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On the determinants of population structure in antigenically diverse pathogens

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Many pathogens exhibit antigenic diversity and elicit strain-specific immune responses. This potential for cross-immunity structure in the host resource motivates the development of mathematical models, stressing competition for susceptible hosts in driving pathogen population dynamics and genetics. Here we establish that certain model formulations exhibit characteristics of prototype pattern-forming systems, with pathogen population structure emerging as three possible patterns: (i) incidence is steady and homogeneous; (ii) incidence is steady but heterogeneous; and (iii) incidence shows oscillatory dynamics, with travelling waves in strain-space. Results are robust to strain number, but sensitive to the mechanism of cumulative immunity.

Keywords: infection; multiple strains; cross-immunity; population dynamics; pattern formation

1. INTRODUCTION

Single-strain pathogens (e.g. measles, mumps and rubella (MMR)) are unusual in generating lifelong immunity to reinfection. Mathematical epidemiological models for the dynamics and control of such infectious diseases have been extensively investigated (Anderson & May 1991). More usually multiple antigenic types exist, in which infection evokes an immune response against the infecting variant that may provide differing degrees of cross-immunity against other variants (Gupta *et al.* 1996, 1998; Andreasen *et al.* 1997; Thompson 2000; Cooper 2001; Grenfell & Gog 2001; Gupta & Maiden 2001) (e.g. influenza A and respiratory syncytial viruses, meningococcus and pneumococcus bacteria and malaria parasites) and as a consequence repeated infection arises. Pathogen population dynamics and genetics are driven by competition for the susceptible host resource; transmissibility and immune recognition are the two main phenotypic characteristics of pathogens that determine this competition (May & Anderson 1983; Anderson and May 1991; Gupta *et al.* 1994*b*, 1996, 1998; Andreasen *et al.* 1997; Castillo-Chavez *et al.* 1998; Thompson 2000; Cooper 2001; Grenfell & Gog 2001; Gupta & Maiden 2001). Here we consider transmissibility as a stress parameter (Manneville 1990), which initially we assume is insensitive to antigenic variability, and explore the role of evoked cross-immunity profiles in structuring the pathogen population. We observe that, despite all variants having the same 'fitness', pathogen populations self-organize into three different patterns depending on the magnitude and distribution of immune stresses. First, patterns of prevalence are homogeneous in antigen-space if cross-immunity is weak and second, they are highly clustered if cross-immunity is strong. These patterns are stationary and very robust to alterations in model assumptions. A third pattern is found for intermediate levels of cross-immunity: clusters emerge and cross antigen-space in a travelling-wave fashion. These dynamic patterns are very sensitive to some model assumptions. In particular, important characteristics such as wavelength and wave speed depend critically on how immunity accumulates as a result of sequential infections.

One of the major challenges in modelling the population dynamics of antigenically diverse pathogens is the establishment of a parameter definition method. We initially make two homogeneity assumptions. First, we assume that pathogen transmissibility, as measured by the basic reproduction number, R_0, is the same for all variants (the effects of relaxing this assumption will be demonstrated and discussed at the end). Second, there are no immunologically dominant variants, i.e. the reciprocal cross-immunity profiles are equal (see figure 1). Consequently, the structures that we derive are not predicated upon differences in either innate transmissibility or immunogenicity, or upon differences in host immunocompetence. Patterns of cross-immunity are sufficient to maintain and structure pathogen diversity.

Two-strain models (Gupta *et al.* 1994*a*; McLean 1995; White *et al.* 1998) are well understood and, in theory, can be generalized to accommodate as many strains as required, but with an exponential increase in the number of variables and parameters (Ferguson & Andreasen 2001; Gomes & Medley 2001). Previous multistrain models (Gupta *et al.* 1996, 1998; Andreasen *et al.* 1997) make a variety of simplifying assumptions to overcome these issues, but their inherently discrete implementation of 'strain-space' makes emerging patterns difficult to interpret. We reduce parameter number by incorporating assumptions on the structure of antigen space that are generalizable to a continuum and permit a finer classification of resulting patterns.

2. METHODS

We consider a genetically diverse pathogen population distributed as a continuous variable, i.e. the 'strain-space', which we assume to be of circular configuration. Cross-immunity parameters are defined in this setting (figure 1). This model is then

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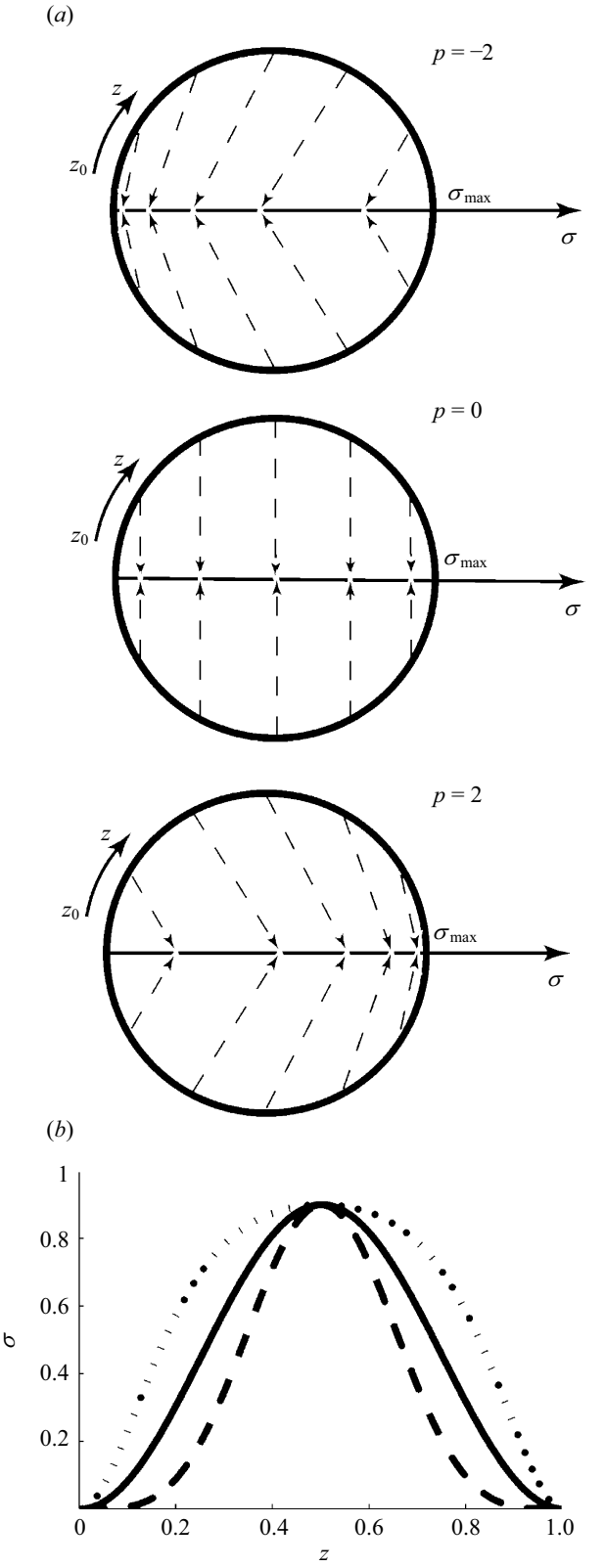

Figure 1. Characterization of strain-space and cross-immunity. (*a*) Strains are uniformly distributed on a circle with diameter σ_{max}. Given a reference strain, z_0, the σ-axis has its origin at z_0 and bisects the circle. The antigenic distance from any strain z on the circle to z_0 is measured by its projection onto the axis (see § 2). σ_{max} sets the level of susceptibility between most distantly related strains; increasing p increases the degree to which strains are clustered around z_0 (illustrated for $p = -2$, 0 and 2). (*b*) Plots of the susceptibility reduction function for $p = -2$ (dashed line), $p = 0$ (solid line) and $p = 2$ (dotted line).

discretized into a number (n) of arcs by dividing the circle into n non-overlapping parts and representing each strain by the mid-point of the corresponding arc

$$z_i = \frac{i}{n} - \frac{1}{2n},$$

where the indices i are in the set

$$\boldsymbol{N} = \{1,2,\ldots n\}.$$

For convenience of notation, a strain is represented either by z_i or simply by its index, $i \in \boldsymbol{N}$, and this will be clear from the context. How finely the strain-space is divided does not measure diversity, but determines the precision of the cross-immunity measurements. We assume that an immune response to a previous infection with strain j infers a reduction of susceptibility to strain i by a factor, σ_j^i. This factor is implemented as the projection of strain j on to the σ-axis with reference strain i (figure 1*a*)

$$\sigma_j^i = \frac{\sigma_{max}}{2}(1 - \cos(2\pi d_p(z_j - z_i))),$$

where

$$d_p(z) = z + pz\left(z - \frac{1}{2}\right)(z - 1).$$

It is natural to think of distances in strain-space as indications of relatedness, i.e. nearby strains are more closely related. An individual infected by a strain at any point on the circle has a susceptibility to a reference strain reduced by a factor (σ) relative to the distance between the two strains: susceptibility is reduced to its lowest levels by closest strains. Cross-immunity ($1 - \sigma$) between strains is defined by two parameters: σ_{max} ($0 \leq \sigma_{max} \leq 1$) determines the range of strain diversity and p determines the distribution of antigenic differences within the range. Antigenic diversity increases with σ_{max}, where $\sigma_{max} = 0$ indicates no differential recognition of strains by the immune system, i.e. infection with any strain gives total cross-immunity to all strains. This might be thought of as the MMR paradigm, in which the genetic diversity observed does not manifest as antigenic (immunologically functional) diversity (Rima *et al.* 1995). As p decreases, the degree to which strains are clustered around a reference strain increases and consequently the effects of cross-immunity are more localized in strain-space (figure 1).

Individuals, totally susceptible at birth ($\sigma_\varnothing^i$ for all $i \in \boldsymbol{N}$), are assumed to accumulate cross-immunity as their infection experience of different strains grows. To our knowledge, there is no empirical information on sequential reduction of susceptibility. We implement and compare two different mechanisms: multiplicative and minimum. The multiplicative assumption has the susceptibility factors decreasing geometrically so that sequential infection decreases susceptibility to all strains:

$$\sigma_{\mathcal{J}}^i = \prod_{j \in \mathcal{J}} \sigma_j^i.$$

As $0 \leq \sigma \leq 1$, the susceptibility factor keeps decreasing as hosts experience further infections. Under the minimum assumption, susceptibility to a reference strain is reduced to the minimum susceptibility reduction factor over all the strains that have been experienced:

$$\sigma_{\mathcal{J}}^i = \min_{j \in \mathcal{J}} \sigma_j^i.$$

Using previous notation (Andreasen *et al.* 1997), there are two

types of dynamic variables in the model. $S_{\mathcal{J}}$ is the proportion of individuals that have been infected by all strains in the subset $\boldsymbol{J} \subseteq \boldsymbol{N}$. We refer to $\boldsymbol{J}$ as the history of infection, and there are 2^n such classes. Λ^i is the force of infection of strain $i \in \boldsymbol{N}$. This is proportional to the proportion of individuals that are currently infectious with strain i and there are n such classes.

We use a susceptible – infections – recovered (SIR) framework as previously proposed (Andreasen *et al.* 1997; Gupta *et al.* 1998) and assume that individual hosts can be coinfected by different strains and transmit each at a rate that is insensitive to the presence of others (May & Nowak 1995). This assumption leads to a great simplification of the model (Ferguson & Andreasen 2001; Gomes & Medley 2001), and we consider it appropriate for the rates that we are interested in (we consider recovery rates three orders of magnitude higher than the death rate: $12\ \mathrm{yr}^{-1}$ and $0.015\ \mathrm{yr}^{-1}$, respectively). Note also that we assume reduced susceptibility rather than transmission, although these approaches lead to similar results (Ferguson & Andreasen 2001). The model is defined by a system of coupled ordinary differential equations as

$$\dot{S}_{\varnothing} = e - \sum_{i \in N} \sigma^i_{\varnothing} \Lambda^i S_{\varnothing} - e S_{\varnothing},$$

$$\dot{S}_{\mathcal{J}} = \sum_{i \in \mathcal{J}} \sigma^i_{\mathcal{J}\setminus i} \Lambda^i S_{\mathcal{J}\setminus i} - \sum_{i \notin \mathcal{J}} \sigma^i_{\mathcal{J}} \Lambda^i S_{\mathcal{J}} - e S_{\mathcal{J}},$$

$$\dot{\Lambda}^i = R_0 - \sum_{\mathcal{J} \subseteq N} \sigma^i_{\mathcal{J}} \Lambda^i S_{\mathcal{J}} - \Lambda^i.$$

As described by Andreasen and colleagues (1997), this model was made non-dimensional by assuming a host population of constant size (birth rate = death rate), hence by recording the various host classes as proportions of the total population and also by measuring time in units of the average infectious period. Thus, e (= 0.00125) is the non-dimensional death rate and R_0 is the basic reproduction number for each strain. We assume that homologous immunity is total and lifelong.

3. RESULTS

We are currently investigating an approximation to a continuum strain-space model, which is beyond the scope of this paper. The discretized version presented here allows for a greater variety of assumptions to be tested, is more easily placed in perspective with previous work (Gupta *et al.* 1996, 1998; Andreasen *et al.* 1997) and provides necessary baseline information for the development of the continuum approximation. Given this motivation for generality, particular emphasis will be given to results that are independent of the chosen number of strains. We have performed simulations for the two extreme mechanisms of susceptibility reduction: multiplicative and minimum. In the multiplicative model, increasing experience of different strains reduces susceptibility geometrically, limiting the total number of strains that hosts are likely to experience to four or five, even if the number of circulating strains is much larger (figure 2*a*). By contrast, in the minimum model (Gupta *et al.* 1996, 1998; Andreasen *et al.* 1997) the effects of different history strains on the reference strain overlap, and susceptibility reduces much less effectively. In this case, a typical host is likely to experience many reinfections and this is dependent on the number co-circulating (figure 2*b*). This might be testable from careful examination of age-specific reinfection rates in communities, in combination with more detailed mathematical models.

The equilibria of the system and corresponding stability analysis as the three parameters (R_0, $\sigma_{\max}$ and p) are varied, are shown for the particular case of four strains with sequential infections reducing susceptibility multiplicatively (figure 3). Although we have not performed a stability analysis with more strains, simulations show good agreement. The behaviour of models with fewer than four strains is significantly simpler and not reported here. Increasing transmissibility increases all rates of infection and this globally enhances differences in cross-immunity, so that heterogeneity is enhanced by increasing either $\sigma_{\max}$ or R_0. The effect of p is to control the strength of local interactions relative to the absolute range and increasing p produces a sharper clustering effect due to enhanced localized competition.

For $R_0 < 1$, the pathogen does not persist and the only equilibrium corresponds to a totally susceptible host population (A_0 of figure 3*a*) and is stable. For $R_0 > 1$, a variety of patterns emerges. There is a homogeneous endemic equilibrium, which, when stable, is characterized by a constant persistence of all strains at the same prevalence (A_1). Stability analysis confirms that A_1 is stable when 'global' cross-immunity is low (low $\sigma_{\max}$ and R_0) and 'local' cross-immunity is weak (roughly, this is the positive p scenario). The homogeneous endemic equilibrium loses stability to heterogeneous strain distributions when these conditions break down. As a result, two heterogeneous endemic population structures can be identified: either clusters move in strain-space in a travelling-wave fashion (A_2) (increasing $\sigma_{\max}$ or R_0, maintaining p near zero), or clusters are stationary and separated by regions of extinct strains (A_3) (roughly, this is the negative p scenario). A cluster typically consists of a set of closely associated strains and at any time the two dominating clusters are diagonally opposed in the circle of strain-space.

Although the structure of patterns is inherent to the configuration of strain-space, we argue that the most important characteristics are expected to adapt to a wide range of configurations. For example, the mechanism sustaining the oscillatory dynamics in the travelling-wave regimen is very general. It is well known that the simplest single-strain SIR models converge to a steady equilibrium in a damped oscillatory manner. The same is true for two- or three-strain systems implemented into a model such as the one considered in this paper. Oscillations are sustained in systems with four or more strains due to a positive feedback mechanism generated by the coexistence of distantly related strain clusters. Therefore, the basic requirement for sustainability of the oscillatory dynamics is that distant niches are available in strain-space for simultaneous occupation by the pathogen. It seems plausible that realistic spaces of possible antigenic types would satisfy this simple requirement and this is supported by more detailed models for antigen-space (Gupta *et al.* 1996, 1998; Gupta & Maiden 2001).

We speculate that reduction in magnitude of strain-space (reduced $\sigma_{\max}$), which promotes homogeneous strain structure, is analogous to the decreasing diversity of immunodominant antigens in some virus families. For example, in the paramyxoviruses, amino–acid sequence homology in the attachment (G) protein of subgroups of

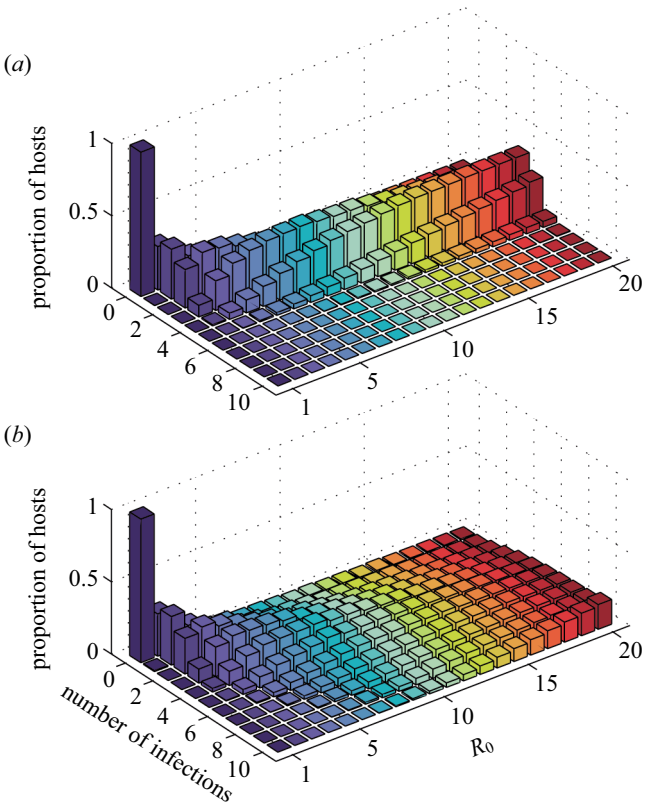

Figure 2. Distribution of the lifetime number of infections experienced by individual hosts for a range of values of R_0 for each of the two mechanisms of accumulating immunity: (*a*) 'multiplicative' mechanism; (*b*) 'minimum' mechanism. Note the assumption that strain-specific immunity is 100% and lifelong and thus that the results relate to total infections with different strains. If specific immunity is less than perfect or wanes, our predictions may underestimate the true numbers of reinfections.

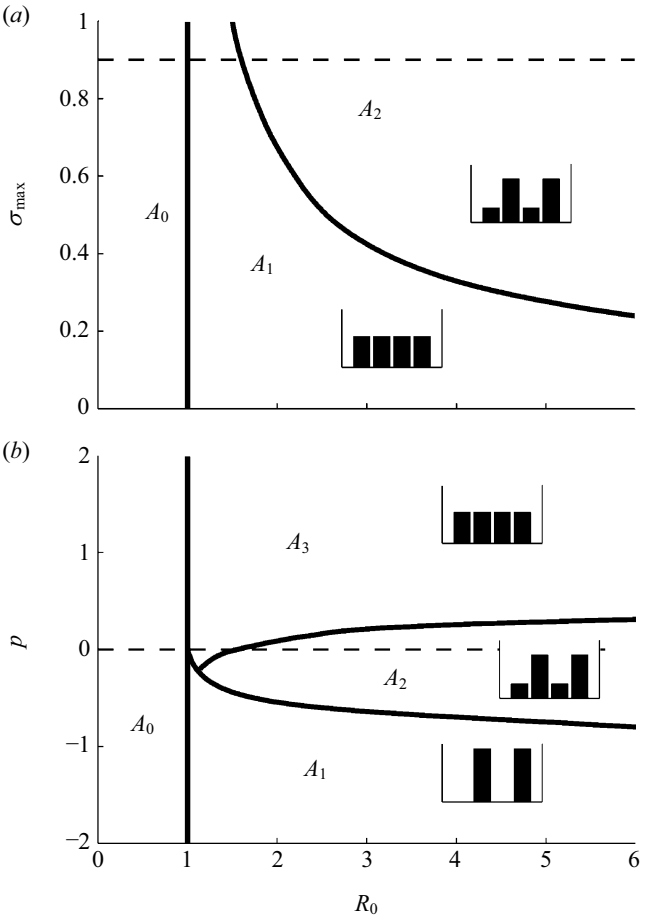

Figure 3. Organization of patterns of strain structure with $n = 4$ and 'multiplicative' accumulation of immunity. (*a*) Stability diagram in parameter space (R_0, σ_{max}) for $p = 0$ (see figure 1). Infection does not persist in region A_0 where $R_0 < 1$. In A_1 the system converges to a homogeneous steady state in which all strains are equally prevalent. As the parameters are varied across the curved line, strain prevalence becomes heterogeneous (A_2), taking the form of oscillatory waves (see figure 4). (*b*) Partial stability diagram in the parameter space (R_0, p) for $\sigma_{max} = 0.9$. Increasing p to positive values has the effect of homogenizing strain prevalence, i.e. increasing the region of stability for A_1. Decreasing p to negative values enhances the heterogeneity emerging in region A_2, increasing wave amplitude until stability region A_3 is formed, in which only some clusters of strains persist. The position in strain-space of the persisting clusters is determined by the initial conditions. Patterns of strain prevalence are illustrated. Simulations support the generalization of these results for higher numbers of strains. Consideration of the 'minimum' accumulation of immunity leads to equivalent stability diagrams. For a more detailed analysis of the transitions between the regions identified in this figure, see the recent work of Dawes & Gog (2001).

the human respiratory syncytial virus (RSV) (53% amino–acid homology between the most distinct A and B serotypes) is far lower than that for the haemagglutinin (H) protein of measles virus strains (Cane & Pringle 1995; Rima *et al.* 1995). With increased diversity, the expectation is for dominant clusters to emerge and potentially to have changing composition as is clearly seen in RSV (Cane & Pringle 1995).

The mechanism for the accumulation of immunity does not alter the stationary solutions greatly, but numerical exploration (figure 4) shows that it has a significant effect on the dynamic patterns generated in A_2. With multiplicative accumulation, the waves (consisting predominantly of two clusters) are robust to variation in strain number (figure 4*a*,*c*,*e*,*g*,*i*). The minimum accumulation model reveals a rapid increase in the number of clusters (i.e. decrease in wavelength) accompanied by a marked decrease in wave speed as n increases (figure 4*b*, *d*,*f*,*h*,*j*). The travelling waves shown correspond to onset patterns, as these are where the most regular heterogeneous solutions. The objective is to develop an understanding of the primary oscillatory modes as these determine important underlying features of the pattern, such as wavelength and wave speed. Each plot was obtained by fixing $\sigma_{max} = 0.9$ and scanning R_0 for the most regular heterogeneous solution (differences between systems resulted in small differences in R_0 values). Simulations were performed with MATLAB (The Mathworks, Natick, MA, USA) with full regard to numerical instability.

The basic reproduction number, R_0, controls the effect of variability in cross-immunity responses. It is to be expected that the larger the diversity imposed (by σ_{max}) the lower the R_0 required for the onset of patterns and this is confirmed in figure 3*a*. Increasing R_0 beyond onset will further amplify variability and finer structures may

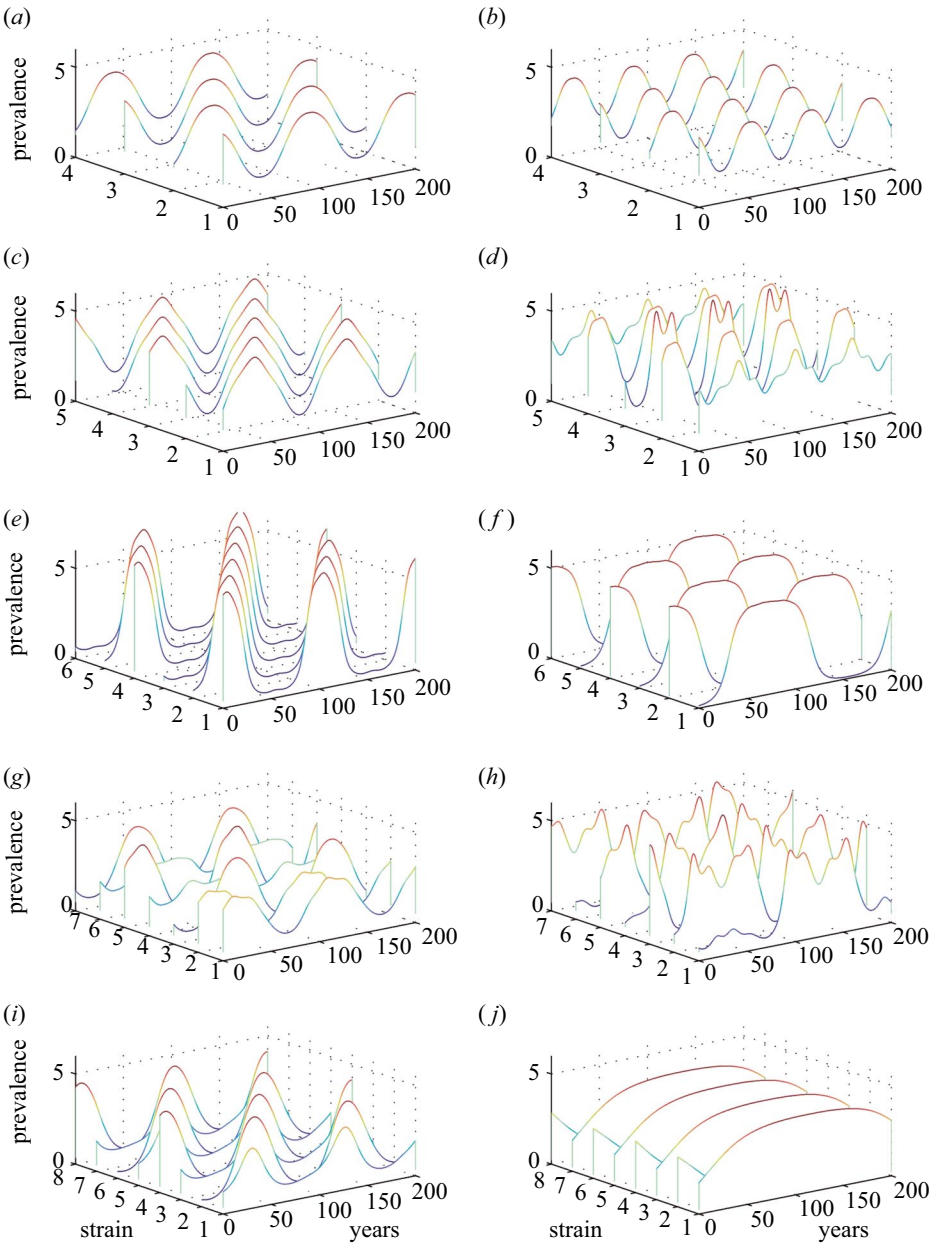

Figure 4. Oscillatory wave strain-structure. Patterns of individual strain prevalence (proportion infectious; prevalence values on the axes are $\times 10^{-4}$) within the stability region A_2 (figure 3) are shown with $\sigma_{max} = 0.9$ and $p = 1.0$ for five consecutive values of strain number ($n = 4$, 5, 6, 7 and 8). At any time point, all strains co-circulate but with cyclic dominance. Comparison is made between the 'multiplicative' (*a*,*c*,*e*,*g*,*i*) and 'minimum' (*b*,*d*,*f*,*h*,*j*) implementation of accumulation of immunity. Parameter values: (*a*,*b*) $n = 4$, $R_0 = 1.7$; (*c*,*d*) $n = 5$, $R_0 = 2.1$; (*e*) $n = 6$, $R_0 = 2.1$; (*f*) $n = 6$, $R_0 = 2.0$; (*g*) $n = 7$, $R_0 = 2.1$; (*h*) $n = 7$, $R_0 = 2.0$, (*i*) $n = 8$, $R_0 = 2.1$; (*j*) $n = 8$, $R_0 = 2.2$.

emerge. This expectation is supported by simulations (not shown) at higher values of R_0, showing increased numbers of clusters in the stationary patterns (A_3) and generation of more complicated dynamics as the basic dynamic patterns (A_2) combine with higher frequencies (in time and strain-space). Although this increase in dynamic complexity is consistent with previous observations (Gupta *et al.* 1998), one cannot be conclusive until finer strain spaces are investigated.

4. DISCUSSION

The population dynamics model presented here exhibits behaviour typical of pattern-forming systems (Manneville 1990; Golubitsky *et al.* 1988; Ben-Jacob & Levine 2001; Golubitsky & Stewart 2001), with well-characterized pathogen population structures emerging spontaneously as the non-dimensional number R_0 is increased across a critical value. This number plays the role of a stress parameter, which controls the effect of variability in cross-immunity responses. Depending on how cross-immunity is distributed in strain-space, the emerging patterns are either stationary or take the form of travelling waves.

Induction of waves does not rely on pathogen mutation, but arises from frequency-dependent immunity: high prevalence diminishes the susceptible resource, incidence in the dominant clusters declines and releases those strains

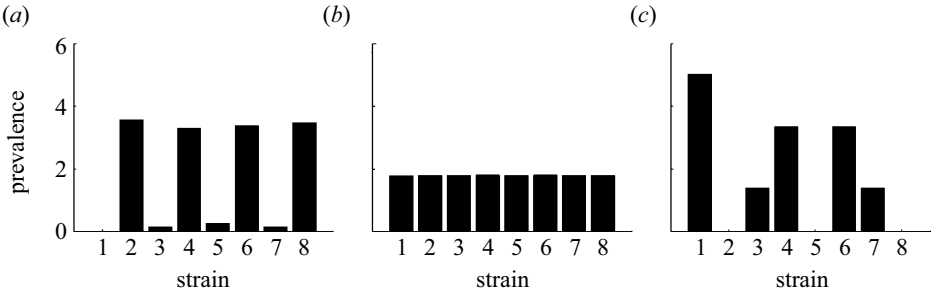

Figure 5. Demonstration of possible effects of heterogeneities in strain-specific transmissibility. (*a*) The result of decreasing R_0 of strain 1 to 1.9. Strain 1 is driven to extinction. This is an oscillatory pattern and the figure shows the time averages. (*b*) A homogeneous prevalence pattern with eight strains is shown for parameter values $\sigma_{max} = 0.9$, $p = 1$, $R_0 = 2.0$. (*c*) The result of increasing R_0 of strain 1 to 2.1. Note that strains 2, 5 and 8 are driven to extinction. The two patterns in (*b*) and (*c*) are time-independent. Prevalence values all $\times 10^{-4}$.

(of intermediate phenotypic characteristics) previously suppressed by competitive immunity. Cluster coexistence enhances this effect and is essential to pattern sustainability. The waves are damped in region A_1, become sustained in A_2 and are lost in A_3 as local competition is strong enough to effectively eliminate suppressed strains. This provides a potential explanation for the observed consistent, annual epidemics of RSV and rotavirus. As susceptibility is generated by births, wave speed is inversely related to the life expectancy of hosts. A comparative analysis of rates of strain replacement for families of pathogens with a range of hosts (e.g. human, herpetic and avian malaria and human, bovine and murine pneumoviruses) would be potentially revealing.

Not much is known about the how the immunity of a single host is altered as a result of further infections by related pathogens. Here we investigate two different implementations for cumulative immunity due to reinfections by related pathogen strains: multiplicative and minimum. Significant differences in the dynamic population structures emerged from our numerical simulations. More detailed implementations of the within-host dynamics of immunity would be very valuable for a more robust characterization of pathogen population dynamics.

The homogeneity assumptions used enable us to identify mechanisms for the structuring of prevalence patterns resulting from selection operating uniformly at the level of the whole system. This approach provides essential background for further investigations, where one may wish to address the effects of heterogeneities on the selective pressure and the evolution of system members (Sait *et al.* 2000; Bjornstad *et al.* 2001). Simulations show surprising consequences of introducing heterogeneity into transmissibility (figure 5). This example shows that small changes in transmissibility of one strain can lead to dramatic changes in the overall pattern, including a high increase in the prevalence of a selected strain at the cost of extinction of others. Furthermore, even in an idealistic strain-space such as a circle, it is sometimes difficult to predict which strains will benefit from interventions. However, regenerating processes such as mutation are expected to dampen these effects and increase system resilience.

Somatic mutation is a random process resulting from reproduction errors and has the potential to generate large numbers of variants. Therefore, simpler frameworks that can accommodate large numbers of strains (or even a continuum) are a necessary basis for more realistic models. Continuum models have been proposed where cross-immunity structure is, to a large extent, removed to allow mathematical tractability (Andreasen *et al.* 1996). These are motivated by influenza A drift, but generalization to other diseases would be very difficult. We are currently using a different approach: sequential infection mechanisms provide the host population with a hierarchy of susceptibility levels, where susceptibility decreases with the number of infections experienced. In particular, results presented here show that if susceptibility decreases in a multiplicative fashion, the system behaviour is essentially independent of the discretization used. This robustness is essential to the existence of a continuum limit and has not, to our knowledge, been observed in previous models. We are presently investigating a continuum model with a formulation that is based on the hierarchical structure of the host population provided by the multiplicative mechanism of susceptibility reduction.

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