PLoS Pathog. 9, e1003104.