



International Institute for  
Applied Systems Analysis  
Schlossplatz 1  
A-2361 Laxenburg, Austria

Tel: +43 2236 807 342  
Fax: +43 2236 71313  
E-mail: [publications@iiasa.ac.at](mailto:publications@iiasa.ac.at)  
Web: [www.iiasa.ac.at](http://www.iiasa.ac.at)

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## **Interim Report**

**IR-07-062**

### **The Influence of Cross-Immunity on the Coexistence, Invasion and Evolution of Pathogen Strains**

Ben Adams ([ben@bio-math10.biology.kyushu-u.ac.jp](mailto:ben@bio-math10.biology.kyushu-u.ac.jp))  
Akira Sasaki ([sasaki\\_akira@soken.ac.jp](mailto:sasaki_akira@soken.ac.jp))

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#### **Approved by**

Ulf Dieckmann  
Leader, Evolution and Ecology Program

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# The Influence of Cross-immunity on the Coexistence, Invasion and Evolution of Pathogen Strains

Ben Adams\* and Akira Sasaki\*#

\* Department of Biology  
Kyushu University  
Fukuoka 812-8581  
Japan

# Evolution and Ecology Program, International Institute for Applied Systems Analysis,  
Laxenburg, Austria

## Abstract

Several epidemic models with many co-circulating strains have shown that partial cross-immunity between otherwise identical strains of a pathogen can lead to three solutions: stable coexistence of all strains, stable coexistence of a subset of strains, coexistence of some or all strains in complex cycles. Here we step back to a three strain model to examine the mechanisms behind some of these solutions. Using a one-dimensional antigenic space, we consider a host population in which two strains are endemic and ask when it can be invaded by a third strain. If the function relating antigenic distance to cross-immunity is linear or a square-root this is always possible. If the function is parabolic it depends on the degree of antigenic similarity between strains and the basic reproductive number. We show that the differences between functional forms occur because their shape determines the importance of secondary infection. The basic reproductive number affects the importance of tertiary infection. These results suggest that pathogens for which the relationship between antigenic distance and cross-immunity has a square-root form will exist as a cloud of strains without significant antigenic structuring. Conversely, pathogens for which the relationship is parabolic will exist in populations with strong antigenic structuring and the number of strains limited by the basic reproductive number. Furthermore, numerical simulation shows that the maximum sustainable number of strains in such populations requires significant instantaneous changes in antigenic structure and cannot be achieved by a sequence of small point mutations alone.

**Keywords:** antigenic structure, mathematical model, pairwise invasibility

## 1 Introduction

In a host-pathogen system the host may be considered as a resource exploited by the pathogen. As more of the host population is infected, recovers and develops immunity the quality of the resource is degraded. Multiple strains of a pathogen with different antigenic structures may therefore indirectly compete when partial cross-immunity derived from antibodies to one strain make infection more difficult for another strain (Janeway and Janeway 1999; Alberts 2002). An evolutionary process will occur if the antigenic structure of a variant strain is such that it can invade the host population and out compete an existing strain. Several previous epidemic models have taken a 'top-down' approach and represented many co-circulating pathogen strains to show that, under certain conditions, a subset of these strains may be lost due to competitive exclusion. Here we take a 'bottom-up' approach and use a three strain model to examine when a mutant strain can invade a host population in which two strains are already at endemic equilibrium, thus leading to conditions restricting the number of coexisting strains. In addition to elucidating the mechanisms behind the behavior of some of the many strain models, this approach indicates the evolutionary trajectory a pathogen might be expected to take and reveals that small point mutations will not necessarily lead to the maximum number of strains that can, theoretically, be supported.

The theory of pathogen evolution has been studied for many years using various SIR type epidemiological models (Anderson and May 1982; Ewald 1994; Dieckmann 2002). Most of these models consider two pathogen strains circulating in the same host population and examine conditions for coexistence or competitive exclusion. The fundamental concept is the basic reproductive number  $R_0$ , defined as the number of new infections arising from a single infected individual introduced to a naive population (Anderson and May 1991). In many models a strain with a higher basic reproductive number is always competitively dominant and drives the other strain to extinction indicating that evolution will maximize  $R_0$ . However, additional conditions such as superinfection (Nowak and May 1994), coinfection (May and Nowak 1995), density-dependent host mortality (Andreasen and Pugliese 1995) and host spatial structure (Haraguchi and Sasaki 2000) may allow two strains with different  $R_0$  values to coexist or show bistability (Kawaguchi, Sasaki et al. 2003; Boots, Hudson et al. 2004) and evolution may not maximize  $R_0$  (Boots and Sasaki 1999; Dieckmann 2002).

The two-strain paradigm has proved particularly useful for studying the evolution of parasite virulence, generally expressed through parameters for transmission and disease induced mortality (Nowak and May 1994; Frank 1996; Boots and Sasaki 1999; Day 2001; Pugliese 2002). It has been less extensively applied to study the evolution of antigenic structure. Partial cross-immunity may allow strains with different basic reproductive numbers to coexist (Castillo-Chavez, Hethcote et al. 1989). However, if the two strains are assigned identical basic reproductive numbers in order to concentrate solely on the impact of partial cross-immunity, strain replacement never occurs as stable coexistence is always possible. Therefore, a number of recent studies have employed models with four or more strains. Due to the rapid increase in complexity as more strains are added to an SIR model the majority of this work has necessarily been numerical and particularly concerned with the emergence of antigenically differentiated clusters of

strains. Three broad patterns have been identified in several different models. All strains may coexist at a stable, symmetric equilibrium. A subset of strains may coexist at a stable equilibrium, excluding the remaining strains. There may be no stable equilibrium but all strains coexist in cyclic or chaotic solutions. Which of these patterns arises has been shown to depend on  $R_0$  and the strength of cross-immunity. Stable coexistence at low values of these parameters is usually seen to switch to cyclic solutions then stable coexistence as they are increased (Andreasen, Lin et al. 1997; Gupta, Ferguson et al. 1998; Ferguson and Andreasen 2002; Calvez, Korobeinikov et al. 2005). The pattern may also depend on the way in which cross-immunity is related to antigenic distance. In a model with a fixed number of non-mutating strains, highly localized interaction (strains within a given distance show strong cross-immunity but this weakens rapidly beyond that distance) has been associated with solutions in which all strains coexist in complex cycles or only a subset of strains persist in a homogeneous steady state. Weakly localized interaction has been associated with all strains coexisting in a homogeneous steady state (Gomes, Medley et al. 2002). Additionally, in a model with mutating strains, stable clusters (discrete persistent groups of closely related strains) have been associated with a long infectious period while cyclic clusters (groups of closely related strains that periodically replace one another) have been associated with a short infectious period (Gog and Grenfell 2002).

All of these models indicate that, under certain conditions structure can emerge as strains occupy niches in antigenic space. However, with one exception (Gog and Grenfell 2002), they tend to focus on the dynamics of systems with many pathogen strains present from the outset and so do not consider the mechanisms behind the structures or how they may be built up. Here we take a step back from the oscillations and clustering of many strain models. Instead this paper examines how partial cross-immunity influences the emergent strain structure when only two strains are at endemic equilibrium and a third strain attempts to invade. Using a simplified one-dimensional construct for antigenic space the antigenic location, or similarity, of the two existing strains can be described with a one parameter. The location of the third strain is described by a second parameter. This allows pairwise invasibility analysis, with one half of the pair in fact composed of the two endemic strains. Within this framework the way in which different forms for the function relating antigenic distance to cross-immunity influence the invasibility of the third strain is considered. It is shown that invasion is always possible for certain forms of the cross-immunity function, but for other forms depends on the antigenic locations of the strains and the basic reproductive number. This is explained by the way in which the number of secondary and tertiary infections respond to changes in the parameter values. Based on these results, and with reference to the requirements for clustering observed previously (Gomes, Medley et al. 2002), the evolution and antigenic structuring of pathogen strains is discussed.

## **1 Model Description**

### **1.1. SIR Framework**

The SIR model, which groups the host population according to immune status (susceptible, infected, recovered/removed), is very well established in the study of host-pathogen dynamics. When multiple pathogen strains co-circulate the number of possible

immune states with regard to each strain rises dramatically. This makes for rather complex models and so a variety of formulations and simplifications have been used in recent years (Gupta, Maiden et al. 1996; Gupta, Ferguson et al. 1998; Gog and Grenfell 2002; Kawaguchi, Sasaki et al. 2003; Andreasen and Sasaki 2006). Here a formulation first used to study influenza (Andreasen, Lin et al. 1997) and subsequently used in a number of other studies (Ferguson and Andreasen 2002; Gomes, Medley et al. 2002; Abu-Raddad and Ferguson 2005) is used with some small changes in notation. A complete description of this model can be found elsewhere (Ferguson and Andreasen 2002) but a brief review is given here for completeness.

If  $n$  pathogen strains are co-circulating then the host population can be divided into  $2^n$  compartments each of which records the number of hosts currently or previously infected with one of the  $2^n$  possible subsets of strains. The original formulation (Andreasen, Lin et al. 1997) uses a generalized set notation to label these compartments but, since this study will only consider a small number of strains, here the strain sets will be written explicitly. For two strains there are four compartments: never infected ( $S_\emptyset$ ), previously/currently infected with strain 1 only ( $S_{\{1\}}$ ), previously/currently infected with strain 2 only ( $S_{\{2\}}$ ) and previously/currently infected with both strains ( $S_{\{12\}}$ ). The host population is assumed to be homogeneous and well mixed. The forces of infection  $\Lambda_1$  and  $\Lambda_2$  are based on the number of hosts currently infectious modified by a transmission rate parameter  $\beta$ . The rate of new infections is proportional to the force of infection and the size of the susceptible host population. The infection rate may be reduced by cross-immunity due to antibodies from a previous infection. Cross-immunity is assumed to reduce susceptibility. Several previous studies have shown that if cross-immunity is configured to reduce transmissibility model behavior is generally similar. The main aim of this study is to investigate how cross-immunity influences the emergence of strain structure in antigenic space. Therefore the antigenic distance between strains 1 and 2 is specified by the parameter  $\alpha_{12}$  and the cross-immunity associated with this degree of similarity is given by the function  $f(\alpha_{12})$ . This is discussed in more detail in sections 2.2 and 2.3. Hosts recover from infection at a constant rate  $\gamma$ . Natural deaths occur in each compartment at rate  $\mu S$  where  $1/\mu$  is the average life expectancy and  $S$  is the size of the compartment. New births have no previous immunity and are added to the  $S_\emptyset$  compartment at rate  $\mu N$  where  $N$  is the total population size. This means that the total population size  $N = S_\emptyset + S_{\{1\}} + S_{\{2\}} + S_{\{12\}}$  is constant. All epidemiological parameters are identical for both strains, only the antigenic structure may be different.

Assuming that all rates are expressed with respect to time  $T$ , the model can be made non-dimensional by the substitutions (Andreasen, Lin et al. 1997)  $t = (\gamma + \mu)T$ ,  $x = S_\emptyset/N$ ,  $y_i = S_{\{i\}}/N$ ,  $y_{12} = S_{\{12\}}/N$ ,  $\lambda_i = \Lambda_i/(\gamma + \mu)$  and letting  $r = \beta N/(\gamma + \mu)$  and  $e = \mu/(\gamma + \mu)$ . Then  $r$  is the basic reproductive number and  $e$  is the ratio of the duration of infection to life expectancy. This is 1 for a permanent infection and small for brief infections. Since each compartment has only been scaled by  $N$  their definitions remain unchanged. However, it is also useful to think of the equivalent definitions:  $x$  - susceptible to primary infection,  $y_i$  - susceptible to secondary infection with strain  $j \neq i$ ,  $y_{12}$  susceptible to tertiary infection. The total population size is now 1. The forces of infection are  $\lambda_1$  and  $\lambda_2$ . The system is described by six differential equations:

$$\begin{aligned}
\dot{x} &= e(1-x) - (\lambda_1 + \lambda_2)x \\
\dot{y}_1 &= \lambda_1 x - (f(\alpha_{12})\lambda_2 + e)y_1 \\
\dot{y}_2 &= \lambda_2 x - (f(\alpha_{12})\lambda_1 + e)y_2 \\
\dot{y}_{12} &= f(\alpha_{12})(\lambda_1 y_2 + \lambda_2 y_1) - e y_{12} \\
\dot{\lambda}_1 &= \lambda_1 [r(x + f(\alpha_{12})y_2) - 1] \\
\dot{\lambda}_2 &= \lambda_2 [r(x + f(\alpha_{12})y_1) - 1]
\end{aligned} \tag{1}$$

All derivatives are with respect to the rescaled time  $t$ .

## 1.2. Antigenic Space

The antigen of a pathogen is formed by a collection of genetically determined proteins. So genetic mutation and recombination can lead to changes in the antigenic structure. As these changes accumulate the antigen of the novel strain becomes less likely to be recognized by antibodies created in response to the original strain. So the antigenic space can be thought of as a range of antigenic structures that is determined by, and potentially constrained by, the possible genetic configurations of the pathogen. Two main approaches have been used to abstract this into a model. Ostensibly the most realistic is the locus-allele system (Gupta, Maiden et al. 1996; Gupta, Ferguson et al. 1998). A strain is represented by a sequence of  $n$  loci, each with  $m$  alleles. The number of locations at which their sequences are identical then determines the relatedness of strains. This formulation is ideal for individual-based simulation models (Sasaki and Haraguchi 2000; Girvan, Callaway et al. 2002; Ferguson, Galvani et al. 2003; Tria, Lässig et al. 2005) when a large number of loci can be employed. However, using a small number of loci may compromise the model by introducing significant discreteness. An alternative approach is to impose a simplified one-dimensional antigenic space as shown in Figure 1 (Sasaki 1994; Andreasen, Lin et al. 1997; Haraguchi and Sasaki 1997; Gog and Grenfell 2002; Gomes, Medley et al. 2002). Strains closer together in this space are considered to have more antigen proteins in common than those that are far apart. Implicit to this is the significant assumption that antigenic variation is one-dimensionally continuous which means there is no one-to-one map between the one-dimensional space and the locus-allele defined space. This is a severe simplification but may not be any less compromising than the discreteness inherent in a low dimensional locus-allele system. The analysis presented in this paper is based on a one-dimensional space. Future work will extend this to a locus-allele defined space.

To construct the antigenic space let  $0 \leq \alpha \leq 2$  describe position and identify the endpoints  $\alpha = 0$  and  $\alpha = 2$ . This effectively imposes a periodic boundary condition and makes the antigenic space circular (Figure 1). The distance between strains may thus be measured in either the clockwise or anticlockwise direction. If strains are located at  $\alpha_1$  and  $\alpha_2$  then the distance between them is either  $|\alpha_1 - \alpha_2|$  or  $2 - |\alpha_1 - \alpha_2|$ . Define two strains to be antigenically identical if the distance between them is 0 and entirely distinct if the distance between them is greater than or equal to 1. Then take the effective antigenic distance to be  $\alpha^{\text{eff}} = \min\{|\alpha_1 - \alpha_2|, 2 - |\alpha_1 - \alpha_2|\}$ . This is always less than or equal to 1.

Without loss of generality place strain S1 at  $\alpha = 0$  and measure the antigenic distance in the clockwise direction. Let strain S2 have antigenic location  $\alpha = \alpha_{12}$ . Then the distance between S1 and S2 is  $\alpha_{12}$  but the effective distance is  $\min\{\alpha_{12}, 2 - \alpha_{12}\}$ . Note that the periodic boundary means that two strains equidistant from  $\alpha = 0$  need not be identical and may, in fact, be entirely distinct. So if strain S2 is located at  $\alpha = 1$  subsequent mutations will result in a strain more similar to strain S1, but by two possible routes.

### 1.3. Antigenic Distance and Strength Of Cross-immunity

The antigenic distance is a measure of the similarity between antigens based on the number of common proteins in their construction. However, these proteins interact in a complex way to modify the binding sites recognized by antibodies and the antigenic distance between two strains may not be directly proportional to the degree of partial cross-immunity. Therefore a variety of functions have been previously employed to model this relationship. In locus-allele systems the most basic approach assumes polar immunity whereby two strains share cross-immunity if they have one or more common alleles and no cross-reaction otherwise (Gupta, Maiden et al. 1996; Gupta, Ferguson et al. 1998; Ferguson and Andreasen 2002). This has also been extended so that the degree of cross-reaction depends on the number of shared alleles (Girvan, Callaway et al. 2002; Ferguson, Galvani et al. 2003). In one-dimensional systems the most basic approach assumes that antigenic distance and cross-immunity are directly proportional so the function relating them is linear but this has been generalized to various non-linear forms (Haraguchi and Sasaki 2000; Gog and Grenfell 2002; Gomes, Medley et al. 2002).

Here three forms will be considered for the cross-immunity function: linear  $f(\alpha) = \alpha^{\text{eff}}$ , parabolic  $f(\alpha) = (\alpha^{\text{eff}})^2$  and square-root  $f(\alpha) = \sqrt{\alpha^{\text{eff}}}$  where  $\alpha^{\text{eff}} = \min\{\alpha, 2 - \alpha\}$ . As shown in Figure 2, in all three cases  $0 \leq f(\alpha) \leq 1$ ,  $f(\alpha)$  is increasing for  $0 \leq \alpha \leq 1$  and symmetric about  $\alpha = 1$ . Furthermore,  $f(0) = f(2) = 0$ , corresponding to identical strains with perfect cross-immunity, and  $f(1) = 1$  corresponding to distinct strains with no cross-immunity. The linear function means that cross-immunity is directly proportional to antigenic distance. The parabolic function means that the rate of change of cross-immunity with antigenic distance is less than linear up to a distance of 0.5, then greater than linear. So, proportionally, short antigenic distances have a much smaller impact on cross-immunity than long distances. The square-root function means that the rate of change of cross-immunity with antigenic distance is greater than linear up to a distance of 0.25, then less than linear. So, proportionally, short antigenic distances have a much greater impact on cross-immunity than long distances.

When three strains are present it is also necessary to define the immune status of hosts who have experienced two previous infections and so are susceptible to tertiary infection. For a host that has previously been infected with strains S1 and S2 and is challenged by strain S3 the tertiary immunity will be written as  $f(\alpha_{12}, \alpha_{13})$ . Very little empirical information relating to this is available and most previous models use either a minimum or a multiplicative method. The minimum method  $f(\alpha_{12}, \alpha_{13}) = \min\{f(\alpha_{12}), f(\alpha_{13})\}$  assumes that only antibodies to the most similar previous infection are produced. The multiplicative method  $f(\alpha_{12}, \alpha_{13}) = f(\alpha_{12})f(\alpha_{13})$  assumes that antibodies to both previous infections are produced and their net benefit is greater than either one of them alone.

Other possibilities include assuming that a maximum of two infections can be experienced so tertiary immunity is always perfect (Cummings, Schwartz et al. 2005) or assuming that the antibodies from both previous infections interfere with one another and using a weighted averaging system to calculate a net benefit weaker than either one of them alone. The minimum function is the most extensively used in previous models. In the absence of any strong evidence for an alternative function, it will be used throughout this paper. Additional work not detailed here shows that results are similar if a multiplicative function is used instead.

## 2 Two Strain Coexistence Equilibrium

Since strain S1 is always located at  $\alpha = 0$  the antigenic distribution of two strains, S1 and S2, can be specified by a single parameter  $\alpha_{12}$  corresponding to both the location of S2 and the clockwise distance between S1 and S2. Recall that the effective distance between strains 1 and 2 is  $\min\{\alpha_{12}, 2 - \alpha_{12}\}$ . If  $r > 1$  there is a unique symmetric coexistence equilibrium to equations (1) with  $y_1 = y_2 = y$  and  $\lambda_1 = \lambda_2 = \lambda$  (Andreasen, Lin et al. 1997) given by:

$$\begin{aligned} x^* &= \frac{2f(\alpha_{12})}{(2r+1)f(\alpha_{12}) - 2 + \Omega} \\ y^* &= \frac{(2r-1)f(\alpha_{12}) - 2 + \Omega}{2rf(\alpha_{12})((2r-1)f(\alpha_{12}) + \Omega)} \\ y_{12}^* &= \frac{((2r-1)f(\alpha_{12}) - 2 + \Omega)^2}{4rf(\alpha_{12})((2r-1)f(\alpha_{12}) + \Omega)} \\ \lambda^* &= \frac{e((2r-1)f(\alpha_{12}) - 2 + \Omega)}{4f(\alpha_{12})} \end{aligned} \tag{2}$$

where

$$\Omega = \sqrt{4 - 4f(\alpha_{12}) + f(\alpha_{12})^2(1 - 2r)^2}$$

Extensive numerical investigation indicates that this is always stable for the forms of  $f$  considered in this paper. The general coexistence equilibrium for  $n$  strains can be found using a elegant recursive formula (Ferguson and Andreasen 2002). However, for  $n > 2$  we have been unable to find a closed form for the coexistence equilibrium and numerical investigation indicates that it is not always stable and solutions are oscillatory. Hereafter, to simplify notation the \* will be dropped and  $x, y, y_{12}, \lambda$  will always refer to the two strain coexistence equilibrium.

## 3 General Invasion Criterion

Given a host population in which two strains S1 and S2 with antigenic distribution  $\alpha_{12}$  are at the coexistence equilibrium a third strain S3 with antigenic location  $\alpha_{13}$  (measured clockwise from 0) can invade if the rate of change of the force of infection  $\lambda_3$  is greater than 0 when the number of strain 3 infections is arbitrarily small. Without writing out the complete three strain system, it is easy to see that the potential hosts for S3 are  $x, y_1 = y, y_2 = y$  and  $y_{12}$ . The immune cross-reactions with S3 are  $x \sim 1, y_1 \sim f(\alpha_{13}), y_2 \sim f(\alpha_{23})$  and

$y_{12} \sim f(\alpha_{13}, \alpha_{23})$ . Hence:

$$\dot{\lambda}_3 = \lambda_3[r(x + f(\alpha_{13})y_1 + f(\alpha_{23})y_2 + f(\alpha_{13}, \alpha_{23})y_{12}) - 1] \quad (3)$$

So invasion is possible if:

$$r(x + f(\alpha_{13})y_1 + f(\alpha_{23})y_2 + f(\alpha_{13}, \alpha_{23})y_{12}) > 1 \quad (4)$$

However,  $y_1 = y_2 = y$  and the total population size is constant. So  $x + 2y + y_{12} = 1$ ,  $y_{12}$  can be eliminated, and the invasion criterion becomes:

$$\zeta = r[(1 - f(\alpha_{13}, \alpha_{23}))x + (f(\alpha_{13}) + f(\alpha_{23}) - 2f(\alpha_{13}, \alpha_{23}))y + f(\alpha_{13}, \alpha_{23})] > 1 \quad (5)$$

#### 4 How Does Invasibility Depend on Antigenic Location and the Cross-immunity Function?

The antigenic distributions that allow invasion can be examined by using the invasion criterion given in equation (5) to conduct a pairwise invasibility analysis in which one half of the ‘pair’, represented by  $\alpha_{12}$ , is the antigenic distribution of the two existing strains S1 and S2, and the other half, represented by  $\alpha_{13}$ , is the antigenic location of the invading strain S3. There are three cases to consider corresponding to the distribution of strains in the two semicircles (arcs of length 1) that constitute the antigenic space. Here we describe each case and give the main results corresponding to linear, parabolic and square-root cross-immunity functions. A more detailed analysis is given in the Appendix.

**Case i:** S1, S2 and S3 are on the same semicircle, S3 is between S1 and S2. Furthermore, S3 is assumed to be closer to S1 than S2 in order to evaluate the minimum function for tertiary cross-immunity  $f(\alpha_{13}, \alpha_{23}) = f(\alpha_{13})$ . Clearly the converse assumption will lead to a symmetric result. So the region considered is  $0 \leq \alpha_{13} \leq \alpha_{12}/2 \leq \alpha_{12} \leq 1$ . In this case, when the cross-immunity function is linear or a square-root, a third strain can always invade an equilibrium population of two existing strains regardless of the distribution of strains in antigenic space  $\alpha_{12}$  and  $\alpha_{13}$ . When the cross-immunity function is parabolic the third strain cannot invade if:

$$0 \leq \alpha_{13} \leq \alpha_{12} \frac{2y}{1-x} \quad \text{or} \quad \alpha_{12} \frac{(1-x-2y)}{1-x} \leq \alpha_{13} \leq \alpha_{12} \quad (6)$$

These thresholds are functions of  $\alpha_{12}$  and, embedded in the equilibrium solutions  $x$  and  $y$ ,  $r$ . It follows that if  $2\alpha_{12} y/(1-x) \geq \alpha_{12}(1-x-2y)/(1-x)$  invasion is not possible at any point between two existing strains. This condition simplifies to  $y \geq 1-x$  and, substituting the explicit equilibrium solutions for  $x$  and  $y$ , invasion is not possible at any point if:

$$\alpha_{12} \leq \frac{2\sqrt{r-1}}{\sqrt{3r^2 - 5r + 2}} \quad (7)$$

Figure 3a shows how this limiting similarity threshold depends on  $r$  and  $\alpha_{12}$ . For  $r < 2$  invasion is not possible at any point between two existing strains on the same semicircle. As  $r$  increases the critical value of  $\alpha_{12}$  decreases asymptotically to 0 indicating that existing strains must be closer together to prevent invasion between them.

**Case ii:** S1, S2 and S3 are on the same semicircle, S3 is not between S1 and S2. Furthermore S3 is assumed to be closer to S2 than S1 with an equivalent result for the converse assumption following by symmetry. So the region considered is  $0 \leq \alpha_{12} \leq \alpha_{13} \leq 1$ . For all three cross-immunity function considered, invasion is possible for all admissible values of  $\alpha_{12}$  and  $\alpha_{13}$  if  $r > 1$ .

**Case iii:** S1 and S2 are on the opposite semicircle to S3 and S3 is closer to S1 than S2 with an equivalent result for the converse assumption following by symmetry. There are two formally equivalent ways to express this. If we assume that S1 and S2 are both on the first half circle clockwise then  $0 < \alpha_{12} \leq 1$  and  $1 + \alpha_{12}/2 \leq \alpha_{13} \leq 1 + \alpha_{12}$ . Alternatively, if we assume that S1 and S2 are both on the second half circle clockwise then  $1 < \alpha_{12} \leq 2$  and  $\alpha_{12} - 1 \leq \alpha_{13} \leq \alpha_{12}/2$ . For linear or square-root cross-immunity functions invasion is always possible. For the parabolic cross-immunity function strain 3 cannot invade if  $0 < \alpha_{12} \leq 1$  and  $2 - \alpha_{13}$  is in the regions bounded by:

$$\frac{1}{1-x}((2-\alpha_{12})y \pm \Gamma) \quad \text{or} \quad \frac{1}{1-x}((2-\alpha_{12})(1-x-y) \pm \Gamma) \quad (8)$$

where

$$\Gamma = \sqrt{(2-\alpha_{12})^2 y^2 - 4(1-x)(1-\alpha_{12})y}$$

For the alternative constraint when  $1 < \alpha_{12} \leq 2$ , the bounds are similar but  $1 - \alpha_{13}$  is replaced by  $\alpha_{13}$  and  $2 - \alpha_{12}$  is replaced by  $\alpha_{12}$ . As  $r$  and  $\alpha_{12}$  are varied these intervals contract. The center-point also moves. Numerical investigation indicates that for  $\alpha_{12} < 1$  these intervals do not span the entire admissible region. Even though they may overlap in the middle invasion is possible at the edges. The center-points do, however, appear to remain within the admissible region until after the span of the interval has contracted to 0. Therefore, invasion is possible at all points on the opposite semicircle when the span of the interval is 0. The value of  $\alpha_{12}$  at which this occurs can be found by solving:

$$y^2(2-\alpha_{12})^2 - 4y(1-x)(1-\alpha_{12}) = 0 \quad (9)$$

This threshold is plotted as a function of  $\alpha_{12}$  and  $r$  in Figure 3b. Even for small  $r$  invasion is possible at all points on the opposite interval unless the two existing strains span almost an entire semicircle, that is  $\alpha_{12}$  is very close to 1.

## 5 Evolution and Strain Structure

The invasion analysis in section 5 shows that, if cross-immunity is related to antigenic distance by a linear or square-root function, then invasion is possible for all antigenic distributions  $\alpha_{12}$ ,  $\alpha_{13}$  and  $r > 1$ . Evaluation of the invasion criterion for a fourth strain when three strains are at endemic equilibrium is complicated by the lack of a closed form for the equilibrium solution but numerical calculations indicate invasion is always possible. For four or more existing strains the coexistence equilibrium may be unstable and so the system shows complex oscillations (Ferguson and Andraesen 2002). This means that an additional strain is effectively attempting to invade in a fluctuating environment. Evaluating this (Tuljapurkar 1990) is beyond the scope of this paper. However, a six strain extension of the model described in section 2 (requiring 70 differential equations) was solved numerically for a range of  $r$  values between 1 and 15 and many random antigenic distributions of strains. In all cases, there was coexistence of all six strains. This suggests, although does not prove, that linear and square-root cross-immunity functions lead to little or no selection pressure due to cross-immunity and pathogen populations will be composed of clouds of strains without strong antigenic structuring.

If cross-immunity is related to antigenic distance by a parabolic function then invasion is not always possible. This can be visualized by constructing pairwise invisibility plots (Dieckmann 2002), as shown for different values of the basic reproductive number  $r$  in Figure 4. When  $r = 1.1$  the point, or distribution,  $\alpha_{12} = 1$  has evolutionary and convergence stability. If two strains are initially close together then mutations leading to a strain between the existing strains will be unable to invade (case i). Mutations leading to a strain not between the existing strain will be able to invade (case ii). Since this will result in the original strain from which the mutant arose being between two strains, the original strain will become extinct (case i). This process will continue, and two strains will become further apart (or more antigenically distinct) until  $\alpha_{12} = 1$ , which is stable because no further mutations are able to invade on either semicircle (case i).

From equation (7) exactly the same reasoning applies for all  $r < 2$ . For larger values of  $r$  the situation is slightly different because, when the two existing strains are sufficiently far apart, a third strain can invade in a region centered on the midpoint between them as shown for  $r = 3$  in Figure 4. However this region is separated from the location of the existing strains by a buffer zone in which invasion remains impossible. Therefore,  $\alpha_{12} = 1$  retains evolutionary and convergence stability as long as the antigenic shift due to each mutation is small but a large shift, most likely the results of recombination or introduction from an external population, can result in three coexisting strains. As  $r$  increases the buffer zone around the existing strains becomes narrower and so the antigenic shift required to escape convergence to  $\alpha_{12} = 1$  becomes smaller. Due to the problems described previously regarding oscillating coexistence solutions, the model is insufficient to predict the subsequent evolution if three strains become established.

However, numerical solutions to the six strain model offer some insight. The evolutionary trajectory predicted by the previous analysis was simulated using a six strain model in which a strain with antigenic location  $\alpha$  produces a mutant strain at antigenic

location  $\alpha \pm \delta_\alpha$  ( $\delta_\alpha = 1/50$ ) with probability  $q$  and any strain with a force of infection less than  $\lambda_E = 10^{-20}$  is considered to be extinct. Since it was only possible to model the dynamics of six strains, the mutation rate had to be set extremely low ( $q = 5 \times 10^{-6}$  per year) in order to ensure that extinction and mutation occurred at approximately the same rate and so the number of strains did not exceed the capacity of the model. We hope to address this problem in the future by using an individual-based approach. Nevertheless, the dynamics should remain qualitatively correct. Many simulations were carried out for each of a range of values of  $r$  between 1.1 and 15. Starting from a single initial strain, as soon as mutation produced two strains, the antigenic distance between them diverged until it reached 1, after which there were no further changes in antigenic location (Figure 5a). Continued persistence of more than two strains was never observed. In a second experiment  $r$  was set sufficiently large to allow invasion at some point between two existing strains on the same semicircle and three strains were initially present. Two were initially set sufficiently far apart to create a region between them where invasion was possible and the third strain was placed at a random point in this region. Then the two most distant strains continued to diverge while the third strain evolved towards the midpoint between them until all three strains were equally distributed (at distance 2/3) around the circle (Figure 5b). At least three strains were always present but continued persistence of a fourth strain was never observed. In a third experiment the model was initialized with a random distribution of six strains and solved, without mutation, to equilibrium. The average number of strains remaining at equilibrium was calculated from 100 initial conditions for each value of  $r$  (Figure 5c). This shows that the number of strains that can coexist increases as the basic reproductive number increases. It also indicates that, at least for low values of  $r$ , the maximum number of possible strains cannot be attained by small shift mutation alone.

Together the analytic and numerical results indicate that parabolic cross-immunity will lead to pathogen populations composed of a small number of strains with strong antigenic structuring and pathogens with lower basic reproductive numbers supporting fewer strains. Furthermore, the theoretical maximum strain diversity may not be achieved by a sequence of small mutations alone and recombination or evolution in an independent host population is required to disrupt convergence to an alternative stable state composed of a sub-maximal number of strains

## 6 Why Do the Form of the Cross-immunity Function and the Value of $r$ Influence Invasibility?

The results of section 5 raise two key questions. Why is invasion possible for any antigenic distribution of strains when cross-immunity is linear or square-root but not when it is parabolic? Furthermore, when cross-immunity is parabolic, why does invasibility depend on the basic reproductive number  $r$ ? The most significant differences arise when all strains are on the same semicircle and S3 is between S1 and S2 (case i). So these questions are now addressed by investigating the detailed structure of the invasion criteria for this case. In the original invasion criterion given in equation (4) the contributions of primary ( $x$ ), secondary ( $y$ ) and tertiary ( $y_{12}$ ) infections are easily distinguishable. For linear, parabolic and square-root cross-immunity functions the corresponding invasion criteria (after the substitution  $\alpha_{23} = \alpha_{12} - \alpha_{13}$  as appropriate to case i) are, respectively:

$$\begin{aligned}\zeta_L &= r(x + \alpha_{12}y + \alpha_{13}y_{12}) > 1 \\ \zeta_p &= r(x + (\alpha_{13} + (\alpha_{12} - \alpha_{13})^2)y + \alpha_{13}^2y_{12}) > 1 \\ \zeta_s &= r(x + (\sqrt{\alpha_{13}} + \sqrt{\alpha_{12} - \alpha_{13}})y + \sqrt{\alpha_{13}}y_{12}) > 1\end{aligned}\tag{10}$$

Here  $x$ ,  $y$  and  $y_{12}$  refer to the equilibrium solution evaluated with the appropriate cross-immunity function. Fixing  $\alpha_{12}$  at 0.8 in order to reduce the number of active parameters, Figure 6 shows how the contribution of each of these components varies with  $\alpha_{13}$  and  $r$ . The shape of the complete invasion criterion corresponds to the shape of the cross-immunity function. All components of the criterion are symmetric about the midpoint between the existing strains  $\alpha_{13} = 0.4$ . For linear and square-root cross-immunity each side of the total invasion criterion is monotonic increasing as  $\alpha_{13}$  moves from the endpoint at 0 or 0.8 to the midpoint. However, for parabolic cross-immunity the invasion criterion decreases as  $\alpha_{13}$  moves away from the endpoint, reaches a minimum and then increases again. This creates the region in which invasion is impossible.

Considering the individual components, it can be seen in Figure 6 and equation (10) that the  $x$  component never depends on  $\alpha_{13}$ . This is expected since cross-immunity does not affect primary infection. For linear cross-immunity the  $y$  component is also independent of  $\alpha_{13}$ , indicating that the total number of secondary infections with strain S3 does not depend on the antigenic location of strain S3. This occurs because the antigenic distance and cross-immunity are directly proportional. So, as  $\alpha_{13}$  moves away from 0, the increase in S1 followed by S3 secondary infections is exactly balanced by the decrease in S2 followed by S3 secondary infections. For parabolic and square-root cross-immunity equation (10) shows that the contribution of the  $y$  component depends in a relatively complex way on the relationship between  $\alpha_{12}$  and  $\alpha_{13}$ . For parabolic cross-immunity secondary infections decrease as  $\alpha_{13}$  moves away from 0. This is because cross-immunity initially weakens slowly with antigenic distance. Hence the increase in S1 followed by S3 secondary infections is smaller than the decrease in S2 followed by S3 secondary infections. For square-root cross-immunity the converse occurs. Since cross-immunity initially weakens rapidly with antigenic distance, as  $\alpha_{13}$  moves away from 0 the increase in S1 followed by S3 secondary infections is larger than the decrease in S2 followed by S3 secondary

infections. This leads to a net increase in the total number secondary infections. For all three cross-immunity functions the impact of tertiary infections increases monotonically as  $\alpha_{13}$  moves away from 0 since tertiary cross-immunity is based on the nearest strain, in this case S1. The value of the invasion criterion at the exact location of an existing strain must be 1 or the existing strain would not be at equilibrium. Hence the monotonic increase in tertiary infections ensures that, if cross-immunity is linear or square-root, the invasion criterion is greater than 1, and invasion is possible, everywhere except the exact location of an existing strain. For parabolic cross-immunity, at a certain value of  $\alpha_{13}$  the increase in tertiary infections compensates for the decrease in secondary infections to make invasion possible.

The balance between tertiary and secondary infections also explains why the basic reproductive number  $r$  influences invasibility. Table 1 gives the two strain equilibrium solutions for parabolic cross-immunity and different values of  $r$ . It also gives the same solutions when multiplied by  $r$ , the key form in which they appear in the invasion criteria. Although both  $x$  and  $y$  decrease significantly as  $r$  increases, this change is approximately proportional to  $r$  and so the change in  $rx$  and  $ry$  is much smaller. However,  $y_{12}$  increases with  $r$ , leading to an even more rapid increase in  $ry_{12}$ . When the basic reproductive number is higher the pathogen spreads more easily and so less of the population has never been infected or infected with only one strain, more of the population has been infected with both strains. If cross-immunity is linear or square-root this large increase in the tertiary susceptible population is reflected in large increase in the invasion criterion indicating that invasion becomes much easier. If cross-immunity is parabolic it means that tertiary infections compensate for the decrease in secondary infections at a lower value of  $\alpha_{13}$ . So, as  $r$  increases, the region of antigenic space in which invasion is possible becomes wider.

## 7 Discussion

This study has considered the coexistence and evolution of several pathogen strains primarily by analyzing when a third strain can invade a host population in which two existing strains are at endemic equilibrium. If the function relating antigenic distance to cross-immunity is linear or square-root then invasion is always possible. If the function is parabolic invasion depends on the antigenic locations of all three strains and the basic reproductive number. Comparing the components of the invasion criteria for each of these functional forms showed that the shape of the function determines the importance of secondary infections. This analysis further indicates that any expression for cross-immunity as a function of antigenic distance that has gradient less than 1 for  $0 \leq \alpha \leq \alpha_T$  and greater than 1 for  $\alpha_T \leq \alpha \leq 1$  where  $0.5 \leq \alpha_T$  will behave in a similar way to the parabolic function and invasion will not always be possible. Conversely, any expression for which the gradient is greater than 1 for  $0 \leq \alpha \leq \alpha_T$  and less than 1 for  $\alpha_T \leq \alpha \leq 1$  where  $\alpha_T \leq 0.5$  will behave in a similar way to the square-root function and invasion will always be possible. This agrees with the numerical results in (Gomes, Medley et al. 2002). They use a more complex expression for cross-immunity  $f(\alpha) = (\sigma/2)[1 - \cos(2\pi(\alpha + p\alpha(\alpha - 0.5)(\alpha - 1)))]$ , with a periodic antigenic space  $0 \leq \alpha \leq 1$  and two strains defined to be as distinct as possible at an antigenic distance of 0.5. The parameter  $\sigma \leq 1$  defines the cross-immunity between the most distinct strains. Unlike the model presented in this paper, this may be less than 1, meaning that strains can never be entirely distinct. This slightly skews their results in comparison to the analysis presented here. However, when  $p > 0$  numerical solutions from a four strain model generally showed homogeneous coexistence of all strains. When  $p < 0$  the solutions showed either coexistence of all strains in complex cycles or competitive exclusion of a subset of strains. The form of this cross-immunity function is shown in Figure 7. When  $p > 0$  the gradient is less than 1 for  $0 \leq \alpha \leq \alpha_T \leq 0.5$ , corresponding to the square-root case. When  $p < 0$  the gradient is greater than 1 for  $0 \leq \alpha \leq \alpha_T$  where  $0.5 \leq \alpha_T$ , corresponding to the parabolic case.

Examining the components of the invasion criteria also showed that the contributions of primary and secondary infections are not very sensitive to the value of the basic reproductive number. However the contribution of tertiary infections is sensitive to  $r$  and, in the parabolic case, is the main determinant of the region in which invasion is possible between two existing strains. Given the importance of tertiary infections here, a key goal for future work must be to develop more accurate functions for determining the immune response of a host that has previously been infected with two, or more, strains.

In terms of pathogen evolution, the results of this study indicate that a parabolic type relationship between antigenic distance and cross-immunity will result in pathogen populations with strong antigenic structuring and pathogens with lower basic reproductive numbers will exist as fewer strains. For a linear or square-root type relationship it was shown that at least six strains can coexist and it seems likely that this will extend to any number of strains. Hence this will result in pathogen populations composed of a cloud of strains without significant antigenic structuring. If the host population is thought of as a resource for the pathogen then the various host immune

states when multiple strains are co-circulating constitute niches. The function relating antigenic distance to cross-immunity can be thought of as a resource exploitation kernel. So the analysis presented here resembles that of species packing in ecology (May and MacArthur 1972). That study showed that, in a deterministic model with species equally distributed along a linear resource axis, an infinite number of species can coexist if the resource exploitation kernel is linear. The corresponding result in our model is that a linear or square-root exploitation kernel allows a large, possibly infinite, number of strains to coexist. So niches can be very, possibly infinitesimally, narrow. A parabolic exploitation kernel only allows a small number of strains to coexist. So niches must be relatively broad and, effectively, have a minimum width. However, the evolutionary analysis presented here has also shown that, even when there are a limited number of niches, evolution by a sequence of small shifts in the preferred resource (antigenic location) may not result in all niches being exploited and maximum diversity can only be realized if there are large instantaneous shifts in the preferred resource most likely resulting from recombination or introduction from a previously independent population.

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## Appendix

### Evaluation of Invasion Criteria

**Case i:** S1, S2 and S3 are on the same semicircle, S3 is between S1 and S2, S3 closer to S1. Hence  $\alpha_{23} = \alpha_{12} - \alpha_{13}$ ,  $f(\alpha_{13}, \alpha_{23}) = f(\alpha_{13})$ ,  $0 \leq \alpha_{13} \leq \alpha_{12}/2 \leq \alpha_{12} \leq 1$ .

#### Linear cross-immunity $f(\alpha) = \alpha$

The invasion criterion given in equation (5) is now:

$$r((1-x-2y)\alpha_{13} + x + \alpha_{12}y) > 1 \quad (11)$$

Here  $x$  and  $y$  are the equilibrium solutions when  $f(\alpha) = \alpha$ . From the  $\lambda$  components of equation (1), at equilibrium  $x + \alpha_{12}y = 1/r$ . Hence the invasion criterion simplifies to:

$$r(1-x-2y)\alpha_{13} > 0 \quad (12)$$

Since  $1-x-2y = y_{12}$  this is always satisfied unless  $\alpha_{13} = 0$ . Hence invasion is always possible except at the exact location of an existing strain.

#### Parabolic cross-immunity $f(\alpha) = \alpha^2$

The invasion criterion is:

$$r((1-x)\alpha_{13}^2 - 2\alpha_{12}\alpha_{13}y + x + \alpha_{12}^2y) > 1 \quad (13)$$

Here  $x$  and  $y$  are the equilibrium solutions when  $f(\alpha) = \alpha^2$ . From the  $\lambda$  components of equation (1), at equilibrium  $x + \alpha_{12}^2y = 1/r$ . Hence this simplifies to:

$$r((1-x)\alpha_{13}^2 - 2\alpha_{12}\alpha_{13}y) > 0 \quad (14)$$

Clearly equation (14) is zero when  $\alpha_{13} = 0$  or  $\alpha_{13} = 2\alpha_{12}y/(1-x)$ . Differentiating equation (14) with respect to  $\alpha_{13}$  shows that  $\alpha_{13} = \alpha_{12}y/(1-x)$  is a unique minimum. Hence the invasion criterion is not satisfied if  $0 \leq \alpha_{13} \leq 2\alpha_{12}y/(1-x)$  or, from the symmetric condition if S3 is closer to S1, if  $\alpha_{12}(1-x-2y)/(1-x) \leq \alpha_{13} \leq \alpha_{12}$ .

#### Square-root cross-immunity $f(\alpha) = \sqrt{\alpha}$

After adding  $\sqrt{\alpha} - \sqrt{\alpha}$  and using  $x + \sqrt{\alpha_{12}}y = 1/r$  the invasion criterion is:

$$r((1-x-y)\sqrt{\alpha_{13}} + (\sqrt{\alpha_{12} - \alpha_{13}} - \sqrt{\alpha_{12}})y) > 0 \quad (15)$$

Numerical investigation indicates that this is satisfied for all values of  $r > 1$ .

**Case ii:** S1, S2 and S3 are on the same semicircle, S3 is not between S1 and S2, S3 closer

to S2. Hence  $\alpha_{23} = \alpha_{13} - \alpha_{12}$ ,  $f(\alpha_{13}, \alpha_{23}) = f(\alpha_{23}) = f(\alpha_{13} - \alpha_{12})$ ,  $0 \leq \alpha_{12} \leq \alpha_{13} \leq 1$ .

**Linear cross-immunity  $f(\alpha) = \alpha$**

The invasion criterion given in equation (5) becomes:

$$r((1-x)(\alpha_{13} - \alpha_{12}) + x + \alpha_{12}y) > 1 \quad (16)$$

Again, using  $x + \alpha_{12}y = 1/r$  this simplifies to:

$$r(1-x)(\alpha_{13} - \alpha_{12}) > 0 \quad (17)$$

Since there are existing infections in the population  $x < 1$ . By assumption,  $\alpha_{12} \leq \alpha_{13}$  so this criterion is always satisfied unless  $\alpha_{12} = \alpha_{13}$ . Hence invasion is always possible except at the exact location of strain 2.

**Parabolic cross-immunity  $f(\alpha) = \alpha^2$**

The invasion criterion is:

$$r((1-x)\alpha_{13}^2 - 2\alpha_{12}\alpha_{13}(1-x-y) + \alpha_{12}^2(1-x-y) + x) > 1 \quad (18)$$

Adding  $\alpha_{12}^2y - \alpha_{12}^2y$  and using  $x + \alpha_{12}^2 = 1/r$  this simplifies slightly to:

$$r((1-x)\alpha_{13}^2 - 2\alpha_{12}\alpha_{13}(1-x-y) + \alpha_{12}^2(1-x-2y)) > 0 \quad (19)$$

Clearly equation (19) is zero when  $\alpha_{13} = \alpha_{12}$  or  $\alpha_{13} = \alpha_{12}(1-x-2y)/(1-x)$ . However, the last of these is not in the admissible range since  $\alpha_{12}(1-x-2y)/(1-x) < \alpha_{12}$ . Hence the sign of equation (19) does not change in the region  $\alpha_{12} \leq \alpha_{13} \leq 1$ . Differentiating equation (19) with respect to  $\alpha_{13}$  shows that  $\alpha_{13} = \alpha_{12}(1-x-y)/(1-x)$  is a unique minimum. Hence invasion is always possible except at the exact location of S2.

**Square-root cross-immunity  $f(\alpha) = \sqrt{\alpha}$**

After adding  $\sqrt{\alpha} - \sqrt{\alpha}$  and using  $x + \sqrt{\alpha_{12}y} = 1/r$  the invasion criterion is:

$$r(\sqrt{\alpha_{13} + \alpha_{12}}(1-x-y) + (\sqrt{\alpha_{13}} - \sqrt{\alpha_{12}})y) > 0 \quad (20)$$

This is always satisfied since  $\alpha_{13} > \alpha_{12}$  by assumption.

**Case iii:** S1 and S2 are on the opposite semicircle to S3, S3 closer to S1. Here this is expressed by the constraints  $0 < \alpha_{12} \leq 1$  and  $1 + \alpha_{12}/2 \leq \alpha_{13} \leq 1 + \alpha_{12}$ . Hence  $\alpha_{23} = \alpha_{13} - \alpha_{12}$  and  $f(\alpha_{13}, \alpha_{23}) = f(\alpha_{13}) = 2 - \alpha_{13}$ .

**Linear cross-immunity  $f(\alpha) = \alpha$**

The invasion criterion given in equation (5) becomes:

$$r((1-x-2y)(2-\alpha_{13})+x+2y-\alpha_{12}y) > 1 \quad (21)$$

Adding  $\alpha_{12}y - \alpha_{12}y$  and using  $x + \alpha_{12}y = 1/r$  this simplifies to:

$$r((1-x-2y)(2-\alpha_{13})+2(1-\alpha_{12})y) > 0 \quad (22)$$

Since  $1-x-2y = y_{12}$  and  $1-\alpha_{12} > 0$  by assumption this is always satisfied. Hence invasion is always possible.

### **Parabolic cross-immunity $f(\alpha) = \alpha^2$**

The invasion criterion is:

$$r((1-x)\alpha_{13}^2 + 2\alpha_{13}(\alpha_{12}-2)y + 4y(1-\alpha_{12}) + x + \alpha_{12}^2y) > 1 \quad (23)$$

Using  $x + \alpha_{12}^2 = 1/r$  this simplifies to:

$$r((1-x)(2-\alpha_{13})^2 + 2(2-\alpha_{13})(\alpha_{12}-2)y + 4y(1-\alpha_{12})) > 0 \quad (24)$$

Equation (24) is zero when

$$2-\alpha_{13} = \frac{1}{1-x} \left[ (2-\alpha_{12})y \pm \sqrt{(2-\alpha_{12})^2 y^2 - 4(1-x)(1-\alpha_{12})y} \right].$$
 Differentiating equation

(24) with respect to  $(2-\alpha_{13})$  shows that  $(2-\alpha_{13}) = (2-\alpha_{12})y/(1-x)$  is a minimum. Hence invasion is impossible if  $2-\alpha_{13}$  is in the region bounded by

$$\frac{1}{1-x} \left[ (2-\alpha_{12})y \pm \sqrt{(2-\alpha_{12})^2 y^2 - 4(1-x)(1-\alpha_{12})y} \right]$$
 or, by symmetry,

$$\frac{1}{1-x} \left[ (2-\alpha_{12})(1-x-y) \pm \sqrt{(2-\alpha_{12})^2 y^2 - 4(1-x)(1-\alpha_{12})y} \right].$$

### **Square-root cross-immunity $f(\alpha) = \sqrt{\alpha}$**

After adding  $\sqrt{\alpha} - \sqrt{\alpha}$  making using  $x + \sqrt{\alpha_{12}y} = 1/r$  the invasion criterion is:

$$r \left( \sqrt{2-\alpha_{13}}(1-x-y) + \left( \sqrt{\alpha_{13}-\alpha_{12}} - \sqrt{\alpha_{12}} \right) y \right) > 0 \quad (25)$$

Numerical investigation indicates that this is satisfied for all values of  $r > 1$ .

## Figures

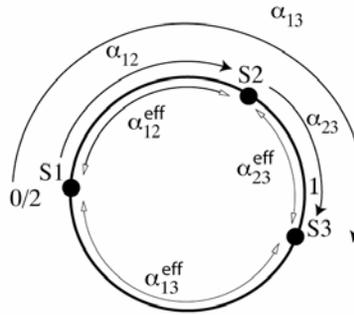


Figure 1: Schematic diagram of a one-dimensional antigenic space with periodic boundary. S1, S2 and S3 indicate the locations of strains 1, 2 and 3.  $\alpha_{ij}$  is the clockwise distance between strains  $i$  and  $j$ .  $\alpha_{ij}^{\text{eff}}$  is the effective distance, defined as the shortest of the clockwise and anticlockwise distances. Note that the two distance are identical for S1 - S2, S2 - S3 but different for S1 - S3.

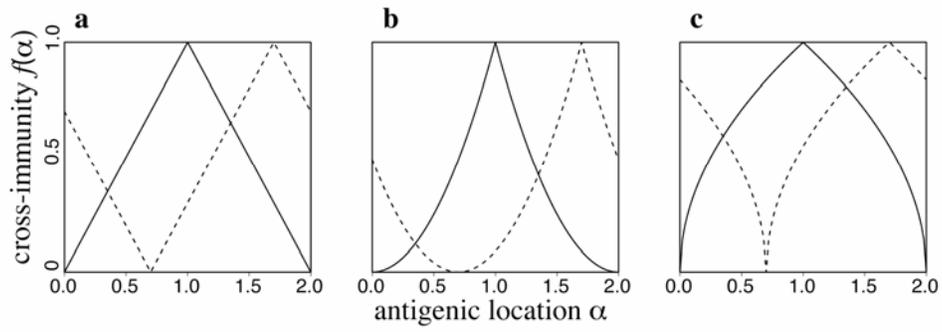


Figure 2: Form of cross-immunity functions  $f(\alpha)$ . All figures show the degree of cross-immunity as a function of antigenic location  $\alpha$  for strain S1 located at  $\alpha = 0$  (solid line) and strain S2 located at  $\alpha = 0.7$  (dashed line). **a**) Linear  $f(\alpha) = \alpha^{\text{eff}}$ . **b**) Parabolic  $f(\alpha) = (\alpha^{\text{eff}})^2$ . **c**) Square-root  $f(\alpha) = \sqrt{\alpha^{\text{eff}}}$ .

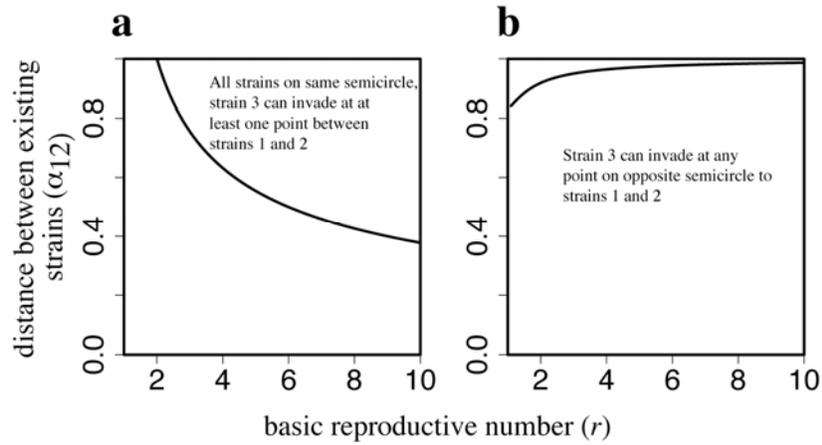


Figure 3: **a**) Limiting similarity threshold condition from equation (7) relating  $r$  to the distance  $\alpha_{12}$  between two existing strains on the same semicircle at which it first becomes possible for strain 3 to invade at some point between them. **b**) Threshold condition from equation (9) relating  $r$  to the distance  $\alpha_{12}$  between two strains on the same semicircle at which it is possible for strain 3 to invade at all points on the opposite semicircle to strains 1 and 2. This figure is based on the constraints  $0 < \alpha_{12} \leq 1$  and  $1 \leq \alpha_{13} \leq 1 + \alpha_{12}/2$ , as discussed in section 5.

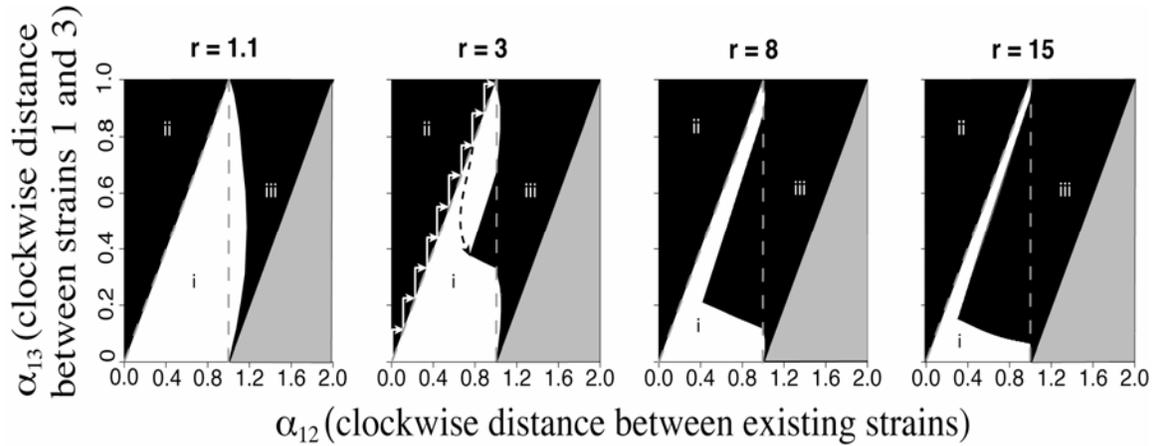
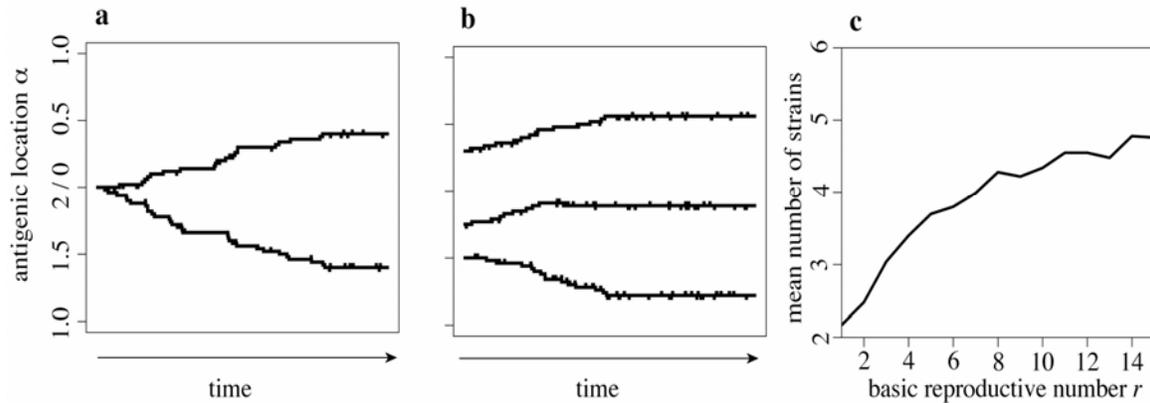


Figure 4: Pairwise invasibility plots for parabolic cross-immunity function. One half of the pair is composed of the two existing strains defined by their antigenic distribution  $\alpha_{12}$  and the other half is composed of the invading strain defined by its antigenic location  $\alpha_{13}$ . White denotes regions in which invasion is impossible (negative invasion criterion). Black denotes regions in which invasion is possible (positive invasion criterion). Grey dashed lines indicate which of the cases discussed in section 5 applies. i – all strains on same semicircle, S3 between S1 and S2 (equation (6)), ii – all strains on same semicircle, S3 not between S1 and S2, iii – S1 and S2 on opposite semicircle to S3 (equation (8)), note that here this has been expressed by the constraints  $1 < \alpha_{12} \leq 2$  and  $\alpha_{12} - 1 \leq \alpha_{13} \leq 1$  and so the grey shaded region corresponds to the inadmissible region  $\alpha_{13} \leq \alpha_{12} - 1$ . In the panel for  $r = 3$ , white arrows indicate the expected evolutionary trajectory resulting from small shifts in antigenic structure, the dashed black line indicates the jump to a three strain system with different evolutionary dynamics that could occur when the two existing strains are far apart ( $\alpha_{12}$  is large) and a large shift in antigenic structure of a mutant strain ( $\alpha_{13}$ ) is possible.



**Figure 5:** Numerical solutions from a six strain extension to the model described in (1). **a)** Evolution of a single strain. A strain at antigenic  $\alpha$  location was allowed to mutate with probability  $5 \times 10^{-6}$  per year to create an additional strain with antigenic location  $\alpha \pm 1/50$ , strains were considered to be extinct if their force of infection was less than  $10^{-20}$ . System was initialized with a single strain at  $\alpha = 0$ . Here  $r = 8$ . **b)** Evolution of three strains. As in (a) but system was initialized with strains at  $\alpha = 0.3$ ,  $\alpha = 1.5$  and  $\alpha = 1.74$ . Here  $r = 8$ . **c)** Average number of strains supported depending on  $r$ . System was initialized with 6 strains randomly distributed in antigenic space and solved, without mutation, to equilibrium. Average number of strains remaining was calculated from 100 initial conditions for each value of  $r$ .

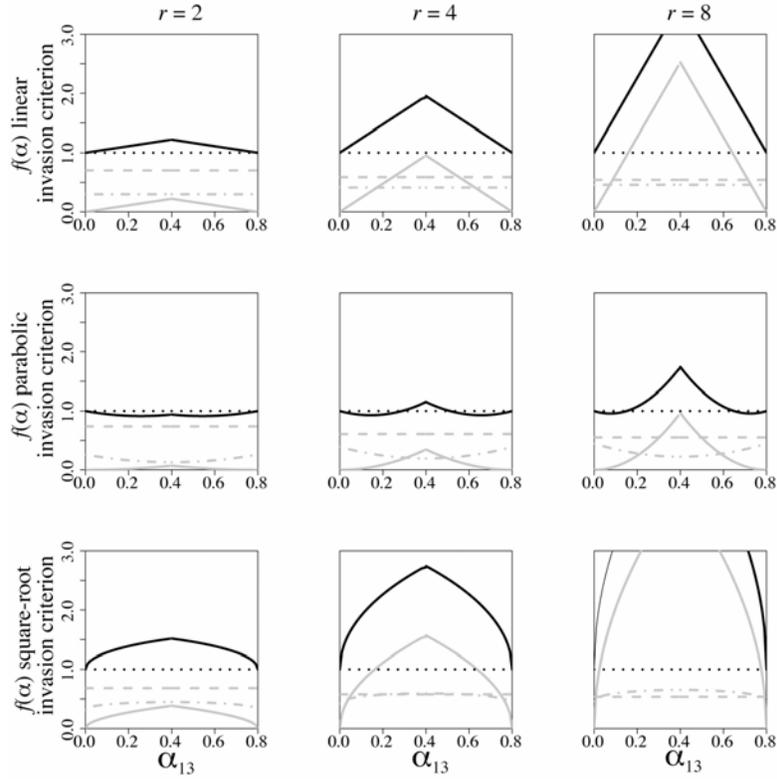


Figure 6: Invasion criteria and their components given by equation (10) when  $\alpha_{12} = 0.8$  and  $0 \leq \alpha_{13} \leq \alpha_{12}$ . Top row corresponds to a linear cross-immunity function, middle row parabolic, bottom row square-root. The solid black line denotes the total invasion criterion. Invasion is possible when this is greater than 1, marked with a dotted black line. Gray lines denote the components of the invasion criterion: dashes -  $x$  (primary) component, dot-dash -  $y$  (secondary) component, solid -  $y_{12}$  (tertiary) component.

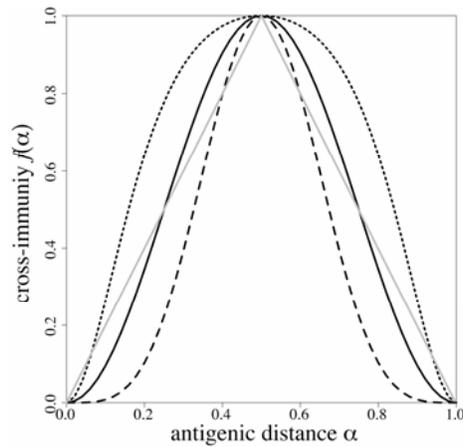


Figure 7: Cross-immunity function used by (Gomes, Medley et al. 2002)  $f(\alpha) = (\sigma/2)[1 - \cos(2\pi(\alpha + p\alpha(\alpha - 0.5)(\alpha - 1)))]$  with  $\sigma = 1$ . Black lines: dotted -  $p = 2$ , solid -  $p = 0$ , dashed -  $p = -2$ . Gray line shows the linear cross-immunity function for comparison. Clearly  $p = -2$  has similar form to the parabolic function used in this paper,  $p = 2$  is similar to the square-root form and  $p = 0$  is transitional. Note that the original antigenic space used by (Gomes, Medley et al. 2002) has been retained - this is based on an interval of length 1 with the endpoints at 0 and 1 identified and two strains considered entirely distinct at an antigenic distance of 0.5

## Tables

$r$	$x$	$rx$	$y$	$ry$	$y_{12}$	$ry_{12}$
2	0.37	0.74	0.20	0.40	0.22	0.44
4	0.15	0.60	0.15	0.60	0.54	2.16
8	0.07	0.56	0.09	0.72	0.76	6.08
16	0.03	0.48	0.05	0.80	0.87	13.92

Table 1: Two strain equilibrium solutions depending on  $r$  when cross-immunity is parabolic and  $\alpha_{12} = 0.8$ .