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Pathogen evolution and the immunological niche

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Host immunity is a major driver of pathogen evolution and thus a major determinant of pathogen diversity. Explanations for pathogen diversity traditionally assume simple interactions between pathogens and the immune system, a view encapsulated by the susceptible–infected–recovered (SIR) model. However, there is growing evidence that the complexity of many host–pathogen interactions is dynamically important. This revised perspective requires broadening the definition of a pathogen's immunological phenotype, or what can be thought of as its immunological niche. After reviewing evidence that interactions between pathogens and host immunity drive much of pathogen evolution, I introduce the concept of a pathogen's immunological phenotype. Models that depart from the SIR paradigm demonstrate the utility of this perspective and show that it is particularly useful in understanding vaccine-induced evolution. This paper highlights questions in immunology, evolution, and ecology that must be answered to advance theories of pathogen diversity.

Keywords: infectious diseases; host–pathogen interactions; phylodynamics; evolutionary epidemiology; niche theory; viruses; bacteria; influenza

Introduction

Pathogens comprise an extraordinarily diverse and rapidly evolving community of organisms, including viruses of several thousand base pairs to trypanosomes of 10^4 genes. Pathogens' large population sizes, relatively fast generation times, and cosmopolitan methods of varying their genomes make them opportune study populations in which to test ecological and evolutionary models.[1–4]

Since an organism's fitness is defined by its environment and a pathogen's environment is usually its host, it stands to reason that pathogen fitness—and hence pathogen evolution—is best understood in the context of interactions with the host. These interactions include pathogen exploitation of the host as a resource for replication and transmission, as well as antagonism between the host and pathogen via the host's immune system.

In this article, I argue that these immune-mediated interactions are a major force shaping pathogen evolution, although there is much about them that is not understood. To bridge the gap between immunological observations and models of pathogen evolution, I introduce the concept of the pathogen's *immunological phenotype*. Expanding classic models of pathogen competition to include more realistic aspects of host–pathogen interactions, such as the simultaneous influence of specific and nonspecific responses of different strengths and durations, increases the breadth of phenomena that can be explained and demonstrates the importance of these interactions for anticipating the evolutionary impacts of vaccines. I argue that progress in this field awaits both empirical and theoretical advances.

Host immunity shapes pathogen evolution

The diversity of pathogens reflects strong and enduring selection to escape host immunity. Escape takes several basic forms. For example, many pathogens have evolved strategies to limit immune detection or to manipulate the immune response to their advantage; selection for these traits is generally purifying. A related approach is variation in appearance to avoid recognition by adaptive immunity; positive selection of this form can sometimes be

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Box 1. A primer on host defense

Immune systems have evolved, at great cost, partly to attenuate the impacts of pathogens on host fitness.[142,143] In vertebrates, they accomplish this goal by reducing the growth rates of pathogen populations through innate and adaptive mechanisms.[57] This description focuses on human immunity, although analogues exist to the prokaryotic level.[144]

Innate immunity includes the activities of the complement system, phagocytes, and natural killer cells. The complement system marks and eliminates pathogens by recognizing surface carbohydrates. Neutrophils, dendritic cells, and macrophages kill bacteria through phagocytosis. Natural killer cells that have been activated by cytokines destroy cells that have been recognized as infected by their low levels of MHC class I expression.

Adaptive immunity consists of two arms: cell-mediated and humoral. Cell-mediated immunity is marked by the proapoptotic activities of $CD8^+$ T cells and other cells that promote the destruction of intracellular pathogens. $CD8^+$ T cells detect peptides presented by MHC class I molecules on cell surfaces. Antibodies, which are generated by the B cells of humoral immunity, enhance the activities of other immune cells and can neutralize extracellular pathogens directly. The antigenic phenotype of a pathogen is defined by interactions with adaptive immune responses, and the sites of interactions with T cells and antibodies are known as epitopes.

There is extensive communication and interaction between the different branches of the immune system, such that many cell types and factors affect both the innate and adaptive components.[57] Direct interactions between components of the immune system and pathogens may be neutral to antagonistic,[145,146] but some pathogens, like HIV and Epstein–Barr virus, directly benefit from the proliferation of certain immune cells.[147–150]

observed over short timescales. These forms of escape partially explain the different patterns of evolution among pathogens, although a challenge is to identify where phenotypic change may be limited by functional constraints.

Avoidance and suppression

The immune system mounts a multifaceted attack on infectious agents (Box 1). Predictably, pathogens have developed ways to reduce detection by some forms of immunity. Suppression of the immune response is also common. These strategies are usually described as fixed traits of the pathogen, implying that they are strongly conserved.

Mechanisms to evade the immune system are diverse.[5] For example, *Streptococcus pneumoniae*, *Klebsiella pneumoniae*, and other bacteria possess polysaccharide capsules that reduce susceptibility to phagocytosis.[6–8] *Staphylococcus aureus* and *Treponema pallidum* use surface proteins to aggregate host antigens on their surface.[9,10] Many pathogens replicate in ways that minimize interaction with the immune system.[11] Influenza quickly infects and replicates in respiratory epithelial cells, limiting the window of exposure to $CD8^+$ T cells and antibodies.[12] In contrast, after infecting keratinocytes, human papillomaviruses have exceedingly low expression levels and thus avoid detection until they begin replicating inside cells that are about to be shed.[13,14] Replication of HIV in macrophages requires several proteins to mask its activities.[15]

Avoidance is frequently accompanied by suppression. Influenza infection depends critically on viral suppression of type I interferon, a trait conferred by influenza's nonstructural protein 1.[16,17] *Streptococcus pyogenes* and *S. aureus* secrete compounds that inhibit neutrophil chemotaxis.[18] More invasive forms of manipulation occur in chronic viral infections.[19] Cytomegalovirus produces a mimic of interleukin (IL)-10, an immunosuppressive host cytokine that inhibits the production of other cytokines and expression of major histocompatibility complex (MHC) class I and II molecules.[20]

There has been relatively little investigation of the evolutionary dynamics of evasion to nonspecific components of host immunity. Numerous studies have shown that the removal of avoidance-associated genes is lethal,[17,21,22] which is consistent with the idea that these traits are under purifying selection. But it is interesting to speculate that the

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Table 1. Several pathogens infecting humans, for which positive selection on immune phenotype has been demonstrated

Pathogen	Variable target	Induced response	Sample references
Viruses			
Influenza	Surface proteins hemagglutinin and neuraminidase	Antibodies, $CD8^+$ T cells, $CD4^+$ T cells	Refs. 44, 157, and 158
Hepatitis C	NS3 and NS5A regions	$CD8^+$ T cells	Ref. 42
Norovirus	Surface proteins	Antibodies	Ref. 33
HIV	Gag protein gp120	$CD8^+$ T cells, antibodies	Refs. 35, 40, and 159
Rhinovirus	Surface proteins	Antibodies	Ref. 160
Rotavirus	Surface proteins VP3 and VP7	Antibodies	Ref. 161
Bacteria			
Streptococcus pneumoniae	Polysaccharide capsule, subcapsular protein antigens	Antibodies, $CD4^+$ T cells	Refs. 32 and 85
Neisseria meningitidis	PiLE pilus protein	Antibodies	Refs. 162
Protozoa			
Plasmodium falciparum	PfEMP1	Antibodies	Ref. 48
Trypanosoma spp.	Surface glycoprotein VSG	Antibodies	Ref. 163

costs of evasion, such as the potential induction of autoimmunity,[23] might create directional selection or balanced polymorphism in complex immunological environments.

Changing appearance

Many pathogens avoid specific immune memory by varying their appearance to the adaptive immune system. These pathogens show an array of patterns of positive diversifying selection at epitopes targeted by antibodies and $CD8^+$ and $CD4^+$ T cells (Table 1).

This variation can exhibit complex spatiotemporal patterns.[8] Influenza viruses infecting humans display two general patterns of antigenic diversity.[24] The dominant surface protein hemagglutinin undergoes rapid turnover in all major lineages: type A (subtype H3N2), A (H1N1), and both lineages of B (B/Victoria and B/Yamagata).[24,25] For each major lineage, the most recent common ancestor arose less than 10 years before the present, and often much more recently.[24,26] This turnover is driven by point mutations and the addition of N-linked glycosylation sites, which confer escape from prevailing antibodies.[27–30] These lineages stably coexist at the global level despite competing for hosts, although influenza A subtypes occasionally drive each other extinct. Other pathogens, including *Neisseria meningitidis*,[31] *S. pneumoniae*,[32] noroviruses,[33] HIV,[34,35] enteroviruses,[36] *Plasmodium*,[37] and trypanosomes,[38] demonstrate positive selection in sites targeted by antibodies.

Positive selection to escape specific T cell memory occurs conspicuously in fast-mutating pathogens that establish persistent infections, and it may also influence the evolution of acutely infecting pathogens. Rapid adaptation to host MHC alleles occurs in the early stages of infections with HIV[39,40] and hepatitis C virus (HCV), although strains adapted to heterologous alleles can be found when transmission occurs rapidly, relative to the timescale of infection.[41] In a chimpanzee model of HCV infection, increases in viremia correlated with the appearance of amino acid mutations conferring $CD4^+$ T cell escape.[42] Influenza A (H3N2) may also experience positive selection for escape from $CD8^+$ T cell epitopes.[43,44]

Weak selection and functional constraints

Since host immunity has such a large impact on host fitness, it is puzzling that antigenic variation isn't more common. Pathogens' strategies to evade immunity suggest two explanations. The first hypothesis is that adaptive immunity has a relatively small impact on pathogen fitness. *Mycobacterium tuberculosis*, which causes tuberculosis, is a widespread intracellular bacterial pathogen that partially escapes adaptive immune responses to establish dormant infections.[45] It appears to undergo mostly strong

purifying selection, with the few selective sweeps not clearly related to immune escape.[46] Similarly, the ability of herpesviruses to establish latent infections, inhibit MHC presentation, and move directly between cells could reduce selective pressure to escape from antibodies and $CD8^+$ T cells. In these cases, escape from specific immune memory may not affect fitness or, if immune pressure is weak, escape phenotypes may be slow to evolve.

The second hypothesis is that functional constraints limit antigenic diversity. Exposed elements of the pathogen capsules are not only potential antibody targets but are also usually involved in host cell receptor tropism or other traits.[47] For example, the multigene *var* family of *Plasmodium falciparum* encodes the surface protein PfEMP1, which induces immunodominant antibody responses and mediates cytoadherence, a major factor in pathogen survival and virulence.[37] This sequential expression of diverse surface antigens might result from the interplay of selection to avoid immunity and the need to transmit to partially immune hosts.[48] Another pathogen that appears not to demonstrate variation in immune-escape phenotype is measles. The lack of variation is surprising considering that as an RNA virus, measles has a relatively high mutation rate, and it is also easily transmitted among unvaccinated hosts.[1] The basis of its lack of antigenic variability is poorly understood. A few epitopes could be immunodominant and evolutionarily constrained, or the immune response may be so polyclonal that simultaneous escape mutations at all epitopes is unlikely.[49]

Pathogens may eventually evolve to escape these functional tradeoffs. For example, the regions of the influenza hemagglutinin that are under strong positive selection in humans tend to be near the receptor binding site, which enables viral entry into the host cell. Many mutations in this area interfere with binding or with the complementary function of the neuraminidase protein.[50] Influenza may have developed ways to mitigate these costs: the receptor binding site is recessed in hemagglutinin, and an offset protruding loop or hypothesized decoy epitopes could induce immunodominant responses that are less apt to be neutralizing.[51] Phylogenetic analysis suggests that even the oldest proteins have not yet fully explored genotype space.[52] Since protein fitness landscapes appear rugged,[53] current truisms (e.g., that measles is antigenically trapped, that a vaccine-induced antibody neutralizes circulating viruses) may not be robust. Hard-to-predict epistatic interactions should not of course be limited to influenza. They can be expected to shape the antigenic evolution of other pathogens.[54,55]

Interactions define a pathogen's immunological phenotype

The ways in which pathogens interact with host immune systems and in which immunity shapes pathogen evolution through purifying and positive selection are undoubtedly complex and incompletely understood. The concept of the pathogen's immunological phenotype can help bridge the gap between the complexity of these interactions and theoretical models of pathogen evolution.

The immunophenotype

A pathogen's immunological phenotype, or *immunophenotype*, is a dimensional reduction of the pathogen's interactions with different parts of the immune response. These parts differ primarily in the strength of their impacts on pathogen fitness. The lipopolysaccharides of Gram-negative bacteria, for example, directly activate macrophages and other innate immune responses but are not well neutralized by antibodies.[56] Viruses, which must replicate inside cells, tend to be suppressed by a combination of $CD8^+$ T cell–induced cell suicide and antibody-mediated neutralization.[57] The strength of each interaction quantifies its impact on pathogen fitness, which can be defined by the pathogen's within-host growth rate or the infected host's ability to infect another host.

With strength, the duration and breadth of interactions define the immunophenotype. The duration of the pathogen's impact on host immunity ranges from relatively short surges of innate cytokines that last for hours to days[58,59] to the establishment and reactivation of memory B cells, which may persist for the lifetime of the host.[60] The breadth captures the extent to which each form of immunity is shared with other pathogens. As described later, this trait may be defined in different ways.[61]

As a low-dimensional approximation, a pathogen's immunophenotype can be imagined to occupy some region in a space defined by the strength, duration, and breadth of its interaction with the immune system (Fig. 1A). These interactions

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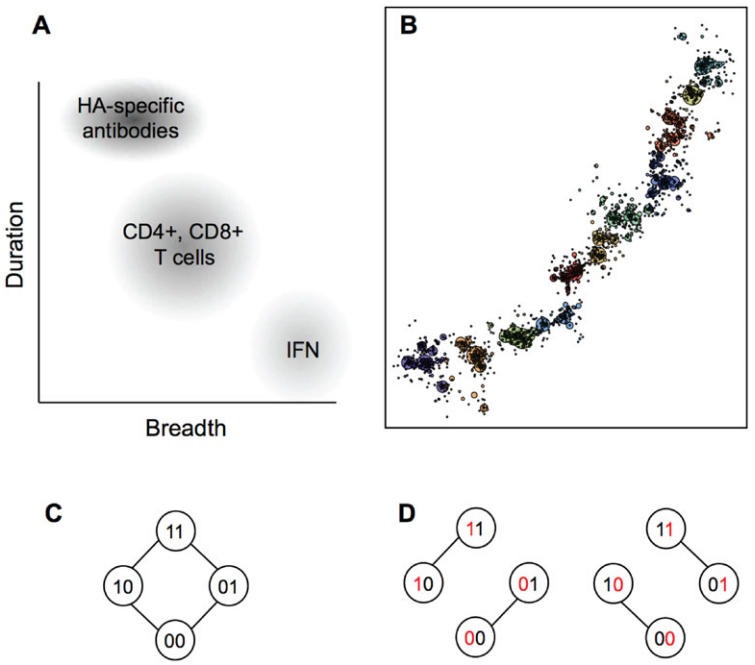

Figure 1. Four views of a pathogen's immune phenotype. (A) The approximate strength, duration, and breadth of influenza virus's interactions with three major components of host immunity. The strength of the response, measured by its impact on fitness, is illustrated by the darkness of the shading. (B) The antigenic evolution of a simulated influenza virus population, collapsed into two arbitrary antigenic dimensions (principal components), from Ref. 100. (C) Network of shared epitopes of a population of four pathogen strains, each with two potential alleles at each of two loci. No population substructure is apparent. (D) Networks of realized relationships for two individual hosts. One host has developed immunity or is restricted (e.g., by MHC) to developing immunity to the first locus, and the other host to the second locus. Each host views a structured population of two phenotypes, but these population structures vary between hosts.

describe the pathogen's role in the community of immune factors and other pathogens, and hence the immunophenotype encompasses several of the definitions of the concept of the ecological niche.[62] Following mathematical niche theory,[63–65] the immunophenotype P of a pathogen p in host H in a pathogen community C can be formalized as:

$$\boldsymbol{P}\left(p, \boldsymbol{H}, C\right) = \mathcal{F}\left(\boldsymbol{R}, D\left(\boldsymbol{R}\right), B\left(\boldsymbol{C}\right)\right), \quad (1)$$

with the arguments of F corresponding to the strength, duration, and breadth of interactions, respectively. The host $\boldsymbol{H}$ is a vector defined by the abundances of h immune components, which may be individual cytokines or aggregated responses, such as polyclonal antibodies; $\boldsymbol{H} \in \{n_1, n_2, \ldots, n_h\}$. Each element in $\boldsymbol{H}$ can affect the growth of the pathogen and, in turn, be affected by the pathogen. These relationships are given by the impact and sensitivity functions,[65] which together define the population regulation variable $\boldsymbol{R}$. Variable $\boldsymbol{R}$ describes the dependence of growth rates of the pathogen and members of $\boldsymbol{H}$ on their population sizes, or the strength of host–pathogen interactions. The duration of these impacts is defined by function $D(\boldsymbol{R})$. This function could be a simple cutoff, such as the time for cytokine populations to decline from their maximum values in the presence of the pathogen to their values at pathogen-free equilibrium. The breadth of the response, $B(\mathbf{C})$, is analogous to the population regulation variable $\boldsymbol{R}$ of the pathogen p, except the community matrix $\boldsymbol{C}$ includes p as well as all other pathogens in the system. It can also be decomposed into impact and sensitivity vectors, which measure the impact of each pathogen on host immunity and thereby each other.

Representations of competitive interactions

The breadth of each response is a window into the pathogen's competitive interactions, mediated

indirectly through the host. At one extreme are pathogens that induce less specific responses: to the innate immune system, these pathogens look alike, and competition may be broad. At the other extreme are pathogens that induce more specific responses, such as influenza (Fig. 1B). Hemagglutination inhibition (HI) assays measure the ability of polyclonal antibodies induced by infection with one influenza strain to prevent the same or a different strain from binding to erythrocyte receptors similar to receptors on respiratory epithelial cells. Antibodies specific for one virus that bind well to another virus, thereby preventing agglutination of the erythrocytes, indicate a short antigenic distance (high cross-reactivity) between the two viruses. Techniques adapted from multidimensional scaling visualize strains' antigenic relationships from the HI data.[66,67] HI assays correlate well with more advanced measurements, despite the fact that these assays cannot detect neutralization by stalk antibodies that inhibit intracellular conformational changes.[68,69] Although these representations are low-dimensional abstractions of binding patterns that miss, for example, asymmetric interactions,[70] they demonstrate a method to simplify complex patterns of cross-reactivity.

Between these extremes are pathogens that induce responses of intermediate cross-reactivity. Compared to the diversity of antibody-binding sites on influenza's hemagglutinin, epitopes of $CD4^+$ and $CD8^+$ T cells are relatively conserved,[71] and unlike influenza,[72] pathogens such as malaria, *Trypanosoma* spp., and *N. meningitidis* have a finite set of allelic variants of the surface proteins. For these targets of adaptive immunity, homologous epitopes induce cross-reactive responses. Such relationships can be represented as networks, with edges connecting strains that share identical epitopes (Fig. 1C).[73] In any individual host, a small fraction of these links may have the potential to be realized. For example, MHC restriction may prohibit certain epitopes from being recognized in hosts lacking a particular MHC allele, or the immunodominance of one response may interfere with the effectiveness of another.[74] Thus, the pathogens that hosts perceive as identical (at least with respect to their interactions with the immune system) or equivalently, the pathogens' phenotypic identities, vary depending on which individual host is reading it. The multi-degenerate mapping of genotype to phenotype can affect strain dynamics (Fig. 1D).[75]

Immunophenotypes vary and change

The immunophenotype may thus acquire different meanings in individuals and host populations, and its definition in each may change over time. Antibodies and $CD4^+$ and $CD8^+$ T cells induced by infection target a set of pathogen epitopes, but immunodominance can shift.[76,77] Depending on a host's infection or vaccination history, the immune response may focus on more or less conserved epitopes, creating individual differences in the breadth of the induced response.[78,79] Very young, old, or immunocompromised hosts may mount weaker responses, causing shifts in strength over time.[80]

These differences may partly explain challenges in measuring the impact of immunity on pathogen fitness. Some induced immune responses have no perceivable effect on the growth rate of the pathogen population. For example, serum antibodies from natural carriage with *S. pneumoniae* appear uncorrelated with protection from colonization in some adults,[81] although in others, they can be associated with protection from rechallenge up to 11 months after experimental infection.[82] Multiple approaches may be necessary to characterize interactions. Longitudinal observational studies and vaccine trials correlate protection with immune factors.[83–85] Challenge experiments demonstrate reductions in susceptibility or infectiousness (measured through shedding rates) as a function of immune correlates, typically antibody titers.[86] Genetic knockout and depletion experiments can demonstrate the aggregated direct and indirect causal impact of particular components of immunity on pathogen fitness,[87] although inferences from these studies are usually limited by the fact that the animal model is not a natural host of the pathogen. In the next section, I will describe how models fitted to observational data, especially involving vaccination, can provide another source of insight into host–pathogen interactions.

Theories of immune-mediated pathogen evolution

Although there have been notable exceptions,[88] especially for within-host models,[89] variations of the susceptible–infected–recovered (SIR) model[90,91]

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(Box 2) have served as the major framework for understanding pathogen diversity and evolution. Recent departures from this model show that a more complex immunological niche, reflecting more complex host–pathogen interactions, can offer new explanations for pathogen diversity.

Evolution of the SIR model

Multistrain derivations of the classic SIR model[90,92,93] demonstrate surprisingly different outcomes from simple assumptions. For example, assuming that all strains of a malaria-like pathogen have the same fitness in a susceptible host population and vary only by which antigens (of a fixed repertoire) they express, antigenically structured populations with low or high diversity can result, depending on the transmission rates and strengths of cross-immunity.[92] Additionally, these structured populations can persist at a steady prevalence in time, maintain stable limit cycles, or undergo chaotic dynamics, with the latter scenarios reflecting stronger negative frequency-dependent selection. A key result in these models is that each set of co-occurring strains appears to minimize competition by minimizing antigenic competition or antigenic niche overlap: strains sharing fewer alleles tend to co-occur, a result that is broadly consistent with niche models of species diversity.[94] These kinds of models can also reproduce qualitative features, such as the incidence and periods of oscillations and of the dynamics of dengue,[95] cholera,[96] and trypanosomes.[97]

More recently, SIR models incorporating open-ended evolutionary dynamics have simulated immune-mediated competition and evolution in RNA viruses. A model of influenza that assumed one-dimensional antigenic trait space found that clusters of antigenically similar strains would arise and serially replace one another,[98] yielding patterns of strain turnover similar to those of H3N2 hemagglutinin.[28,67] Antigenic evolution in more dimensions generally shows that the extent of diversity is sensitive to the mutation rate, the mutational accessibility of antigenically distinct phenotypes, and the strength of competition between strains.[88,99–102] Highly accessible beneficial mutations can lead to antigenic branching,[100] a form of character displacement suggested in the recent evolution of the hemagglutinin of influenza B.[103] Strong competition between strains, potentially from nonspecific immune responses, can restrict diversity.[88]

A limitation of these models is uncertainty over the plausibility of the representation of phenotypic evolution. It is unclear what fraction of mutations should lead to antigenic escape and if these mutations should be costly. Some models have attempted to incorporate evolutionary constraints by tuning the ruggedness of the fitness landscape during the evolution of the immune phenotype, but there are little data to justify particular parametrizations.[30,101,104]

Uncertainty over evolutionary constraints and the strength of competition is a sticking point in these models of pathogen evolution. The presence of mutations that could, relative to the wild type, reduce fitness in a completely naive host population but might nonetheless be favored in a partially immune population implies that models of pathogen competition and evolution should accommodate variation in intrinsic fitness, or R_0, between strains or species (Box 2). Niche theory predicts that as niche overlap declines, competition decreases, and species with lower fitness more easily coexist.[94,105] From the perspective of the immune system, species that induce cross-reactive responses occupy overlapping niches and thus compete with one another. Low niche overlap might, for example, explain the coexistence of influenza B and influenza A subtypes.[106] Although H3N2 appears to have higher fitness than influenza B and H1N1,[24] observations suggest that low levels of cross-reactivity and hence weak competition between them[107] permit coexistence on a global scale.[88,106,108]

New mechanisms for coexistence and evolution

SIR models typically assume only one form of host immunity, and SIR models of multiple strains typically assume this form drives immune-mediated competition. If strains differ in intrinsic fitness, then coexistence between them should only be possible if they compete very weakly.[109,110]

The coexistence of dozens of serotypes of *S. pneumoniae*, or pneumococcus, seemed to violate this logic. Pneumococcal serotypes vary in fitness. They have unique polysaccharide capsules, which vary in their thickness and charge. The thicker serotypes are consistently associated with fitness-enhancing traits, such as resistance to nonopsonic

Box 2. The SIR model and its descendants

The original SIR model[90] assumes that host immunity can be described by three states: susceptible, infected, or recovered (immune). Hosts move into the infectious class from becoming infected and into the immune class upon recovery. The model has been extended to include many features, including seasonally varying transmission rates, latent periods, age-assortative mixing of hosts, and births and deaths in the host population. The intrinsic fitness of a pathogen is given by the intrinsic reproductive number, R_0, which equals the expected number of secondary cases caused by an infected individual in an otherwise susceptible population.[91]

The impact of immunity in SIR models has been investigated in two major contexts, multistrain competition and boosting and waning. Seemingly neutral multistrain SIR models can include competition in ways that bias toward particular outcomes.[151] Immunity to one strain may reduce susceptibility to, or accelerate clearance of, another, or infection with one strain may alter others' dynamics.[152–155] Waning and boosting are usually modeled by allowing individuals to pass through one or more immune states, which may be associated with reduced susceptibility and/or reduced infectiousness.[15,124,156]

phagocytosis, longer durations of carriage, and resistance to clearance by other co-colonizing types.[111,112] Initial simulations of interacting serotypes showed that to obtain diversity on par with observations, antibody-mediated immunity to the capsules had to be much more protective than is indicated by epidemiological studies.[85,110] Furthermore, traditional SIR models with strong cross-immunity generate dynamics inconsistent with pneumococcal carriage rates.[110,113]

Models that include another mechanism of acquired immunity—induction of $CD4^+$ T helper (T_H) 17 cells not specific to the capsule[114]—enable coexistence at plausible levels of antibody protection.[110] This noncapsule-specific immune response was assumed to be acquired incrementally and to reduce the duration of carriage of all serotypes; in teenagers and adults, serotypes take, on average, several weeks to clear.[115] In this model, the host population becomes a resource gradient bounded by two extremes: naive patches (infants) where the fittest serotypes with thick capsules consistently outcompete other serotypes, and highly immune patches (adults) where all serotypes have comparable fitness. In these latter patches, competition is effectively neutral. This expansion of the immunological niche, which includes the stabilizing effects of serotype-specific immunity and the equalizing effects of nonspecific acquired immunity, encompasses a small breadth of the diversity of host–pathogen interactions. The idea that species' distributions may arise from such a balance of stabilizing and equalizing mechanisms has been a recent focus of research in community ecology.[94,116]

Vaccine-induced evolution

An ideal vaccine provides complete protection from infection or disease against a pathogen population. To minimize the chance of vaccine escape, the vaccine would instill herd immunity in the host population, or the pathogen population would display no diversity with respect to the vaccine-induced immunity and would be unable to escape it. In practice, pathogens are diverse, and vaccines usually provide imperfect protection that differs from that induced by natural infection.[117] By changing the pathogen's immunological environment, vaccines can thus shape evolution.

Models of competing strains predict that vaccination against a subset of strains will increase the abundance of untargeted strains.[118,119] This pattern has been observed with influenza vaccines in poultry[120] and following the introduction of the pneumococcal conjugate vaccine, which induces antibody responses more protective than those from natural carriage.[85,121] In the United States, high vaccination rates in young children nearly eradicated the targeted serotypes and increased the abundances of the untargeted serotypes such that overall carriage rates have not declined.[122] This phenomenon has been named serotype replacement.[119]

When pathogens interact with multiple components of host immunity, vaccines can have particularly unexpected effects that depend on their mechanism of protection. Models of pneumococcal vaccination showed that *transient* serotype replacement might arise under two scenarios: when anticapsular immunity from the vaccine is lower than

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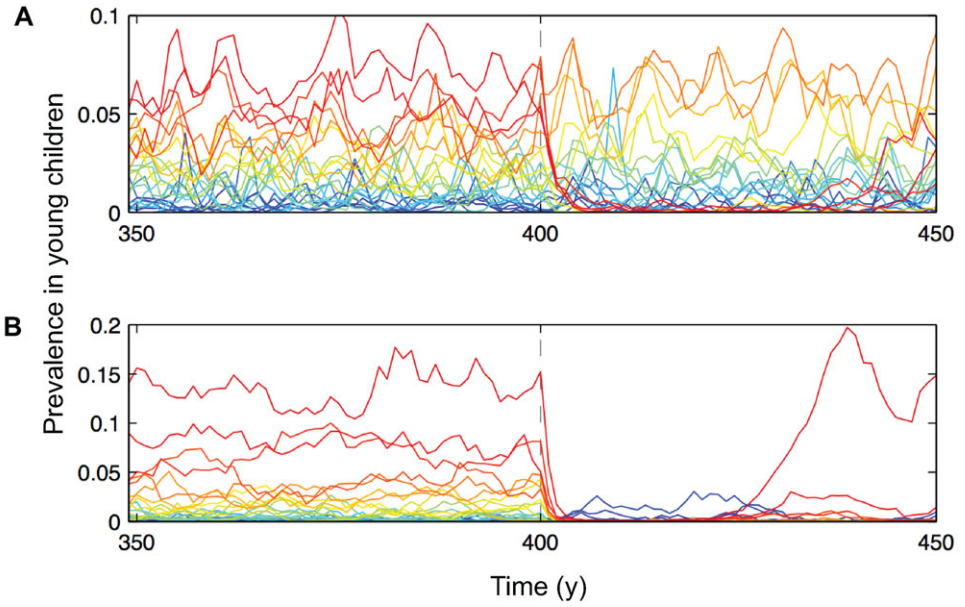

Figure 2. The potential effects of a multivalent vaccine on the evolution of pneumococcal serotypes depend on two mechanisms of immune interaction and differences between natural and vaccine-induced immunity. Natural immunity to pneumococcus includes serotype-specific (antibody-mediated) and nonspecific ($CD4^+$ T cell–mediated) components. Vaccine-induced immunity confers antibody protection only. Acquired serotype-specific immunity from natural carriage is assumed to reduce susceptibility to future colonizations with that serotype by a fraction σ_c (with $\sigma_c = 1$, implying complete protection; estimates are $\sigma_c \sim 0.3$–0.6). Figures show the prevalence of each serotype in pre- and postvaccine eras. Simulations assume 100% of the population is vaccinated beginning in the year 400.[110] (A) Vaccine-induced serotype-specific immunity σ_v is slightly weaker than natural serotype-specific immunity σ_c ($\sigma_c > \sigma_v$). Some of the targeted serotypes (red) return a few decades following vaccination. (B) Vaccine-induced serotype-specific immunity is stronger than natural serotype-specific immunity ($\sigma_c < \sigma_v$). A vaccine with high valency can allow targeted serotypes to return due to the gradual loss of nonspecific immunity.

anticapsular immunity from natural carriage, and also when it is higher.[110] In both scenarios, targeted serotypes disappear following the introduction of the vaccine, but they can later invade (if introduced through immigration) and cause an epidemic.

In the first scenario, vaccine-induced immunity temporarily eradicates targeted serotypes even when the immunity conferred by vaccination is weaker than that from natural carriage (Fig. 2A). The eradication arises from a net increase in the level of anticapsular immunity in the population due to widespread vaccination on top of natural immunity. After the targeted serotypes go locally extinct, anticapsular immunity in the population decays to levels provided by the vaccine. A lack of herd immunity can cause targeted serotypes to reinvade.

In the second scenario, even when vaccine-induced anticapsular immunity is stronger than natural anticapsular immunity, serotype replacement can be transient due to the waning of acquired nonspecific immunity in the population: natural infection induces nonspecific immune memory but the vaccine does not. This erosion of nonspecific immunity can also allow targeted serotypes to return if anticapsular immunity is imperfect (Fig. 2B). Related dynamics might underlie the recent resurgence of pertussis. Usage of the cellular vaccine was discontinued when an acellular vaccine associated with fewer side effects became available. Immunity conferred by the acellular vaccine is shorter lasting, which has led to an increase in cases.[123] This effect may have been amplified by the waning of natural immunity during the era of the cellular vaccine from the absence of asymptomatic boosting infections.[124]

The concept of the immunophenotype illustrates how a successful vaccination campaign against one pathogen may affect competing pathogens in unexpected ways. A randomized controlled trial found that rates of respiratory illness were higher in individuals who received the inactivated influenza

vaccine than in unvaccinated individuals,[125] suggesting that natural infection with influenza may partially protect against infection with other respiratory pathogens (and may promote others[126]). The absence of known cross-reactive antigens between the different pathogens suggests that this protection is conferred by innate immunity or is specific but concentrated in infected tissues. Such a result raises the hypothesis that receipt of the live attenuated vaccine, which induces cellular as well as humoral immunity, may protect broadly against respiratory viruses. Similar issues arise with respect to vaccination against individual strains of influenza.[127,128] If most competition between influenza types and subtypes comes from cellular or innate immunity, then protection against all influenza may be best conferred by vaccines that mimic natural infection rather than inactivated vaccines, which currently generate only strain-specific antibodies.[107,129]

Questions for a general theory

Advancing models of immune-mediated pathogen evolution requires progress on empirical and theoretical questions. The most pressing empirical questions are: How do different pathogens interact with host immunity, and how do these interactions vary within host populations? Immunity to several common pathogens has been heavily studied (Table 1), but the strength, duration, and breadth of most host–pathogen interactions have not been systematically analyzed, and even the heavily studied pathogens retain mysteries. Progress in this direction could arise from animal experiments and from examining homologous pathogens of nonhuman hosts.[130,131] Observational longitudinal analyses of antibody repertoires[76,132–134] and other immune responses, especially when accompanied by infection history, will be especially useful for revealing differences between individuals and test predictions from animal experiments. Inferential population genetic and phylodynamic models that include phenotypic information can shed further light on how pathogen diversity arises from evolutionary pressures.[24,135,136] A more complete picture of the immunophenotype should help predict vaccine efficacy and the potential for vaccine-induced evolution.

The largest theoretical challenges echo basic questions in ecology and evolution. First, how many pathogens can coexist in a host population described by a particular set of resources (e.g., tissue types) and immune environment? This is closely related to the question of limiting similarity in ecology: How similar can species be and still coexist?[137] Dynamical models of interacting species in environments of varying complexity[138] and analytic insights[63] could be feasible. Second, will pathogens' evolutionary constraints in avoiding immunity persist indefinitely? In other words, how robust are any conclusions about phenotypic tradeoffs and the accessibility of new traits? The evolution of resistance to neuraminidase in H1N1 viruses required the accumulation of permissive mutations whose importance had not been anticipated.[139] Such concerns about the generalizability of molecular evolution have motivated criticisms of the utility of gain-of-function experiments in influenza viruses.[112] Progress in this area may first come from massive experimental evolution studies in simpler systems,[140] which might reveal whether predictive models are feasible, or possibly from fitting models to well-sampled pathogen populations.[30,141]

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Conflict of interest

The author declares no conflicts of interest.

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