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Consequences of host heterogeneity, epitope immunodominance, and immune breadth for strain competition

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ABSTRACT

Consumer-resource dynamics of hosts with their pathogens are modulated by complex interactions between various branches of hosts' immune systems and the imperfectly perceived pathogen. Multistrain SIR models tend to sweep competitive interaction terms between different pathogen strains into a single parameter representing cross-immunity. After reviewing several hypotheses about the generation of immune responses, we look into the consequences of assuming that hosts with identical immune repertoires respond to new pathogens identically. In particular, we vary the breadth of the typical immune response, or the average number of pathogen epitopes a host perceives, and the probability of perceiving a particular epitope. The latter quantity in our model is equivalent both to the degree of diversity in host responses at the population level and the relative immunodominance of different epitopes. We find that a sharp transition to strain coexistence occurs as host responses become narrow or skewed toward one epitope. Increasing the breadth of the immune response and the immunogenicity of different epitopes typically increases the range of cross-immunity values in which chaotic strain dynamics and competitive exclusion occur. Models attempting to predict the outcomes of strain competition should thus consider the potential diversity and specificity of hosts' responses to infection.

1. Introduction

The consequences of strain competition have major implications for vaccination strategies and assessments of epidemic risk. Models of strain competition often implicitly assume that cross-immunity between strains is invariant among hosts: If hosts have the same infection history or immune repertoire, they share the same probability of being infected or infectious upon challenge with a new strain. Cross-immunity under this assumption can yield complex dynamics determined by the intensity of competition (Gupta et al., 1998). For realistic ratios of infection times and host lifespans, three general outcomes are possible. Intense strain competition leads to minimal pathogen diversity: All strains die out except a subset of discordant phenotypes. At intermediate levels of competition, groups of discordant strains undergo cyclical or chaotic dynamics, causing diversity to vary in time. When cross-immunity is low, strains can coexist at an endemic equilibrium. These outcomes imply dramatic differences in the number of circulating strains and how the pathogen population might respond to the appearance of new strains or mutation.

The nature of cross-immunity is central to efforts to understand the dynamics of many multistrain pathogens, such as influenza. The recent pandemic has drawn attention to the extent and diversity of preexisting immunity to the new strain of influenza A H1N1 (e.g., Greenbaum et al., 2009). Theoretical models propose that some level of cross-immunity between strains is essential to constrain influenza A H3N2 diversity to observed levels (Ferguson et al., 2003; Gog and Grenfell, 2002; Gokaydin et al., 2007; Koelle et al., 2006; Tria et al., 2005). Several posit that a necessary element of strain competition is a many-to-one mapping between individual strains, defined by their amino acid sequences, and their antigenic phenotypes. A common implicit assumption in many models of multistrain pathogens is that the cross-immunity between any two strains is invariant among hosts with the same infection histories. This assumption might not be appropriate. Several biologically plausible mechanisms exist that could allow hosts with the same infection history or immune repertoire to perceive genetically identical strains differently.

This study is a foray into the consequences of competition between strains when their phenotypes vary among hosts. We begin by reviewing evidence for several mechanisms of heterogeneity in host responses, with an emphasis on influenza. We then present our model, which incorporates only the simplest level of

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heterogeneity, variability in which epitope (or epitopes) generates an immune response. Our general result is that coexistence of strains becomes dramatically easier when responses by individual hosts are narrow, focused on one epitope, and when responses at the population level are very diverse, with different hosts targeting different epitopes. These findings suggest it might be important to show that theoretical predictions of strain extinction through immune-mediated competition are either robust to within-population heterogeneity, that typical immune responses are quite broad at the individual level, or that these differences disappear with further incorporation of biological detail.

2. Diversity in host responses

Both cellular and antibody-mediated immunity contribute to differences in hosts' adaptive immune responses. The genetic basis of heterogeneity in cellular immune responses has been well studied: an individual host's assortment of MHC class I alleles determines which CD8+ T-cell epitopes can be recognized (Murphy et al., 2007), affecting the speed with which the host can clear an infection. Antibody responses can not only attenuate but also block infection, and there is evidence that they can differ among humans infected with the same and similar strains of a pathogen. Nakajima et al. (2000) found age-related patterns in the acute phase and convalescent sera of nine people infected with influenza A (H3N2) during the 1990–1991 season. The sera of the three and four year old children had antibodies only to site B1, while older subjects had antibodies binding to sites A, B1, B2, C, and C/E. In a follow-up study, Sato et al. (2004) examined the sera of 35 people who had been infected with the same strain of influenza and found that almost all young children developed antibodies to B1 and many to A. Older children and adults developed unique responses that were polyclonal, in that they involved antibodies from multiple lineages of B cells. Most commonly, these lineages produce antibodies directed to different epitopes. In this analysis, we assume that responses are polyclonal if they target more than one epitope and monoclonal if they target only one. Interestingly, Sato et al. (2004) found that antibodies in the polyclonal responses often reacted more strongly to epitopes other than B1.

These patterns could arise because hosts differ in which strains they have seen before, with polyclonal responses becoming more common as antibodies to formerly encountered epitopes accumulate. There are several lines of evidence suggesting that factors other than the number of prior infections might contribute to variability in responses. Hosts that have encountered the same sets of strains might respond differently depending on the order in which strains were encountered, a phenomenon known as original antigenic sin (OAS) (Francis, 1960; Fazekas de St. Groth and Webster, 1966; Hoskins et al., 1979; Smith et al., 1999) (Fig. 1a). If strains x, y, and z are arranged consecutively in linear antigenic space, a host with immunity to strain x might reuse its antibodies to x when exposed to strain y (thereby avoiding infection or reducing infectiousness with y) and then be relatively defenseless upon encountering strain z. A host that encounters strain y first could, in contrast, be partially protected against both x and z.

A likely source of differences is host-dependent immunodominance, which might operate alone or with OAS. The study by Sato et al. (2004) found that while two epitopes seemed especially immunogenic (attractive to antibodies) in children, the relative strengths of their antibody responses to each epitope could be very different. These differences might simply reflect the signature of OAS – B1 may be immunodominant, but some children had encountered epitope A before – but differences might arise even if the subjects' initial immune repertoires are identical. Experimental infections of influenza in naïve animals have shown not only that hosts can vary in which epitopes they target, but also that when targeting the same epitopes, hosts often have quantitatively different responses (Cleveland et al., 1997; Laver et al., 1976). This pattern has also been found in humans' antibody responses to tuberculosis (Lyashchenko et al., 1998) and is suggested by analysis of repertoires of memory B cells in patients infected with HIV (Scheid et al., 2009).

Such differences in host responses might be random, perhaps dependent on which B cells (which generate antibodies) and CD4+ helper T-cells (which stimulate select B cells) encounter epitopes first, or which antibodies have the highest avidity for their epitope (Fig. 1b) (Fairlie-Clarke et al., 2009). These differences might also involve some degree of genetic predetermination. An individual's MHC class-II alleles determine which helper T-cell epitopes are recognized by the immune system. MHC class-II alleles, which are essential for B-cell selection, could thus predispose hosts for particular humoral responses (Crowe et al., 2006). Hosts might thus fall into groups depending not only on which CD8+ T-cell but also which B-cell epitopes they are genetically prone to recognize (Fig. 1c).

There is ample evidence that other mechanisms might shape the dynamics of immune responses. For example, two hosts reacting to the same epitope can form antibodies that bind with the same avidity but have different potentials for cross-reactivity to other antigens (Fairlie-Clarke et al., 2009; Fleury et al., 2000; Scheid et al., 2009). Strain dynamics might be further complicated by asymmetry in cross-immunity: Antibodies against x may be more effective against y than antibodies to y are against x (Underwood, 1980). The strength of immune responses to particular epitopes might decay in time (Nowak et al., 1995), and might differ between primary and secondary responses (Crowe et al., 2003; Lambkin and Dimmock, 1996). Epitopes can also vary in their ability to induce protective immune responses, and this ability may correlate negatively with an epitope's immunogenicity (Ndifon et al., 2009).

These examples suggest abundant, largely unexplored opportunities for dynamical complexity in strain competition. This analysis begins to address the consequences of differential immune responses of hosts by assuming that epitopes compete for immunodominance. In our investigation, not all hosts infected with the same strain necessarily recover with antibodies to every epitope, and which epitope(s) a host develops immunity to is determined stochastically. Except for their antigenic variation, strains are identical and share the same intrinsic fitness.

3. Model

We begin by describing a general model of strain competition by Gupta et al. (1998) and then introduce our adaptation that allows for differences in host responses.

Strains have n loci, each defined by m possible alleles. Each locus corresponds to an epitope, and each allele a possible phenotype of the epitope. Cross-immunity is set by γ, which gives the reduction in transmission probability conferred by previous infection with one strain; $(0 \leq \gamma \leq 1)$. Without heterogeneous immune responses, the fraction immune to a strain i from infection with i, z_i, changes as

$$\frac{dz_i}{dt} = (1-z_i)\lambda_i - \mu z_i, \tag{1}$$

where λ_i is the force of infection of strain i (the per capita rate of rate of acquiring infection, which is linearly proportional to the number of infectious individuals), μ is the birth and death rate, and $(1-z_i)$ is the fraction of the population not immune to strain i from infection with i. An assumption of this model is that immunity to i is conferred immediately upon infection with strain i. Variable z_i thus

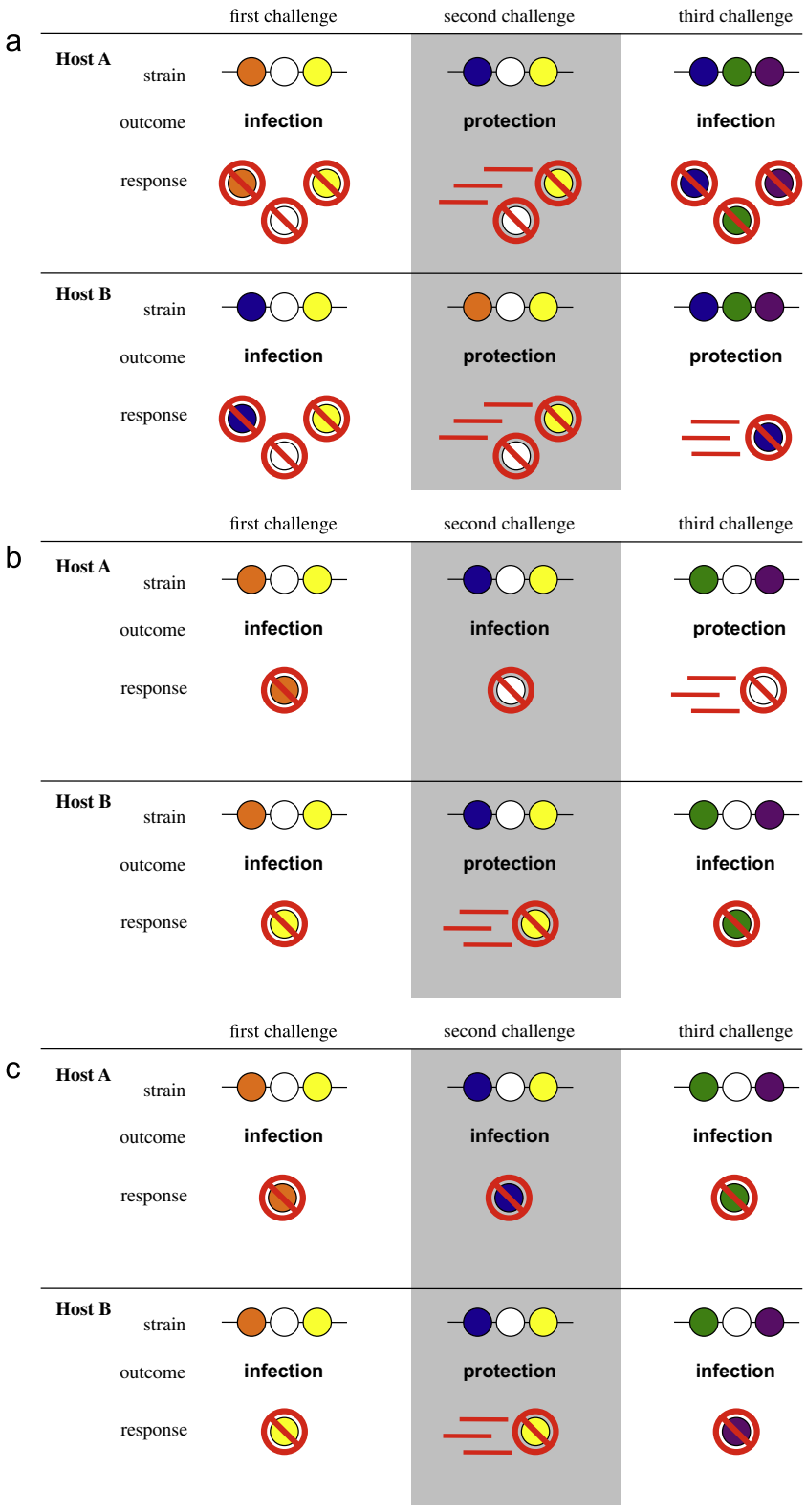

Fig. 1. Three possible mechanisms of heterogeneity in hosts' immune responses. Hosts are immunologically naïve before the first challenge. Each of the three circles in a strain corresponds to a different epitope/locus; each color corresponds to a different phenotype/allele at that epitope/locus. Circles crossed in red represent specific adaptive immune responses (e.g., antibodies or T-cells) to a particular phenotype/allele. The presence of horizontal lines preceding them indicates activation of one or more preexisting responses, which confer protection. (a) Original antigenic sin (OAS). OAS posits that strains that are closely antigenically related may not inspire novel immune responses. Thus, hosts exposed to the same strains but in different sequences will accumulate different immune repertoires and can respond differently upon infection with the same challenge strain. This example shows OAS with a multilocus and polyclonal response; it can also operate for a single locus and monoclonal response. (b) Random immunodominance. This mechanism, the basis of the model explored in this paper, assumes that hosts usually only perceive or develop a strong response to a subset (here, one) of available epitopes. Epitopes have certain probabilities of being immunodominant, and these probabilities do not vary among hosts. (c) Predetermined immunodominance. Hosts intrinsically vary in their propensities to mount immune responses to different epitopes. Host A recognizes only the first locus, and host B only the third. Host A thus perceives three distinct strains and host B two distinct strains.

represents cumulative incidence of i: it increases from direct infections with i and decreases only through mortality.

Compartment w_i represents hosts immune to all strains j that share alleles with i, including i itself

$$\frac{dw_i}{dt} = (1-w_i)\sum_{j\sim i}\lambda j - \mu w_i, \tag{2}$$

The expression $j\sim i$ refers to all strains j sharing alleles with i, and $(1-w_i)$ is the fraction of the population that has never been infected with a strain that shares alleles with i. The difference between z_i and w_i is that the former acquired immunity to i from infection with i, and the latter acquired immunity to i via infection with strain j that shares alleles with i. Thus, z_i is a subset of w_i. The w_i compartment thus tracks cumulative immunity to i, including in individuals currently infectious with i and in individuals who were never infected with i but who attained immunity through infection with j.

The population of individuals infectious with strain i, y_i, changes as

$$\frac{dy_i}{dt} = \left[(1-w_i)+(1-\gamma)(w_i-z_i)\right]\lambda_i - \sigma y_i, \tag{3}$$

where σ is the rate of recovery. The quantity $(w_i - z_i)$ is individuals who acquired immunity to i through infection with a different strain. Eqs. (2) and (3) show that cross-immunity in this model acts through a reduction in infectiousness: fraction γ of individuals who are immune to i from infection with a different strain, γ (w_i-z_i), cannot become infectious with i (though these individuals still become infected as z_i). The remaining fraction, $(1-\gamma)(w_i-z_i)$, can become infectious with i, as can those individuals who have never been infected with a strain sharing alleles with i, $(1-w_i)$. Thus, y_i is a subset of w_i and z_i.

To incorporate heterogeneity in host immune response into this formalism, we account for the possibility that hosts might not identify shared epitopes between strains due to variable immunodominance. In other words, infection with strain j will not automatically confer immunity to strain i simply because the two strains share common epitopes. An additional requirement must be met, which is that the shared epitope must have triggered a strong immune response during infection with strain j. Let p_n be the probability that individuals develop an immune response to epitope n; p_n thus measures the epitope's immunodominance. Initially, we assume all responses are on average monoclonal to one epitope, so that $\Sigma\, p_n = 1$. Eq. 1 does not change: all people infected with strain i will mount a specific response to one of its epitopes and will not transmit i in the future. But now not all hosts with immunity to strain j, which shares epitopes with i, will have immunity to i. Only the fraction of hosts infected with j that mount responses to epitopes shared with i will then be immune to i. Let S_{ij} be the set of shared epitopes between strains i and j: $S_{ij} \equiv i \cap j$. The probability r_{ij} of developing a response to i if infected with j is

$$r_{ij} = \sum_{n\in S_{ij}} p_n \tag{4}$$

Thus, Eq. (2) becomes

$$\frac{dw_i}{dt} = (1-w_i)\sum_{j}\lambda_j r_{ij} - \mu w_i. \tag{5}$$

We retain the assumption that cross-immunity is effected by a reduction in infectiousness γ between immune responses to i and j, but this now only occurs in hosts recognizing shared epitopes. Eq. 3 thus remains the same.

Our analysis focuses on the effects of changing epitopes' immunodominance. Values of p_n are drawn from a normalized negative binomial distribution, which can allow every epitope to have the same immunodominance or for the probabilities to be highly skewed (Appendix A): Skewed distributions correspond to less diverse immune responses at the population level (since hosts tend to react to the same epitope) and even distributions correspond to more diverse responses or, equivalently, reduced immunodominance. We initially assume that hosts retain immunity on average to only one epitope. Mathematically, this is equivalent to $\Sigma\, p_n = 1$. We then allow polyclonal responses ($\Sigma\, p_n > 1$) to the limit where infected hosts develop immune responses to potentially every epitope, $\Sigma\, p_n = n$. To increase the breadth of individual hosts' immune responses, we multiply each response p_n by a "polyclonality" factor c, which ranges from 1 to n, and further require $p_n \leq 1$. Hosts' immune responses are therefore identical not only when immunodominance is maximally skewed ($b=1$) but also when every epitope is guaranteed to be targeted ($b=0$, $c=n$): at these extremes, $p_n=0$ or 1 for every epitope n (Fig. S1). The ordinary differential equations were simulated numerically for the three locus ($n=3$), two allele ($m=2$); three locus ($n=3$), three allele ($m=3$); and four locus ($n=4$), two allele ($m=2$) cases (Appendices B and C).

4. Results

When hosts respond to on average one epitope (i.e., responses are monoclonal, $c=1$), coexistence inevitably results (Fig. 2). After initial oscillations, strains settle at an endemic point equilibrium, comparable in prevalence to the regime of low cross-immunity in the original model (Fig. 3). This pattern results regardless of the relative immunodominance of the different epitopes or the strength of cross-immunity. Additionally, whenever one epitope is completely immunodominant ($b=1$), responses are effectively monoclonal, and coexistence always ensues.

As the breadth of the average immune response increases ($c>1$), complex dynamical behavior becomes possible at high levels of cross-immunity (Fig. 2). Because these dynamics can involve large amplitude fluctuations in strain prevalence, in finite host populations they correspond to regions of parameter space where competitive exclusion is especially likely. In the three-locus, two-allele system, when hosts recognize most epitopes ($c=2$), increasing the cross-immunity γ above approximately 0.65 (at $b=0$, where all epitopes have equal probability of dominating) results in the onset of chaotic dynamics, followed by a regime of increasingly strong competitive exclusion and eventually (at approximately $\gamma > 0.90$) the dominance of one antigenically discordant set (Fig. 4). As the immunodominance distribution becomes more skewed ($b=0.85$), the chaotic dynamics shift to a slightly higher range of γ and are preceded by a growing region of limit cycles. The transition from $b=0$ to $b=0.85$ is continuous and gradual.

Increasing the breadth of the immune response even further ($c=3$) expands the regions of cyclic, chaotic, and competitively exclusive behavior; all start at lower γ (Fig. 2). The same patterns appear for the four-locus, two-allele and three-locus, three-allele scenarios (Figs. S2 and S3). For a given breadth of immunity c, the size of the range of cross-immunity values γ over which these complex dynamics occur can expand and contract as b increases, though it is always smallest at high levels of b (e.g., Fig. S3).

Since the dynamics analyzed in the original model (Gupta et al., 1998), correspond to the case where $c=3$ and $b=0$, our results show that reducing the breadth of the immune response ($c<3$) increases the minimum cross-immunity required for the onset of periodic and chaotic dynamics. Changing the immunodominance distribution of the epitopes has quantitative consequences for these regimes. What is interesting is that the transition from coexistence at a stable equilibrium in the case where $c=1$ (monoclonal responses) or $b=1$ (homogenous host response to a single

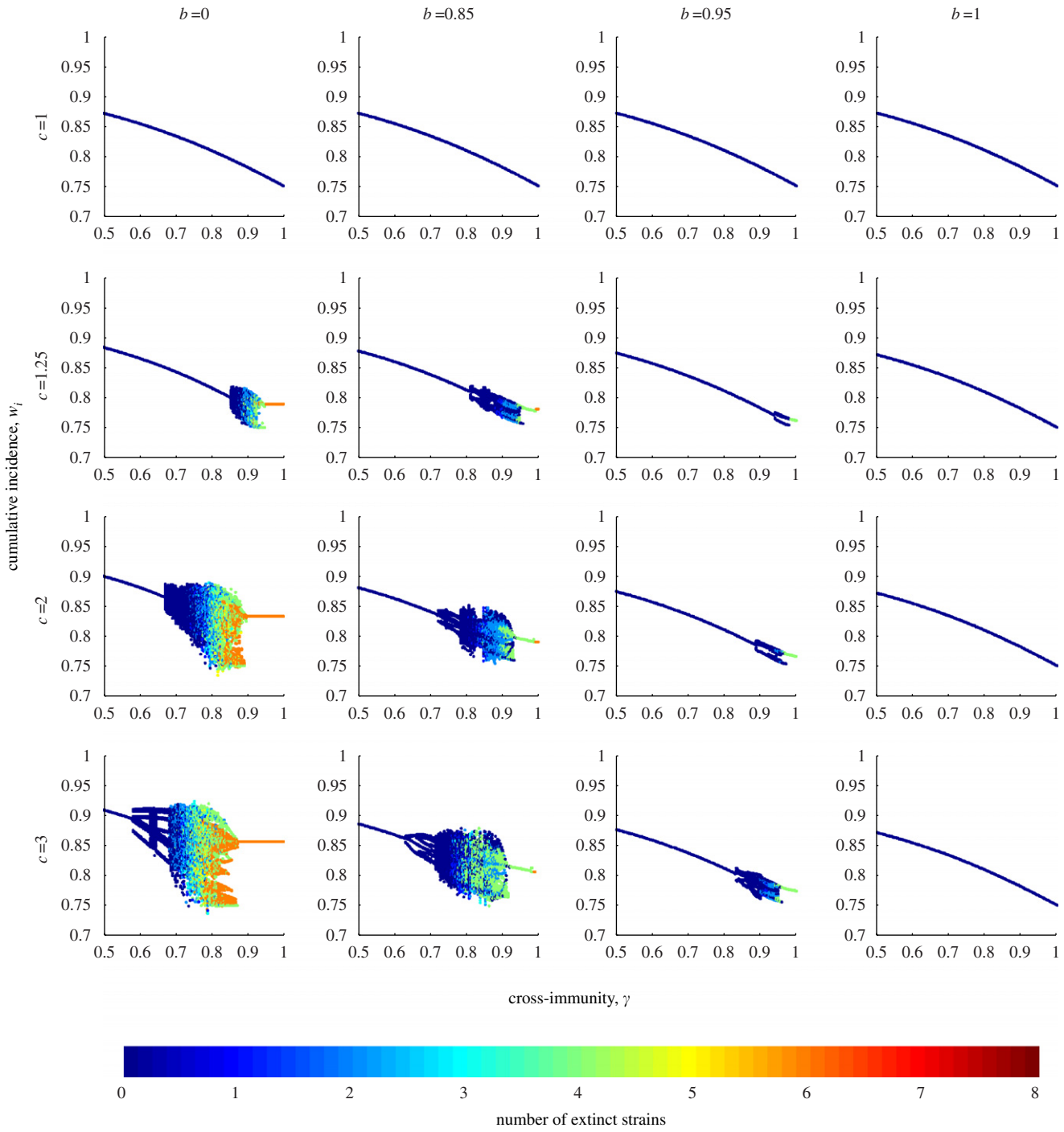

Fig. 2. Equilibrium strain dynamics generated with monoclonal ($c=1$) and polyclonal ($c>1$) host responses for different levels of host diversity or epitope immunodominance b for the three locus ($n=3$), two allele ($m=2$) case. The color of each point indicates the number of strains with an infection prevalence below 10^{-8} at that time.

dominant epitope) to more complex dynamics happens with only a modest increase in the breadth of the immune response ($c=1\rightarrow1.25$), increase in the diversity of host responses ($b=1\rightarrow0.95$), or increase in the other epitopes' immunogenicity ($b=1\rightarrow0.95$). Equivalently, the dynamics of the original model (Gupta et al., 1998) show slight quantitative changes but overall robustness until individual responses become narrow (close to monoclonal) or skewed to one epitope. The regime of chaotic behavior and potential for competitive exclusion appears more sensitive to changes in b than c: the effect of decreasing each is generally to increase the amount of cross-immunity required for complex dynamics to occur.

5. Discussion

Experiments suggest that hosts that have been exposed to the same strains will not necessarily develop the same immune repertoires, and hosts with identical immune repertoires will not necessarily respond identically upon infection with the same challenge strain. Understanding the outcome of strain competition is the motivation for many models of infectious disease, and yet many models are grounded on simple assumptions about the nature of cross-immunity (cf. Kryazhimskiy et al., 2007). The aim of this study was to minimally relax a common assumption. Narrow immune responses that were focused on one epitope on average

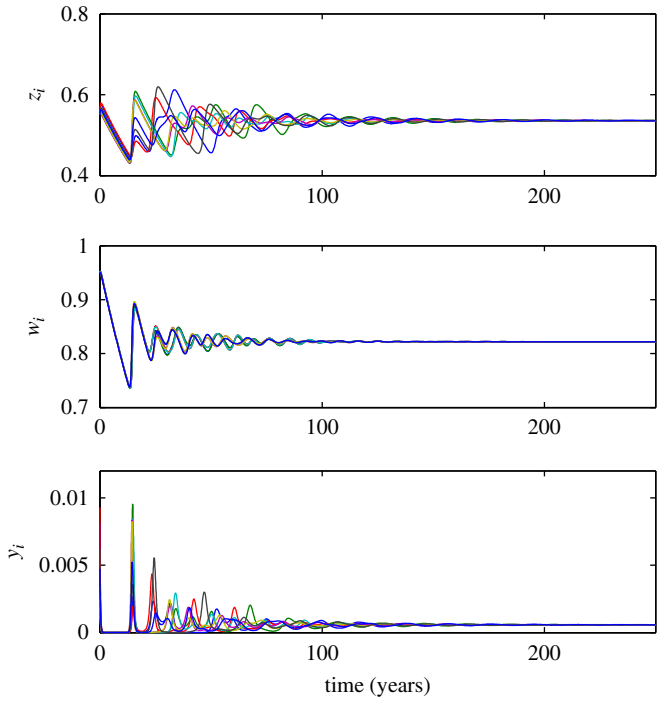

Fig. 3. Sample time series showing transients of z_i, w_i, and y_i with $\gamma=0.75$, $c=1$, and $b=0.85$. Each color corresponds to a different strain. Note differences in the ranges of the y-axes between plots.

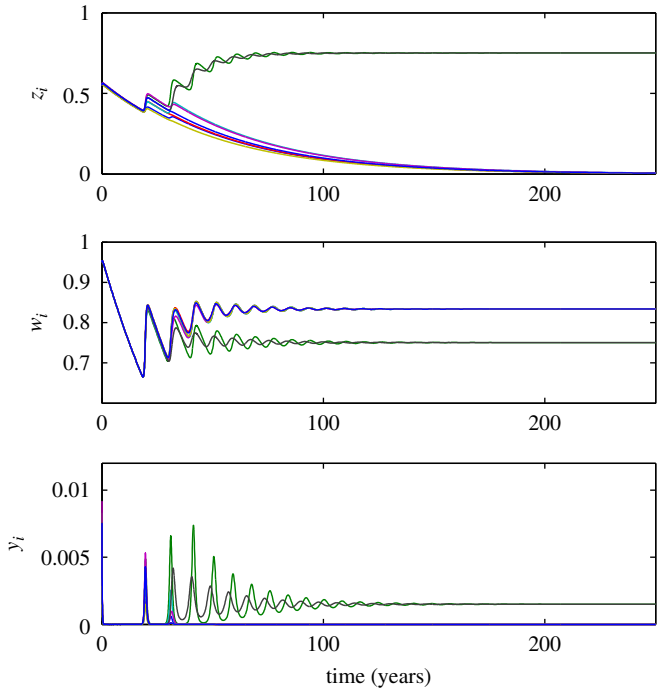

Fig. 4. Sample time series showing transients of z_i, w_i, and y_i with $\gamma=0.95$, $c=2$, and $b=0$. Each color corresponds to a different strain.

($c=1$) generated a stable equilibrium for any level of cross-immunity and any amount of diversity in host responses. A small increase in the breadth of the immune response ($c>1$) created limit cycles and chaos at high levels of cross-immunity. A single immunodominant epitope (creating a homogeneous host response; $b=1$) also induced a stable equilibrium, with complex dynamics returning after a small increase in host diversity or decline in immunodominance. If we assume that stochastic extinction is most likely when strains fluctuate in abundance, these results imply that the risk of competitive exclusion disappears only toward the extremes of monoclonal responses or highly immunodominant epitopes. Otherwise, the effect of incomplete host responses is usually to increase slightly the level of cross-immunity at which competitive exclusion might occur.

Other models exploring the consequences of heterogeneous host immune responses for strain competition obtained complementary results. Gupta and Galvani (1999) considered a population of two host genotypes. Genotype "A" followed the dynamics outlined in the original model (Eqs. (1)–(3)) and genotype "B" recognized a locus common to all strains (i.e., perceived all strains as identical). Increasing the proportion of genotype B hosts gradually reduced the threshold level of cross-immunity γ required for strain structure to appear and increased the period of oscillations of discordant antigenic sets. In populations comprised solely of genotype B hosts, oscillations disappeared, and the strain with the highest R_0 dominated. Thus, increasing the intensity of strain-transcendent competition (the fraction of genotype B hosts) reduced strain diversity, and the presence of hosts forming incomplete, strain-specific responses increased strain diversity. This result is consistent with the effects of generalized immunity, a transient strain-transcendent immunity could constrain diversity in simulations (Ferguson et al., 2003). It is also consistent with our results, which show a decrease in diversity as hosts' immune responses broaden to encompass all epitopes.

Rather than assuming that the degree of cross-immunity between two strains is independent of the number of shared epitopes (for strains sharing at least one), Recker and Gupta (2005) introduced another class of individuals immune to any strain k that shares more than one allele with strain i. Individuals immune to i via prior infection with k have a greater reduction in infectiousness (higher cross-immunity, γ_2) than individuals immune to i via prior infection with strains sharing only one allele with i (with cross-immunity from the latter given by γ_1, and $\gamma_1<\gamma_2$). A high degree of cross-immunity between more closely related strains, γ_2, could precipitate the onset of the transition to discrete strain structure even when γ_1 was relatively low. In other words, including some immunological precision about the extent of phenotypic similarity reduced diversity compared to the original model.

Our results suggest that the reductions found by Recker and Gupta (2005) could be attenuated by the breadth and diversity of the immune response. Dynamically, changing c, the breadth of the immune response, appears to have similar but not identical effects on dynamics to changing the number of immunodominant epitopes, n (Gupta et al., 1998). Our model is also convergently similar to the approach of polarized immunity (Gog and Swinton, 2002): Rather than cross-immunity acting through a partial reduction in infectiousness or susceptibility in all immune hosts, strain competition is effected when some fraction σ_{ij} of hosts infected with j develops immediate immunity to i. If $\gamma=1$, we obtain a model of polarized immunity with $\sigma_{ij}=r_{ij}$, the effective similarity of the strains' phenotypes. When $\gamma<1$, our model allows cross-immunity to epitopes shared by strains i and j to be imperfect. To our knowledge, the status-based approach has not previously been described or applied in the context of immunodominance and natural heterogeneity in host responses.

More detailed investigation of the different components of our model should increase the relevance of the conclusions to epidemiology. The summaries here are of equilibrium conditions, deterministically obtained, and ignore extinctions that would result from demographic stochasticity. Less obviously, our model, like models of polarized immunity, assumes the effects of many probabilistic outcomes (response versus non-response to epitopes by individual hosts) can be represented by average rates. The conclusions thus

reflect less variance in host immunity than one might observe in an individual-based representation of this system. Such differences might be dwarfed by inclusion of more realistic mechanisms, such as the degree to which individuals may be genetically predisposed to respond to particular epitopes. Incorporating our assumptions into a more classical history-based formulation (e.g., Castillo-Chavez et al., 1989; Andreasen et al., 1997) may yield slightly different results (Ballesteros et al., 2009). Finally, to provide a foundation for future work, we assumed that all strains shared the same intrinsic reproductive rate. Though some pathogens might be capable of neutral or nearly neutral antigenic variation, this assumption must be relaxed for those pathogens in which antigenic escape comes at a cost to intrinsic fitness.

Our findings underscore that research into the breadth and diversity of human immune responses to influenza could be important for developing accurate models. Since T-cell epitopes are recognized by a limited set of MHC alleles, whereas B-cell adaptation is relatively unrestricted, we might expect greater coexistence of antigenically diverse strains in pathogen populations that compete mainly against the narrow repertoires of hosts' cellular immunity. This pattern could, however, be offset by the highly immunogenic nature of certain epitopes in some pathogens, which reduce immune diversity at the population level. Because pathogens are under selective pressure to minimize their numbers of immunogenic, neutralizing epitopes, the potential diversity of immune responses might change as pathogens develop immunogenic, non-neutralizing epitopes or more polymorphism at immunogenic, neutralizing sites. Understanding the breadth and diversity of immune responses might shed light on how mutants appear and spread. For example, Nakajima et al. (2000) and Sato et al. (2004) posit that antigenic drift in influenza results from serial adaptation to monoclonally responding subpopulations. Cleveland et al. (1997) propose the existence of four different "human genetic groupings" with consistent, nonoverlapping epitope biases. Viruses drift as they move from group to group, acquiring a critical amino acid change in each.

More broadly, this work shows how consumer-resource dynamics can be qualitatively affected by the phenotypic resolution of one of the parties. The idea that multiple genotypes can map to a single phenotype is familiar to most biologists, and there is evidence that this degeneracy shapes competition among influenza strains (Koelle et al., 2006): many strains that differ genetically are perceived as roughly identical to the host's immune system. A less explored assumption is how the assignment of genotype to phenotype might vary among members of the opposing population. Here, we have explored the consequences of how the phenotype of one party (the pathogen or resource) depends on stochastic variation in the other's response (the immune system or consumer), and we found an occasionally dramatic difference in outcomes. It would be interesting to revisit other consumer-resource systems in which phenotypes are not a fixed trait, and in which a multidegenerate genotype–phenotype mapping is plausible.

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Appendix A. Immunodominance distributions

The negative binomial distribution is typically written as

$$f(k;r,p)=\binom{k+r-1}{r-1}p^r(1-p)^k, \tag{A.1}$$

where $0<p<1$ and $r>0$. To avoid confusion with epitope immunodominance, we refer to p above as b. We set $r=1$. The per epitope immunodominance p_k is

$$p_k=\min\left(1,\frac{cf(k;r,b)}{\sum_{k=1}^{n}f(k;r,b)}\right), \tag{A.2}$$

where k refers to the epitope ($k\in\{1,\ldots,n\}$) and c is the degree of polyclonality (main text). To accommodate $b=0$ and $b=1$, we approximate flat and skewed distributions with $b=10^{-10}$ and $b=1-10^{-10}$, respectively.

Appendix B. Parameters

All rate parameters are the same as those used in Gupta et al. (1998): birth and death, $\mu=1/50\ \mathrm{y}^{-1}$; recovery, $\sigma=10\ \mathrm{y}^{-1}$; $R_0=4$. Random starting conditions were used for the sample time series in Fig. 3 and also for each bifurcation diagram at $\gamma=0.5$. For subsequent values of γ in the bifurcation diagrams, initial values were copied from the final values simulated for the previous value of γ. Values of $y_i(0)$ were drawn from a uniform random interval over (0, 0.01], and $z_i(0)=0.55$ and $w_i(0)=0.95$, which is near the stable equilibrium.

Appendix C. Numerical solution of the ordinary differential equations

We simulated the equations using a fourth- and fifth-order Runge–Kutta solver implemented in Matlab (function ode45) with absolute error tolerance of 10^{-8} and relative error tolerance of 10^{-5}. Simulations were run for 2000 years and then sampled annually for the next 500 years. The diagrams show all maxima and minima over the sampling period, with the color of each point indicating the number of strains with an abundance below 10^{-8} at that time. The inflection points were obtained using Matlab's findpeaks function, which returns every point that is greater than both its neighbors.

Appendix D. Supplementary materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jtbi.2010.11.009.

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