

Dynamics and selection of many-strain pathogens

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Strain structure is of fundamental importance in the underlying dynamics of a number of pathogens. However, previous models have been too complex to accommodate many strains. This paper offers a solution to this problem, in the form of a simple model that is capable of capturing the dynamics of a large number of antigenic types that interact via host cross-immunity. We derive the structure of the model, which can manage the complexity of many strains by using a status-based formulation, assuming polarized immunity and cross-immunity act to reduced transmission probability. We then apply the model to address basic questions in strain dynamics, focusing particularly on the interepidemic dynamics of influenza. This model shows that strains have a tendency to “cluster.” For a long infectious period, relative to host lifetime, clusters may coexist. By contrast, a short infectious period leads to a single dominant cluster at any given time. We show how the speed of cluster replacement depends on the specificity of cross-immunity and on the underlying pathogen mutation rate.

In recent years, a large body of empirical and theoretical work has underlined the importance of strain structure for the dynamics, evolution, and control of pathogens. Models, often in concert with empirical analysis, have explored a range of issues arising from the emergent dynamics of pathogen strains. With *Plasmodium falciparum*, considerations of distinct antigenic types can give an order of magnitude difference in estimates for the basic reproduction ratio (1). In the case of dengue virus, strain models show how complex behavior is generated in the case of enhancement between strains (2). In influenza, repeated vaccination is not always effective because of subtle strain interference (3, 4). The wider problem of developing a modeling framework for multiple strains interacting through cross-immunity is the subject of much current research (for example, refs. 5–8).

For reasons of tractability, much of this work has focused on the dynamics of relatively few strains, typically up to four. This is reasonable for some systems, when genetic variability of the pathogen does not affect the crossreactivity of the immune response. For example, to a very good approximation, we can consider measles to be a single strain (9–11). However, the “few-strains” assumption flies in the face of observation for many systems. Variation of the surface proteins of the influenza virus could in principle lead to thousands of cocirculating distinct types, in terms of their interaction with the immune system (12). This complexity may well apply to many important diseases [HIV (13), malaria (14), dengue (15), and meningitis (16)].

The main obstacle to modeling systems with more than a few strains is the fact that the number of dynamic variables tends to grow explosively with the number of strains. If there are n functionally different types, then typically we would need $2n$ host variables. For 10 strains, this means a formidable 1,024 variables. Gomes *et al.* (6) give numerical results for up to 10 strains, but it is clear that this approach will not extend to, say, 100. The necessary computing power will double for every single strain added. Ferguson and Andreasen (17) discuss the case when the model bases its variables on host infection history, and cross-immunity acts to reduce transmission rather than susceptibility to future strains. The number of variables can be reduced provided the cross-immunity structure is simple: only certain discrete levels of cross-immunity are possible. This gives a vast

reduction of complexity in these cases, but there is no apparent method to extend this approach for typical cross-immunity structures.

This paper shows that application of a recently developed framework, which considers the current immune state of the host rather than the very complex immune history of exposure, can provide a solution to the problem (7). We begin by deriving the model, which allows us to address two basic problems in strain dynamics.

The motivation for these applications is influenza A, but the model can be used more generally. Influenza is notable for its annual epidemics and antigenic drift dynamics, where many closely related strains cocirculate (12, 18–20). The dominant antigenic sites are on hemagglutinin, a surface protein that can mutate seemingly endlessly. An antibody response raised against one strain may or may not be effective against a mutant. The more “different” a mutant, the fewer hosts will have crossreactive protection against it. This pressure leads to a gradual replacement of strains, and so the overall picture is that of the dominant strain moving with time.

We consider three general questions: How can we model multiple strains without imposing excessive restriction on the cross-immunity structure between strains? How does the pattern of coexistence vary between pathogens that cause acute infections such as influenza and those responsible for a more chronic infection? And what happens if two different directions of mutation are possible, one leading to a less transmissible virus?

Derivation of the Model

The main idea of the status-based formulation is that it takes the pathogen view (7): the approach is to track the host variables according to any impact they are going to have on future infections by all other strains. We refine and apply this idea in the present paper.

In the type of population model developed here, the individual has very few possible discrete states with regard to each strain. For example, we do not consider detailed levels of viremia in different people, just whether or not they are infected. In this discretized system, there are at least two ways to model immunity. Either an infection leaves hosts less likely to be infected by other strains, or it could leave the hosts with a lower chance of being infectious if infected by other strains in the future. The former, known as reduced susceptibility, has the hosts totally impervious to strains to which they have immune memory. Not only will they fend off infection to the point of not being infectious to others, but also they will not gain immunity to additional strains even after prolonged and repeated exposure. In contrast, in the case of reduced transmission, immunity only prevents the host from becoming infectious. Further immune memory may be gained as if the host were totally naïve. Both are necessary abstractions of reality: the dynamics of the individual is simplified down to essence to focus on the full population dynamics. Previous authors have found that model dynamics are relatively insensitive to model choice (17); the resultant dynamics are qualitatively similar except possibly in a small region of parameter space (21). Reduced transmission lends itself to a

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more natural mathematical formulation, and we exploit this useful property here.

As implied above, we use “polarized immunity,” which means that *partial* cross-immunity acts to render *some* of the hosts totally immune. The partial aspect of the immunity is introduced through a probability that a given host will gain immunity; only some hosts gain immunity when exposed to a partially cross-reacting strain; other hosts do not gain immunity from that exposure. The alternative to polarized immunity is that no hosts gain full protection against any other strain, but all hosts gain partial protection, which gives them a reduced rate of being infected. These alternatives are similar to the two models proposed by Smith *et al.* (22) for the action of vaccination.

We combine the reduced-transmission assumption and the status-based framework with polarized immunity. Together, they give the following elegant property: all hosts have the same chance of gaining immunity to a strain, no matter what their current immune state. Thus we need only one variable to describe the host with respect to each strain, rather than the myriad of interconnecting variables needed otherwise. The consequences of this simplifying assumption are discussed below.

Mathematically, the system is described by

$$\begin{aligned} \dot{I}_i &= \beta_i S_i I_i - \nu_i I_i - \mu I_i \\ \dot{S}_i &= \mu - \sum_j \beta_j S_i \sigma_{ij} I_j - \mu S_i \end{aligned}$$

for $i = 1, 2, \dots, n$, where n is the total number of strains. I_i and S_i are the number of people infectious with and the number of people susceptible to strain i , respectively. We suppose the total population size to be at equilibrium, so μ is both the birth and death rate. The two parameters for each strain are β_i , the transmission rate, and ν_i , the rate of recovery from infection. Finally, the network of cross-immunity between strains is given by σ_{ij} , the chance an infection by strain j will give immunity to strain i . Mutation terms can be easily incorporated into the I equations, as in the particular applications below.

This is a tractable system for as many strains as one would wish to model (complexity scales up linearly with n rather than exponentially) and does not impose any constraints on cross-immunity interactions between strains beyond being describable by a matrix σ_{ij} . Further, this model can be immediately extended to describe a continuum of strains.

Application to Antigenic Drift, Coexistence, and Pathogen Timescales

Applying our many-strains model to the dynamics of particular pathogens raises another complex problem: the “strain space” in which pathogens reside. Each point in strain space represents a single strain. Two processes give definition to the geometry of strain space; the first is immunological, and the second is genetic.

First, two different strains may react with the same immune response, so one notion of distance or “relatedness” between strains is that of cross-immunity. If the immune response is mainly antibody-mediated and directed at a single or few epitopes, then a shape space (23, 24) describing the physical properties of exactly those epitopes will describe the antigenic relationships in strain space. If there are many different sites, or if T cell epitopes play an important role, then a more intricate strain space may be required, with either many different components or a suitable overall geometry representative of a multifaceted antigenic structure.

The second process concerns the origins of diversity of strains. Strains that differ by a small number of mutations are close together in terms of genetic distance; there is a short route

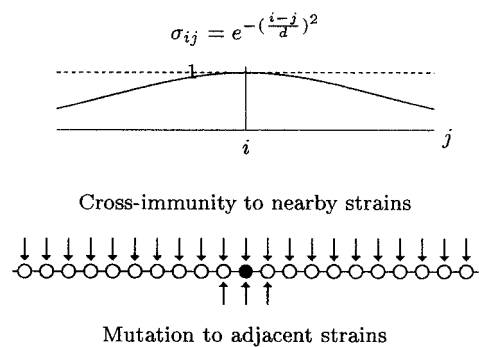


Fig. 1. A linear strain space. Each circle on the line corresponds to a strain. Focusing on strain i , depicted as a black circle, there are two interactions: mutation to immediately adjacent strains and crossimmunity to a range of nearby strains, tailing off with distance from the black strain, as plotted above.

between one strain and another. New strains can also arise by other processes such as reassortment or recombination, so these paths will also play a part in strain space for some problems.

In this section, we focus on a fundamental question, namely how does the pattern of coexistence of strains depend on the typical duration of infection? We approach this question by making the simplest possible assumption about strain space: linear strain space and local movement by stepwise mutation. This strain space is equivalent to the stepping-stone arrangement used by Sasaki for antigenic types within a single host (25). The within-host model was formulated to address different questions, and there was no cross-immunity between strains. A 1D axis of antigenic types has previously been reported in a population model (26), but in that case it was necessary to assume that each strain gives total immunity to all strains to one side, thereby forcing drift-like progression in a prescribed direction.

Our formulation allows us to consider 100 strains, arranged in a line as shown in Fig. 1. Strains interact via cross-immunity to nearby strains, and also they can spontaneously give rise to immediately adjacent types by mutation. The cross-immunity matrix is a gaussian in $(i - j)$ given in Fig. 1, selected as a simple form that varies smoothly and symmetrically about each strain, and tails off with distance (plotted in Fig. 1). Distance d gives the typical length scale involved in cross-immunity.

Mutation is included as a discrete diffusion in the equations for the number of infecteds, with coefficient m . The more of a strain, the more frequently it will mutate into one of its neighbors. All strains have the same basic parameter values (ν, β, m).

Results

Using this simple strain space, we consider the impact of varying the duration of infection relative to a typical host lifetime. Essentially, two different types of behavior emerge (Fig. 2).

For a *prolonged* infection (Fig. 2a), where the infectious period is a substantial proportion of host lifetime, we see a cluster building up and persisting, but it remains localized. Strains further from the first cluster arise at low frequency, but cross-immunity keeps them in check. However, eventually there is sufficient low-level drift that new strains can begin to invade. Increased numbers mean these rapidly give rise to further strains. So at a certain distance, there is a positive feedback loop of increased mutation due to more infecteds and increased advantage through evasion of existing immunity. This cascade leads to the rapid establishment of a second cluster. The process of cluster generation repeats over the entire strain space. Overall, this process leads to the coexistence of a set of discrete strain

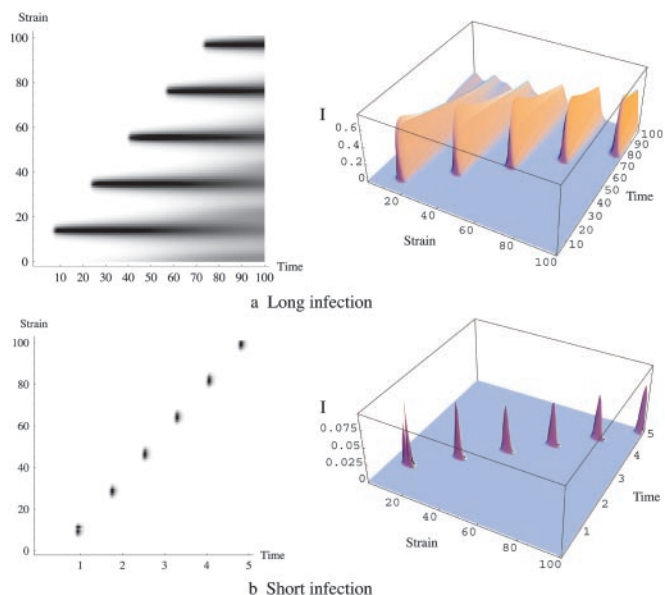


Fig. 2. Numerical results for a linear strain space. Time is in years in both examples; $d = 10$, $\beta = 3\nu$. In *a*, $\mu = 1$, $\nu = 0.5$, $m = 0.02$. In *b*, $\mu = 1/80$, $\nu = 52$, $m = 0.1$. (a) For a long infection, clusters arise sequentially and persist, so that at a given time there are several clusters at high prevalence. (b) For a short infection, the clusters are narrow and appear only for a short time before vanishing again. There is at most one cluster at any given time.

clusters distributed across strain space. Observations at any given time would show several distinct clusters.

A relatively *short* infection generates a contrasting pattern. The initial cluster formation is as before, but because disease turnover is high relative to that of the host, immunity accumulates until the initial cluster is in decline. Meanwhile, the same process of low-level mutation gives rise to increasingly distant strains until the cascade of increasing mutation and invasion leads to the establishment of the second cluster. This new cluster generates much broad immunity, ensuring that the first cluster does not return. This process repeats, and all strains are transient. The strains between clusters are never at a high level, so this pattern would be observed as a series of jumps, hopping along the linear strain space (Fig. 2*b*). The intermediate strains are as transmissible as the strains observed; there is no intrinsic reason for them not to infect the population. Only the occurrence of other strains has suppressed them.

The short-infection/long host-lifetime time scale parameters are chosen to mirror influenza in humans. The patterns shown here suggest that ongoing influenza drift depends on long-lived immune memory in host, orders of magnitude longer than the infectious period. The line was chosen as the simplest strain space, and even for this basic system, the patterns are reminiscent of influenza drift (18). In addition, the tendency for strains to occur in clusters reflects observed influenza dynamics (20). We have shown how a sequential clustering pattern can be the product of a purely deterministic process and the crudest assumption about strain space.

Drift Speed. Another important question about influenza is how quickly the clusters progress. The time between successive clusters is dictated by the two processes that underly strain space. The time between peaks depends linearly on the width of cross-immunity between strains. The speed of mutation between immediate neighbors depends on the mutation parameter, but in a more complex way. Techniques developed for disease models in geographical space (27–30) can be adapted to address this

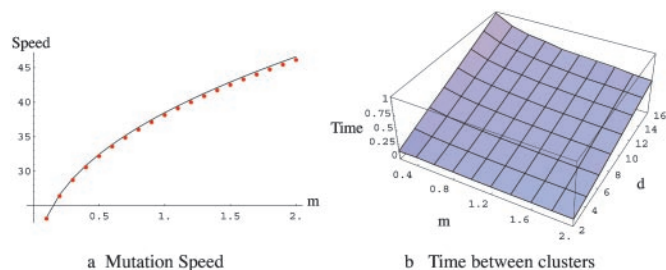


Fig. 3. Drift speeds and intercluster period. (a) The speed of mutation between individual strains (with no cross-immunity). The red points give numerical results, whereas the solid curve shows the suggestion of the linear conjecture (see *Appendix*). Numerical results are given from finding a linear fit in time to the mean strain over the number of infecteds. (b) The time taken between clusters as a function of crossimmunity width, d , and interstrain mutation rate, m .

issue for strain space. Analysis of a linearized system can give us an upper bound on the drift speed as a function of mutation rate. An analogy with the linear conjecture (29) for spatial disease spread suggests this minimal linear speed is the actual speed of the pattern that the full nonlinear system settles to, and indeed this is in excellent agreement with numerical results (Fig. 3*a*). See *Appendix* for further details.

Both the speed of mutation between strains and the distance between clusters will depend on the basic disease parameters, reproduction ratio and infectious period, and host birth/death rate. Overall, the time between successive clusters increases with broadening cross-immunity and decreases with increased mutation rate (Fig. 3*b*).

Two-Dimensional Strain Space and the Dynamics of Side Branch. The phylogenetic tree constructed for the hemagglutinin gene in circulating influenza is characterized as having a long trunk with short-lived side branches (18). The dominant strain gradually accumulates mutations over the years, but short side branches can persist for a few years before vanishing. One can imagine several ways in which these patterns may be generated. One suggestion is that changes along the short branches represent deleterious mutations. These viruses are somehow less fit, and immunity will eventually drive them out (31). To see whether this proposed behavior is supported by our model, we turn to our final question: What happens if there are two directions of mutation, one always leading to a less transmissible virus?

To this end, we use 2D strain space. It is much like that of the previous section, except that instead of a line, we now have a grid of strains. We use 50×15 strains. Each strain can mutate to adjacent strains but not diagonally, and distance in terms of cross-immunity is the sum of horizontal and vertical distances. The cross-immunity distance scale d is now 3, so this corresponds to a coarser strain space than in the previous section. Transmissibility, β , varies in one direction of strain space and is constant in the other direction.

Fig. 4 shows the dynamics after initiating the system with the strain in the front-left corner. Strains further into the y direction have decreasing β . As time increases, we see the dominant strain move along the x axis in a jumpy fashion, although not as marked as for the fine linear strain space. Strains deeper into the y axis do arise but lag behind the dominant strain and at a lower prevalence. We see a wave moving in the x direction, with a tail sweeping back in the y direction.

The general direction of mutation is along the direction that is neutral in terms of fitness rather than in the direction of decreasing fitness. Once this wave has moved past a given x value, less-fit strains can take advantage of their slight immunological differences to evade existing host immunity. The strains may be

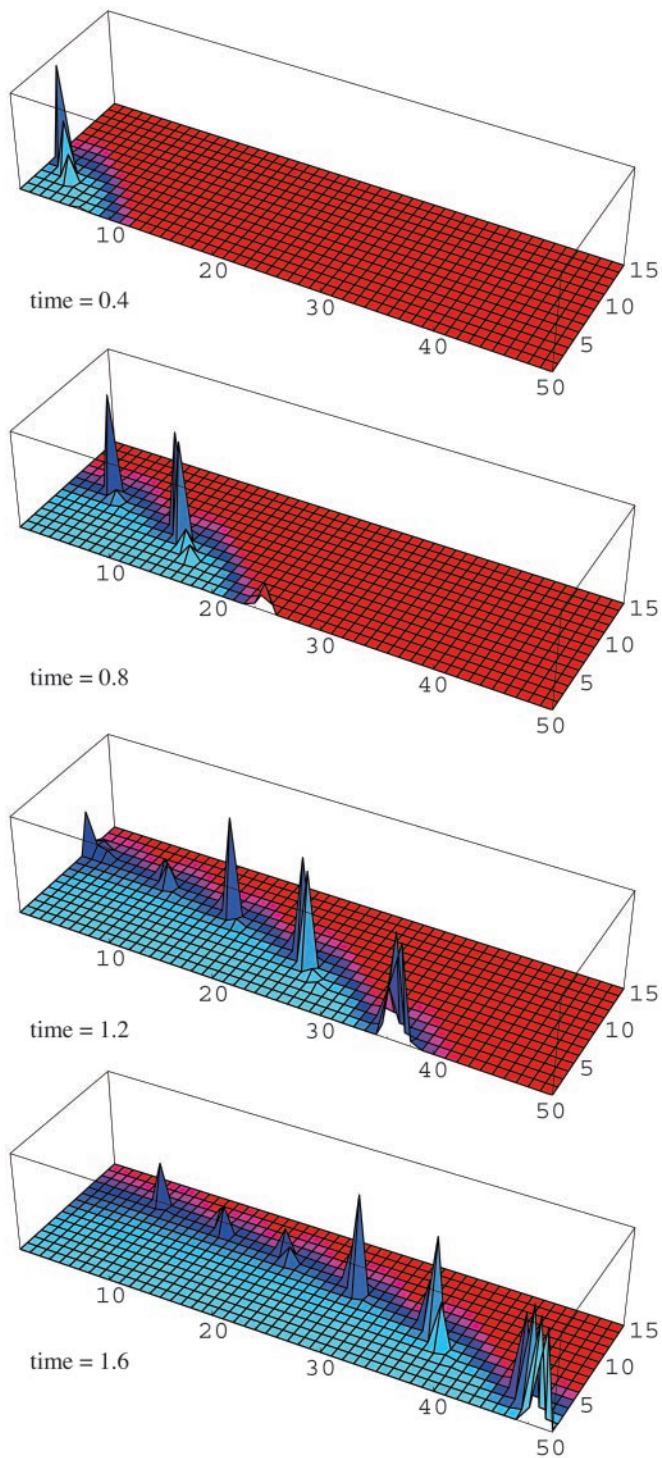


Fig. 4. A 2D strain space. The strain space is a 50×15 grid. The strains nearer the front of the 15 are more transmissible. All hosts start susceptible, $\nu = 52$, $m = 0.02$, $\mu = 1/80$, and β ranges linearly from 5ν to 1ν in the y direction over strain space. The height gives the number of infected; the color blue indicates high immunity to that strain, and red indicates high susceptibility. Each grid point corresponds to one strain. Initially, the system is started with some hosts infectious with the strain in the front-left corner, and the four pictures are sequential snapshots. The general progression is in the x direction, with a tail lagging behind and swinging out into the y direction.

less transmissible, but they can now be infectious in relatively more hosts. The advantage is gained only through the current immune state of the host population.

This example, albeit very simple, demonstrates how an inherently weaker strain can have an advantage that allows it to persist for a short time, slightly after a closely related fitter strain. This model gives a plausible mechanism contributing to the observed influenza phylogenetic pattern of short side branches, but it is of course not the only possible explanation.

In this strain space, a single dimension was given to neutral mutation, because the focus was on side branches. A wider problem is to explain the overall shape of influenza phylogenetic trees. Why is there a single trunk, evolving in time? It will be necessary to develop more complex detailed strain spaces to address this important problem in influenza dynamics.

Discussion

Model Development. The model presented in this paper offers a solution to the problem of the exponential increase in the number of variables as we increase the number of strains. The key is to combine polarized immunity, the status-based approach, and cross-immunity modeled as reducing transmission. All three of these elements are necessary for the number of variables to be reduced to $2n$ if there are n strains. History-based models immediately imply a large number of host classes. Polarized immunity is needed, because many different immunity levels increase the complexity of the model, as observed in ref. 17. It is possible to make a similar model with intermediate levels of immunity, and polarized immunity gives the simplest extreme, with only two immune states: totally immune or susceptible. Finally, reduced transmission is needed so a host's state with respect to one strain can vary independently to its immune status with respect to all other strains, hence the host status can be decomposed into one element per strain. Immunity to one strain does not stop it from affecting immunity to other strains in the future.

We expect most of the dynamics of the many-strain model used here to be generic, i.e., not highly sensitive to simplifying assumptions. An extensive treatment of a range of possible four-strain systems is given by Dawes and Gog (21). In the special case of four strains, the known differences are patterns of persistent cyclic behavior of order host lifetime, which did not occur in the models with polarized immunity (21). Extrapolating to models of many strains, we expect our model to be less likely to have sustained slow oscillations than history-based systems. Testing the dynamics consequences of our many-strain model's assumptions is by definition a difficult task, because more complex models generate a formidable proliferation of variables. One possibility for future work is to focus on important regions of the dynamics, once identified by using our model. For example, more biologically rich 10-strain models could be used to look at cluster generation in the linear strain space.

Although models for antigenic variation in infectious diseases are still in development and evolution, models of the spatial dynamics of disease are well established and have been extensively studied and analyzed. Above, we drew on this extant spatial theory to apply antigenic drift speeds. It is likely there are further parallels to be made between modeling tools and methods in strain and physical space.

To summarize the model development in this paper, the system presented here represents the currently most parsimonious model capable of handling many strains. In addition, other studies have shown how different strain models relate to each other. It is important to continue this mathematical approach to examine the impact of alternative assumptions, which will be of value in either refining the model or lending weight to existing formulations.

Strain Dynamics. This population model allows us to explore the dynamics of many-strain systems, particularly influenza in humans. We presented two simple example systems to consider two

questions. In the first application, we show how not all “good” strains will necessarily appear, and in the second we show how “bad” strains can arise transiently. The relative length of host lifetime, and therefore effectively host immunity, can influence the patterns of coexistence. Long-lived immunity will tend to reduce the range of strains in circulation to, at most, one at a time.

A recent study has shown that observed sequences of the influenza hemagglutinin gene aggregate into clusters, and the location of variation can be correlated with known antigenic sites (20). Even in the simple linear strain space investigated, our model reproduces this tendency to cluster. It is striking that this occurs even without seasons or geographic space in the system, and that a stochastic formulation is not necessary for this behavior. However, the model is simple enough for spatial, seasonal, and stochastic effects to be incorporated.

Processes behind strain selection occur at a number of levels, from single hosts to populations. Models of within-host dynamics and individually-based models offer routes to explore these different scales, which are complementary to the population approach introduced here. Connecting different scales will add to the global picture of pathogen evolution.

The results of the linear strain space for short infection are tantalizingly like observed influenza dynamics, and one would expect this drift-like behavior to persist in more complex spaces. We reemphasize the importance of characterizing the strain space of influenza, although one caution we can offer from the investigations presented here is that strains that circulate widely may not be representative of the whole possible strain/shape space. The process of building influenza strain space from randomly sampled influenza in humans may not reconstruct the gaps. This subset bias could lead to a suggested strain space of too small a dimension or unsuitable geometry, which may become apparent as conditions change, such as vaccination or antiviral drug usage. Ideally, then, it would be desirable to have a more complete picture from one season or one outbreak. To this end, intensive sampling with antigenic and sequence analysis for a short period, with vigilance for strains that occur at low levels would be invaluable for building reliable models to gain deeper insight into strain dynamics.

Appendix: Wave Speeds

Here we describe a simple strain space in the form of a line. Simulations show how the prevalent strains move along the line with time. The system is given by:

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$$\dot{I}_i = \beta S_i I_i - \nu I_i - \mu I_i + m(I_{i-1} - 2I_i + I_{i+1})$$

$$\dot{S}_i = \mu - \sum_j \beta S_i \sigma_{ij} I_j - \mu S_i.$$

Adapting a technique used for spatial models of infectious disease (25, 27–30, 32), we linearize about $S_i = 1$:

$$\dot{I}_i = \beta I_i - \nu I_i - \mu I_i + m(I_{i-1} - 2I_i + I_{i+1})$$

and look for solutions of the form

$$I_i = e^{\lambda(ct-i)}.$$

These are exponential curves, with exponent λ , moving off to the right with speed c . Substituting this into the linearized equation gives that these are solutions when

$$c = \frac{\beta - \nu - \mu + 2m(\cosh \lambda - 1)}{\lambda}.$$

Because $S \leq 1$, the linearized, \dot{I}_i is always greater than or equal to the full nonlinear \dot{I}_i . If it is possible to bound above a nonlinear solution by an exponential initially, then the linear solution will always stay above. Hence, the nonlinear solution cannot overtake the linear solution. The nonlinear wave speeds must be slower than all the possible linear speeds. Hence, the minimal linear speed provides an upper bound for the nonlinear solution (subject to it being exponentially boundable initially):

$$C_{\min} = \min_{\lambda} \left\{ \frac{\beta - \nu - \mu + 2m(\cosh \lambda - 1)}{\lambda} \right\}.$$

On the other hand, if the front end of the nonlinear solution is sufficiently antigenically distant from the action, most hosts are susceptible to the new strains at the front; it could then be argued that the tail should be moving at a linear speed, hence the linear conjecture suggests C_{\min} as the actual speed of a nonlinear wave (25, 27–30, 32). C_{\min} is plotted as a function of m in Fig. 3a. Numerical results show good agreement for the ranges of parameters explored; however, it is possible that a very broad cross-immunity will mean that the wave speeds will be reduced as the argument above does not hold; this is subject to further investigation.

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