Reservoir and Transmission Dynamics of Multistrain Bacterial Pathogens

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Abstract

Flexible and extensible complex mathematical models provide an *in silico* laboratory for testing ideas about the factors that scale from individuals to populations and affect policy. Here we present a model of transmission and resistance applicable to *Streptococcus pneumoniae* and other clinically important bacteria that commonly colonize hosts and only occasionally cause disease. For these opportunistic pathogens, the colonizing bacteria (but usually not the bacteria in an infection) constitute the reservoir of contagion. Even as medicine focuses on managing invasive disease, public health and policy must also consider the reservoir dynamics that drive vaccine-induced strain replacement and the evolution of resistance to antibiotics. Our new Markov-chain model shows the reservoir and transmission dynamics of colonizing bacteria simultaneously considers several biological phenomena, including differences in the transmissibility, invasiveness, immunogenicity, and persistence of strains; strain-specific, cross-, or strain-transcending immunity; simultaneous colonization with multiple strains with no strain interaction, and with direct inhibition and competitive dominance; bacterial population responses to drug treatment and the evolution of drug resistance; and changes in immunity that are related to the host's age. These factors have been identified as potentially important for bacterial reservoir dynamics and thus for policy. The effects of these biological factors on policy can be evaluated within our flexible framework.

Introduction

Streptococcus pneumoniae is a leading cause of morbidity and mortality of under-5 year-olds, causing an estimated 700,000 to 1 million child deaths each year [1]. Before the introduction of the pneumococcal conjugate vaccine, invasive disease was managed primarily by antibiotic therapy, with little attention to or understanding of the reservoir dynamics of the disease. With the vaccine and the additional possibility of preventing disease and even reducing transmission, significant changes in the ecology of *S. pneumoniae* were observed [2,3]. The lack of clarity on the short- and long-term implications of these changes on the dynamics of disease transmission and drug resistance is a significant barrier to developing tools to reduce the burden of disease.

Understanding the epidemiology of *S. pneumoniae* poses a challenge for three reasons: first, despite being a major cause of diseases such as pneumonia, meningitis, and sepsis, pneumococci commonly colonize hosts without causing infection, creating a reservoir of infection; second, the numerous strains and serotypes have different colonization and infection rates as well as different levels of resistance to drugs; and third, the dynamic effects of immunity are not well understood. This paper presents a mathematical model that captures the dynamic links between the reservoir of pneumococci, pneumococcal transmission, and drug resistance. Although we concentrate on pneumococci, similar models can be applied to other species of bacteria with similar ecology (e.g., *Haemophilus influenzae* type B and *Staphylococcus aureus*).

Mathematical models can help explain the largely unobserved role of asymptomatic carriage. The function of a model is not to describe the precise disease dynamics. Rather, where the dynamics are indiscernible and controlled experiments are impractical or impossible, models can be used to depict scenarios representing reality, conduct virtual experiments illuminating disease epidemiology, identify relevant biological detail, and analyze the merits of different interventions. Prior

models describing pneumococcal transmission dynamics have primarily assumed that individuals can be classified in a single, simple epidemiological state, colonized or infected by either a single strain or a pool of the entire pneumococcus population [4–7]. This type of model, though useful for describing some aspects of the epidemiology, lacks detail on the role of bacterial competition and is not appropriate for describing the changing ecology occurring in the reservoir of infection [2,3].

More complicated pneumococcal models have taken account of some elements of the complex ecological and evolutionary processes by splitting the world into two strains and pooling either resistant strains and susceptible ones [8–10] or vaccine serotypes and non-vaccine types [11–16]. Although these models have been used to describe strain evolution, they overlook the role of bacterial competition, which may compromise analysis and confound assessments and comparisons of policies. For instance, because vaccination reduces resistance in a population in some cases [17,18] and induces the emergence of highly resistant serotypes in others [19], ignoring the role of competition among bacterial strains makes it difficult to evaluate the effect of vaccination interventions on resistance. Other models take into account competition between strains, but do not account for the immune response and its effects on the bacteria population.

Part of the challenge in advancing our understanding stems from the substantial data gaps for pneumococci and other pathogens. One way to address these issues is to construct a model with a high degree of complexity that can simultaneously consider all the sources of uncertainty and then systematically explore the effects of each factor on policy.

This paper describes a flexible framework that is parsimonious but also sufficiently complex in its detail of *S. pneumoniae* strains—including any combination of serotypes and drug-resistant phenotypes, direct and indirect competitive interactions with each other, and interactions with the immune system—while maintaining consistent mathematical theory. One recently published model

incorporates many of these elements [20], but to our best knowledge, this is the first model of pneumococci that considers competition at the serotype level, competition among strains of the same serotype (*e.g.*, resistant and susceptible strains), and host immunological factors. In the following sections we describe the model, a parsimonious parameterization of it, and its extensibility.

The Model

Reservoir Dynamics for a Single Strain

Asymptomatic carriers serve as the ecological reservoir for disease, though colonization rates vary by age, geography, and socioeconomic conditions [21,22]. Colonization generally precedes infection [23,24] but many individuals remain symptom free, making carriage rate largely an ecological or public health problem rather than a medical problem. Data describing carriage are thus not routinely collected, and research on colonization has been limited to a few longitudinal studies [24–36] and cross-sectional ones [37–41]. Consequently, reservoir dynamics and changes over time due to serotype evolution and adaptation to selection are poorly understood.

Reservoir dynamics were described by a generalized Markov-chain model, developed initially for a single strain (Figure 1). Let $X = \{x_0, x_1, ..., x_i, ..., x_L\}$ be the state set, where x_0 denotes the fraction of the population that is not colonized and x_i ($i > 0$) describes a categorical level of colonization: it could describe the portion of the population colonized with density level i or the portion with i colonization sites in the nasopharynx. $i = L$ is the largest colonization level, which describes the maximum density colonizing bacteria could possibly attain, summed over all strains and serotypes. Let the natural death rate of human hosts, u, be exactly balanced by births, such that the population described by X is maintained at a constant size.

Let b_i and d_i be the rates of transitions (growth and decay) between any two consecutive colonization levels (i.e., from i to $i+1$ or $i-1$ defined for all counting numbers). Because of the lack of data describing colonization and changes in bacterial populations within a host, $b_i$and d_i in this model are functions that regulate the duration of colonization and indirectly influence other processes, and they determine the proportion of the population in each state. (In practice, *L* is chosen after b_i and d_i at a value so high it is rarely attained.) In this simple framework they are assumed to be linear functions of the current state of colonization ($b_i = \lambda_i i$ and $d_i = \alpha_i i$). As the model is expanded, these functions will reflect both strain-specific competitive dominance and host factors. The dynamics of this system can be described by a potentially infinite set of coupled ordinary differential equations (S1.1).

In this framework, we assume that colonization is the main driver of transmission and that infection follows a fairly predictable time course. We model this by incorporating invasiveness (σ) (or the rate that colonization becomes infection) and infection clearance (ζ) rates, and coupling infection states, $Y = \{y_0, y_1, ..., y_i, ..., y_L\}$, parallel to carriage states (X). The state y_i indicates infection with a background colonization level i. The force of infection is a factor of the colonization pressure, its dynamics, and the strain invasiveness and clearance parameters.

Let $\Lambda = \beta \sum_{i>0} W_i (x_i + y_i)$ be the colonization pressure experienced by susceptible hosts, where β is the strain transmission rate and $W_i = \gamma i$ is infectiousness as a linear function of colonization levels. In this setup bacterial densities arise through colonization from $x_0 \rightarrow x_1$ at the rate Λx_0. Depending on the interpretation of the states, colonization pressure can also add to b_i leading to an increase in overall growth rates at higher levels. There is no fixed *a priori* assumption made about the gap between any two consecutive levels i and $i+1$.

From a policy evaluation perspective, perverse effects may be overlooked if shifts in the patterns of diversity, or the speed at which they occur, are ignored. Direct observations and age-specific patterns of pneumococcal disease and carriage suggest that immunity has an important influence on the reservoir and transmission dynamics of pneumococci [38,42–48]. Though there is no conclusive theory on the effect of host immunity, it is believed to be the primary mechanism driving the relationship between age, colonization prevalence, and disease incidence [45].

We assume that host immunity can protect from colonization and infection, as well as reduce the severity of disease and the length of colonization. To model immunity, we add another dimension to X (and equivalently to Y) for each strain. The state $x_{i,k}$ describes both the colonization level (i) and the host immunity level (k). We can model immunity to act through each of the aforementioned avenues, or through combinations of them. For simplicity, immunity was assumed to directly affect only the acquisition of bacteria in the process of transmission and the decay rate of a bacterial strain ($d_{i,k}$); the latter indirectly reduces colonization duration and disease incidence. Alternative parameterizations are also possible in which immunity directly reduces the risk of infection. The colonization pressure is $\Lambda_{s,k} = \phi_k(\beta)\sum_{i>0} W_i(x_i + y_i)$, where $_k(\ )$ is a function that reduces the likelihood of acquiring a new bacterial colonization as immunity increases, such that $\frac{d\ _k}{dk} < 0$. The decay function, regulating colonization duration, is $d_{i,k}(\alpha) = \alpha i k^h$, where h is the strain-specific effect of immunity on duration. Immunity waning ($\eta_{i,k}$) and waxing ($\omega_{i,k}$) is described by a Markov-chain process, similar to bacterial growth and decay (S1.1).

Multiple Strains

The population structure of S. *pneumoniae* is characterized by differences in a polysaccharide capsule that protects the bacterium from phagocytosis. More than

90 capsular serotypes have been identified [49] and serve as an important distinguisher of invasive potential and disease outcome [50]. Evolution of *S. pneumoniae* is marked by high rates of horizontal gene transfers [51–53], which contribute to a complicated strain structure [53]. However, although serotype distribution and strain structure vary geographically [22], constancy in the frequency distributions of particular serotypes or serogroups (groups of closely related serotypes) in some locations has been observed over decades ([54] and references therein), suggesting that these frequencies are maintained by strong selective force [54].

The importance of selective forces is supported by the recent introduction of a pneumococcal vaccine that provided protection against the seven most prevalent serotypes. After the introduction of the vaccine, reductions in invasive pneumococcal disease (IPD) were observed, as were reductions in colonization rates with vaccine serotypes [17,54–56], but carriage of vaccine serotypes was replaced to varying extents by carriage of nonvaccine types [2,57–61]. These results, along with laboratory studies, suggest that competitive hierarchies among serotypes exist [62]. Thus, introduction of the vaccine in a geographical setting with different serotype distributions could induce replacement with more virulent serotypes.

One disadvantage of the reservoir dynamics Markov-chain model presented is that almost all of the complexity must be addressed in considering the interactions between a pair of strains. These interactions include two strains that are functionally identical with truly neutrally stable dynamics [63], strains that are functionally independent; direct inhibition of one strain by another (e.g., through the production of allelopathic chemicals), competition for scarce resources (e.g., space), and a range of cross-immunity generated by the immune system.

The advantage of the this Markov-chain model is that strain complexity can be easily added to the model, including any combination of serotypes and drug resistance phenotypes. To expand the model to incorporate N strains the state space, both X

and Y, is expanded to N dimensions (disregarding immunity). Let each strain in $S = \{1,...,s,...,N\}$ be associated with the set of carriage quantities $Q = \{q_1,...,q_s,...,q_N\}$. In the state x_q the bacteria levels are $q_s \in Q \geq 0$. In the two-strain, four-level model in Figure 2, the state $x_{2,0}$ is interpreted as carriage of strains 1 at level 2 and no carriage of strain 2.

The most difficult problem is to find a mathematical formulation that describes neutral dynamics and that also satisfies strong conditions with respect to the neutrality of functionally equivalent strains. To satisfy this condition, a cap $L \geq \sum Q$ implicitly builds competition for resources between functionally equivalent strains into the model. The limit produces an *N*-dimensional triangular half-matrix. Similar to the one-strain model, the function $b_i(\lambda_s)$ and $d_i(\alpha_s)$ determine the rates of growth and decay, regulating the duration of colonization, for strain s. Simple functional forms for the growth and decay functions may be $b_{q_s}(\lambda_s) = \lambda_s q_s$ and $d_{q_s}(\alpha_s) = \alpha_s q_s$, respectively. λ_s and α_s describe the relative duration of colonization of the strains. The higher λ_s (α_s) is relative to other strains, the longer (shorter) its relative duration of carriage; we can similarly model a biological fitness cost for resistant strains.

The colonization pressure from strain s is $_s = _s \quad _{q_s>0} r_{q_s} W_Q\left(x_{q_s} + y_{q_s}\right)$, where β_s is a strain-specific rate and $r_{q_s} = \frac{q_s}{\sum Q}$ is the relative strain density of strain s. We can place an upper limit on the level of new colonizations at some density level $M \leq L$. New colonization beyond that level is considered insubstantial in quantity. Both L and M cap the multiplicity of carriage (MOC). For example, in a model with $L = 10$ and $M = 5$, hosts can carry only five strains at a time, inducing further intrinsic competition in the colonization process (in Figure 2, $M = 2$). Multiplicity of carriage does not affect infectiousness beyond the indirect effect of competition between the strains carried on duration and prevalence of colonization.

Alternatively, we can model strain competition more directly within hosts (e.g., generation of pneumococcal bacteriocins, or pneumocins, targeting other strains) [64], with higher overall colonization levels and relative "dominance" directly affecting decay. Let $\mathrm{P} = \{\rho_1,...,\rho_s,...,\rho_N\}$ be the set describing relative dominance between strains. We assume a decay function for strain s that maintains both equal total decay and the relative densities between strains, $d_{s,Q}(\alpha_s, P) = \alpha_s q_s \sum_{s' \in S} \left[\frac{\rho_{s'}}{\rho_s} q_{s'} \right]$, such that it is a function of relative duration (α_s), the density of strain s (q_s), and the summation of densities weighted by relative dominance ($\frac{\rho_{s'}}{\rho_s}$). Growth can be constructed in a similar manner or, for simplicity, held constant. The functions as described here are by no means the only possibilities, and if, for example, we assume log density levels, we can square quantity levels. The two-strain model is given in the supporting materials S1.2.

Immunity

Host serology in a multistrain model introduces additional complexity and uncertainty. In addition to the short-run effects on prevalence and incidence, the immune response invoked to pneumococcal carriage and infection propagates long-run changes to the strain structure and to the pattern of disease. Uncertainty remains because of the lack of a cohesive theory on naturally acquired immunity and strain interdependencies. A forward-looking policy model needs to capture that long-run uncertainty. Though some research suggests that there may be homologous serotype-specific immunity for a few serotypes [65], other research suggests that more than one mechanism is at work. Serotype-dependent immunity is induced by the protective effects of antibodies to pneumococcal capsular polysaccharides and is acquired through prior colonization or disease [27]. Additionally, there is evidence of antibody cross-serotype protection [65]. Researchers have advocated the recognition of serotype-independent immunity,

posing three hypotheses: the acquisition of antibodies during carriage to pneumococcal protein antigens that exist across strains and serotypes, T-cell mediated immunity, and the general maturation of the immune system [42,45].

Markov-chain processes can describe the different channels of the acquisition of host immunity. For the purpose of generalization, let $K = \{k_1,...,k_v,...,k_V\}$ be the set of immunity levels to subsets of strains. That is, k_v provides protection to the set of strains $v \subseteq S$. Let v' be a set containing all strains of the same serotype. $k_{v'}$ represents serotype-dependent immunity and provides protection for each strain $s \in v'$. The set $v'' = S$ describes strain-independent, or strain-transcending, immunity. Any other set describes cross immunities between strains. Waning (η_{v,q_v,k_v}) and waxing (ω_{v,q_v,k_v}) of immunity to the strains in the set v are functions of the sum of the set of bacterial densities (Q) and the prevailing immunity level (K). The states $x_{Q,K}$ and $y_{Q,K}$ indicate both the colonization level of a strain and the host immunity level to each subset of strains.

Similar to the one-strain dynamics, the effects of immunity were built into the transmission, growth, and decay dynamics, and we ignore direct effects of the host's immune system on infection. If τ is a set of all the subsets of strains to which strain s belongs, the colonization pressure of strain s for an individual with the set of immunities K is $\Lambda_s = \prod_{v\in\tau}\left[\phi_{k_v}(\beta_s,m_v)\right]\sum_{q_s>0} r_{q_s} W_Q(x_{q_s}+y_{q_s})$, where $\phi_{k_v}(\beta_s,m_v) = \frac{\beta_s + m_v}{m_v k_v}$. Colonizing bacteria survival is inhibited by host serology in addition to competition with other strains. The decay function is $d_{s,k_\tau,q_s}(\alpha_s,h_\tau,\mathrm{P}) = \alpha_s \prod_{v\in\tau}[h_v k_v] q_s \sum_{s'\in S}\left[\frac{\rho_{s'}}{\rho_s} q_{s'}\right]$, where h_v is a subset-specific protection, which reduces the duration of carriage. Equations for a generalized immunity model are available in the supporting materials S1.3.

For the purposes of policy evaluation, vaccination would be implemented in the model similarly to immunity. Modeling the pneumococcal conjugate vaccine could incorporate serotype specific immunity, as well as cross-immunities where evidence suggests it exists.

Results

Compartmental models typically represent colonization dynamics as a simple Boolean state (i.e., colonized or not) with a single parameter describing the waiting time to clear. Extensions of these simple compartment models all have specific limitations that would ideally be avoided in a model designed to address the intrinsic complexity of the biology and incorporate new information to inform policy. We developed a Markov-chain model that is capable of describing a large range of complicated dynamics within a host, but given the paucity of data, the parameters can be restricted to consider a one-parameter family of growth and decay that produce similar dynamics. The following sections describe many of the issues that arise in modeling the reservoir dynamics and fitting those models to data. The model assumed similar dynamics in the colonized population and in the infected population (i.e. infection at level i represents infection with a background colonization at that level). Therefore, when we discuss the colonization and reservoir dynamics infection dynamics should be interpreted similarly.

Reservoir Dynamics

A primary issue in any infectious disease model is the duration of carriage. Compartmental models adopt the exponential as a one-parameter family of distributions, for colonization with a single strain with no immunity. The advantage of an exponential distribution is that it is characterized by a single parameter. The disadvantage is the difficulty of extending it to multistrain models while maintaining

neutrality (see below). Another disadvantage is that the exponential family of distributions does not account for variability in the underlying population density over time, so it does not provide a natural method for dealing with the problem of detectability. These problems are dealt with naturally in the Markov-chain model presented here by representing colonization with an entire chain of states.

In these models, time to clear is represented as the waiting time to random-walk from any state of colonization to the state of being uncolonized. The properties of this random walk may be different to an observer who is sampling the population depending on the underlying densities. Figure 3 illustrates results of simulations of carriage from a one-strain model with immunity. The models with simple stage-structured immunity also produce patterns of colonization that are consistent with age cohort colonization distributions. Though the model introduces an enormous amount of structural complexity compared with the simpler compartment model, by representing growth and decay from various states with simple functions, or by imposing some family of parameters with known properties, it is possible to model the duration of carriage by varying a single parameter. The model thus permits a vast amount of parametric complexity but can also be used in the same way as typical compartment models.

The mathematical formulation addresses another issue, the difference between colonization at any level and the relationship that must exist between bacterial colonization levels and the likelihood of detection (Figure 4). This formulation inevitably introduces another parameter or functional relationship describing detection as a function of the underlying states. This approach has the advantage of providing a direct link between studies designed to measure carriage over time when detection is an issue, and it can ultimately provide additional information about the fluctuations in bacterial populations over time.

Bacterial Competition and Neutrality

Bacterial competition is likely to play an important role in determining the frequency of strains and the strain structure of bacteria. It is possible to model competition in compartment models, but the form of competition is often determined by the stiff structure of a model. A properly formed strain model must be capable of modeling the dynamics of two strains that are identical in every way as if they were identical in every way—for example, arbitrarily splitting the population and following the progeny should not guarantee the coexistence of these two new arbitrarily defined entities [63]. At the same time, other kinds of competition and noncompetition must also be possible. Markov-chain models can solve these problems by making competition a function of bacterial states or by considering competitive dominance, allelopathy, or other forms of direct interference by one strain on another through a simple change in the parameters describing bacterial interactions within a host.

To achieve "ecological neutrality," the number of hosts carrying bacterial densities at any level 0 to L is dependent on the ecological state variables $N = \{n_0, n_1, ..., n_l, ..., n_L\}$, where in the two-strain case $n_l = \sum_{q_1+q_2=l} x_{q_1,q_2}$, but is independent of the particular strain [63]. We show that is the case in the supporting materials S2.1.

For "population genetic neutrality" [63], starting from a given relative frequency of bacterial densities between different strains, that relationship should stay constant through time. Strain competition in the model takes place across three avenues: growth, decay, and transmission. To achieve population genetic neutrality, the values for these processes along the diagonal $q_1 = q_2 = ... = q_L$, or in the two-strain model $i = j$, must be equal. For example, total growth from $i + j = 2$ is equal $b_{2,0} = b_{1,1} = b_{0,2}$, total decay is equal $b_{2,0} = b_{1,1} = b_{0,2}$, and infectiousness

$W_{2,0} = W_{1,1} = W_{0,2}$ is equal. Given these constraints, there will be no bias in transitions between states and the model will be neutral.

We define prevalence of carriage in a population as the ratio of colonized hosts over the number of individuals in the population, $V_1 = \frac{\sum_{i>0} x_{i,j}}{X}$ for strain 1; it is insensitive to the bacterial density levels. The abundance of bacterial densities carried in a population for strain 1 is $A_1 = \frac{\sum_{i>0} W_i x_{i,j}}{X}$ and similarly for strain 2. Figure 5 illustrates the intrinsic competition of two strains identical in every way and demonstrates that the ratio $\frac{A_1}{A_2}$ remains constant through time at the value set by the initial conditions ($A_1 = 0.9, A_2 = 0.1$). The prevalence ratio shifts slightly, such that prevalence ratio of strain 1 $\frac{V_1}{V_1+V_2} = 0.89981$ by year 25, to maintain a constant abundance ratio.

In Figure 5 (panels B and C) decay is modeled as described, and total growth (from both strains) is held constant. In panel B strain 1 is more dominant than strain 2 ($\rho_1 > \rho_2$), with all other strain attributes being identical. Duration of carriage is reduced to a higher degree for strain 2 in hosts that carry both. If only one of the two strains is present in a population, there is no difference in their respective prevalence. The prevalence of either strain is lower when both strains are present in a population. However, without selection (e.g., resistance and antibiotic use), the prevalence of strain 2, the less dominant strain, is decreasing. As the reduction in strain 2 occurs, the prevalence of strain 1 increases asymptotically toward its level as the sole strain in the population. In panel C strain 1 remains more dominant when a host carries both; however, in singly colonized hosts, the baseline duration of carriage is slightly greater for strain 2. Because of the low levels of co-colonization in this case, that slight difference has more influence than the relative dominance. We start at year 0 with 100% of the population co-colonized, and the

more dominant strain 1 initially emerges as the more prevalent. However, the longer duration with strain 2 proves to have a stronger effect, and as colonization with it increases, it crowds out strain 1.

The polymorphic attribute of strains (they can represent differing serotypes or be strains of the same serotype) creates a flexible model structure. It insures that increasing strain complexity does not require major reconstruction of the model. The strain-specific parameters here are β_s, λ_s, α_s and P (either λ_s or α_s can be held constant).

Immunity

Pneumococcal models generally ignore natural immunity, set an age-specific force of infection to simulate it [6,12,66], or construct an age-dependent contact network [15]; defining a high contact rate within a community with already high prevalence exacerbates that prevalence. While age may be an important factor in the maturation of the immune system and for social reason, basing dynamics only on age may mischaracterize important aspects of the long-term dynamics in a population that loses its naturally acquired background immunity as vaccination proceeds, as has been suggested for pertussis [67]. In addition, the models may overestimate vaccine efficacy when they ignore naturally acquired immunity or when immunity is simulated solely through an age-specific force of infection. If immunity is at least partially acquired through prior colonization, higher carriage rates early on would offer the population protection.

This Markov-chain model considers stage-structured immunity, in which the presence of bacteria stimulates an immune response after some time. The epidemiological properties of the bacteria change as a result of this immune response. In reality, immunity is likely to be one of the most important factors limiting the duration of colonization, the incidence of disease, and other aspects of transmission and community dynamics.

Figure 6 shows the evolution of colonization and immunity (two levels of immunity) in a two-strain simulation with a higher transmission of strain 2 ($\beta_2 = 0.02$) relative to strain 1 ($\beta_1 = 0.015$); the strains are identical across all other parameters. Panel A simulates serotype-specific immunity. The increased transmission of strain 2 leads to a higher immunity prevalence in the population, reducing the gap in colonization prevalence relative to a model with strain-transcending immunity (panel C) or a model with no immunity. The prevalence of strain 1 (and hence also its immunity level) is affected by the competition with strain 2 in the population, and the prevalence of both oscillates until the equilibrium immunity level is reached. In Panel B, we alter the rate of gaining immunity for strain 1 such that it is double that of strain 2. The prevalence of immunity to strain 1 increases to a level higher than that of strain 2 by the second year, which reduces its colonization relative to strain 1. In panel C, showing strain-transcending immunity, strain 1 is marginalized by the more prevalent strain 2.

Immunity in these models is flexible with respect to the degree of cross-immunity. Increasing immunity can affect two different strains in the same way, as if they were identical, or it can be independent of the strain type. Cross-immunity to any degree can be incorporated for any set of strains. These patterns of cross-immunity, like the patterns of bacterial dominance, are likely to be the underlying causes of the distribution of strains in a community and important mechanisms for understanding strain replacement.

Discussion

We demonstrate a mathematically consistent framework for modeling pneumococci based on a variety of epidemiological, ecological, and immunological mechanisms that remain poorly quantified. The model provides a platform to simulate pneumococcal reservoir dynamics and evaluate policies while respecting the underlying uncertainty. Our framework has a flexible strain structure: different

strains can be defined as different serotypes or as the same serotype with differing markers. Strain interdependencies are built into the model through two channels: through competition via the limiting resource for the bacteria (the susceptible host population) and through host immunology. The resulting model makes it possible to consider many strains in a consistent framework and capture a complex range of biological events. Phenomena that have been considered in independently derived compartment models can thus be considered here as quantitatively different aspects of the same model. Extending the model—for describing specific settings or expounding on new scientific knowledge—requires some recalibration but no massive reconfiguration.

One component we did not elaborate on in this model is important for a full-scale epidemiological model: namely, infection. We assume both that colonization is the main driver of disease spread and that infection follows a fairly predictable time course, and it can be modeled simply by incorporating transmission and clearance parameters and coupling infection states parallel to the carriage-level ones. This modeling framework makes it possible to compare the number of lives saved in different biological scenarios with varying policies. Incorporating the infection dynamics will allow analysis of intervention policies. Taking into account mutations and horizontal gene transfers, resistance can be modeled with a Markov-chain model, similar to colonization and to host immunity. Selective effects of policies, drug pharmacokinetics, and human behavior can be studied.

The Markov-chain design also opens new paths for studying colonization ecology. One of the questions arising from the analysis of PCV-7 effects is how to distinguish between serotype replacement and unmasking [68]. Tests on nasopharyngeal swab samples may fail to detect lower-density serotypes in hosts with multiple carriages. Although vaccination has likely led to serotype replacement, the magnitude could have been exaggerated; with the quantity of vaccine serotypes reduced, tests may have revealed the previously undetectable lower-density serotypes. The Markov-chain model makes it possible to investigate that likelihood in different scenarios.

The framework provides one way to build flexible and extensible yet parsimonious models of the pneumococcus. However, even though the intellectual complexity does not drastically increase with the addition of strains, the computational complexity does rise. To surpass the issue, we are developing an individual-based simulation model that is, in at least one case, analogous to this framework and capable of incorporating other factors (e.g., heterogeneous population mixing) that usually complicate the modeling. The paired development of these models allows for covalidation to more reliably simulate and understand pneumococcus bacterial population. Several issues remain to be addressed to model pneumococcal dynamics in countries, including the geographical variation in the bacteria and their human host populations, and the effect of existing and planned interventions. These represent important future applications of this model.

References

1. O'Brien KL, Wolfson LJ, Watt JP, Henkle E, Deloria-Knoll M, McCall N, et al. Burden of disease caused by Streptococcus pneumoniae in children younger than 5 years: global estimates. Lancet. 2009;374: 893–902. doi:10.1016/S0140-6736(09)61204-6

2. Ghaffar F, Barton T, Lozano J, Muniz LS, Hicks P, Gan V, et al. Effect of the 7-Valent Pneumococcal Conjugate Vaccine on Nasopharyngeal Colonization by Streptococcus pneumoniae in the First 2 Years of Life. Clin Infect Dis. 2004;39: 930–938. doi:10.1086/423379

3. Weinberger DM, Malley R, Lipsitch M. Serotype replacement in disease after pneumococcal vaccination. The Lancet. 2011;378: 1962–73. doi:10.1016/S0140-6736(10)62225-8

4. Huang SS, Finkelstein JA, Lipsitch M. Modeling Community- and Individual-Level Effects of Child-Care Center Attendance on Pneumococcal Carriage. Clin Infect Dis. 2005;40: 1215–1222. doi:10.1086/428580

5. Andersson M, Ekdahl K, Mölstad S, Persson K, Hansson HB, Giesecke J. Modelling the spread of penicillin-resistantStreptococcus pneumoniae in day-care and evaluation of intervention. Stat Med. 2005;24: 3593–3607. doi:10.1002/sim.2199

6. Snedecor SJ, Strutton DR, Ciuryla V, Schwartz EJ, Botteman MF. Transmission-dynamic model to capture the indirect effects of infant vaccination with Prevnar (7-valent pneumococcal conjugate vaccine (PCV7)) in older populations. Vaccine. 2009;27: 4694–4703. doi:10.1016/j.vaccine.2009.05.062

7. Sutton K, Banks H, Castillo-Chávez C. Estimation of invasive pneumococcal disease dynamics parameters and the impact of conjugate vaccination in Australia. Math Biosci Eng. 2008;5: 175.

8. Levin BR. Minimizing Potential Resistance: A Population Dynamics View. Clin Infect Dis. 2001;33: S161–S169. doi:10.1086/321843

9. Samore MH, Lipsitch M, Alder SC, Haddadin B, Stoddard G, Williamson J, et al. Mechanisms by Which Antibiotics Promote Dissemination of Resistant Pneumococci in Human Populations. Am J Epidemiol. 2006;163: 160–170. doi:10.1093/aje/kwj021

10. McCormick AW, Whitney CG, Farley MM, Lynfield R, Harrison LH, Bennett NM, et al. Geographic diversity and temporal trends of antimicrobial resistance in Streptococcus pneumoniae in the United States. Nat Med. 2003;9: 424–430. doi:10.1038/nm839

11. Zhang Y, Auranen K, Eichner M. The influence of competition and vaccination on the coexistence of two pneumococcal serotypes. Epidemiol Infect. 2004;132: 1073–1081. doi:10.1017/S0950268804002894

12. Melegaro A, Choi YH, George R, Edmunds WJ, Miller E, Gay NJ. Dynamic models of pneumococcal carriage and the impact of the Heptavalent Pneumococcal Conjugate Vaccine on invasive pneumococcal disease. BMC Infect Dis. 2010;10: 90. doi:10.1186/1471-2334-10-90

13. Lipsitch M. Vaccination against colonizing bacteria with multiple serotypes. Proc Natl Acad Sci. 1997;94: 6571–6576.

14. Lipsitch M. Bacterial vaccines and serotype replacement: lessons from Haemophilus influenzae and prospects for Streptococcus pneumoniae. Emerg Infect Dis. 1999;5: 336–345.

15. Karlsson D, Jansson A, Normark BH, Nilsson P. An individual-based network model to evaluate interventions for controlling pneumococcal transmission. BMC Infect Dis. 2008;8: 83. doi:10.1186/1471-2334-8-83

16. Choi YH, Jit M, Flasche S, Gay N, Miller E. Mathematical Modelling Long-Term Effects of Replacing Prevnar7 with Prevnar13 on Invasive Pneumococcal Diseases in England and Wales. PLoS One. 2012;7: e39927. doi:10.1371/journal.pone.0039927

17. Klugman KP. Efficacy of pneumococcal conjugate vaccines and their effect on carriage and antimicrobial resistance. Lancet Infect Dis. 2001;1: 85–91. doi:10.1016/S1473-3099(01)00063-9

18. O'Brien KL, Dagan R. The potential indirect effect of conjugate pneumococcal vaccines. Vaccine. 2003;21: 1815–1825. doi:10.1016/S0264-410X(02)00807-1

19. Reinert R, Jacobs MR, Kaplan SL. Pneumococcal disease caused by serotype 19A: Review of the literature and implications for future vaccine development. Vaccine. 2010;28: 4249–4259. doi:10.1016/j.vaccine.2010.04.020

20. Cobey S, Lipsitch M. Niche and Neutral Effects of Acquired Immunity Permit Coexistence of Pneumococcal Serotypes. Science. 2012;335: 1376–1380. doi:10.1126/science.1215947

21. Bogaert D, de Groot R, Hermans P. Streptococcus pneumoniae colonisation: the key to pneumococcal disease. Lancet Infect Dis. 2004;4: 144–154. doi:10.1016/S1473-3099(04)00938-7

22. Hausdorff WP. Invasive pneumococcal disease in children: geographic and temporal variations in incidence and serotype distribution. Eur J Pediatr. 161: S135–S139. doi:10.1007/s00431-002-1066-x

23. Hodges RG, Macleod CM. Epidemic Pneumococcal Pneumonia. Am J Epidemiol. 1946;44: 183–192.

24. Gray BM, Converse GM, Dillon HC. Epidemiologic Studies of Streptococcus pneumoniae in Infants: Acquisition, Carriage, and Infection during the First 24 Months of Life. J Infect Dis. 1980;142: 923–933. doi:10.1093/infdis/142.6.923

25. Lipsitch M, Abdullahi O, D'Amour A, Xie W, Weinberger DM, Tchetgen ET, et al. Estimating rates of carriage acquisition and clearance and competitive ability for pneumococcal serotypes in Kenya with a Markov transition model. Epidemiol Camb Mass. 2012;23: 510–519. doi:10.1097/EDE.0b013e31824f2f32

26. Sá-Leão R, Nunes S, Brito-Avô A, Alves CR, Carriço JA, Saldanha J, et al. High Rates of Transmission of and Colonization by Streptococcus pneumoniae and Haemophilus influenzae within a Day Care Center Revealed in a Longitudinal Study. J Clin Microbiol. 2008;46: 225–234. doi:10.1128/JCM.01551-07

27. Goldblatt D, Hussain M, Andrews N, Ashton L, Virta C, Melegaro A, et al. Antibody Responses to Nasopharyngeal Carriage of Streptococcus pneumoniae in Adults: A Longitudinal Household Study. J Infect Dis. 2005;192: 387–393. doi:10.1086/431524

28. Granat SM, Mia Z, Ollgren J, Herva E, Das M, Piirainen L, et al. Longitudinal Study on Pneumococcal Carriage During the First Year of Life in Bangladesh: Pediatr Infect Dis J. 2007;26: 319–324. doi:10.1097/01.inf.0000257425.24492.11

29. Hussain M, Melegaro A, Pebody RG, George R, Edmunds WJ, Talukdar R, et al. A longitudinal household study of Streptococcus pneumoniae nasopharyngeal

carriage in a UK setting. Epidemiol Infect. 2005;133: 891–898. doi:10.1017/S0950268805004012

30. Smith T, Lehmann D, Montgomery J, Gratten M, Riley ID, Alpers MP. Acquisition and invasiveness of different serotypes of Streptococcus pneumoniae in young children. Epidemiol Infect. 1993;111: 27–39. doi:10.1017/S0950268800056648

31. Cauchemez S, Temime L, Valleron A-J, Varon E, Thomas G, Guillemot D, et al. S. pneumoniae transmission according to inclusion in conjugate vaccines: Bayesian analysis of a longitudinal follow-up in schools. BMC Infect Dis. 2006;6: 14. doi:10.1186/1471-2334-6-14

32. Ekdahl K, Ahlinder I, Hansson HB, Melander E, Mölstad S, Söderström M, et al. Duration of Nasopharyngeal Carriage of Penicillin-Resistant Streptococcus pneumoniae: Experiences from the South Swedish Pneumococcal Intervention Project. Clin Infect Dis. 1997;25: 1113–1117. doi:10.1086/516103

33. Hill PC, Cheung YB, Akisanya A, Sankareh K, Lahai G, Greenwood BM, et al. Nasopharyngeal Carriage of Streptococcus pneumoniae in Gambian Infants: A Longitudinal Study. Clin Infect Dis. 2008;46: 807–814. doi:10.1086/528688

34. Sleeman KL, Griffiths D, Shackley F, Diggle L, Gupta S, Maiden MC, et al. Capsular Serotype–Specific Attack Rates and Duration of Carriage of Streptococcus pneumoniae in a Population of Children. J Infect Dis. 2006;194: 682–688. doi:10.1086/505710

35. Auranen K, Arjas E, Leino T, Takala AK. Transmission of Pneumococcal Carriage in Families: A Latent Markov Process Model for Binary Longitudinal Data. J Am Stat Assoc. 2000;95: 1044–1053. doi:10.1080/01621459.2000.10474301

36. Melegaro A, Gay NJ, Medley GF. Estimating the transmission parameters of pneumococcal carriage in households. Epidemiol Infect. 2004;132: 433–441. doi:10.1017/S0950268804001980

37. Croucher NJ, Harris SR, Fraser C, Quail MA, Burton J, Linden M van der, et al. Rapid Pneumococcal Evolution in Response to Clinical Interventions. Science. 2011;331: 430–434. doi:10.1126/science.1198545

38. Högberg L, Geli P, Ringberg H, Melander E, Lipsitch M, Ekdahl K. Age- and Serogroup-Related Differences in Observed Durations of Nasopharyngeal Carriage of Penicillin-Resistant Pneumococci. J Clin Microbiol. 2007;45: 948–952. doi:10.1128/JCM.01913-06

39. Finkelstein JA, Huang SS, Daniel J, Rifas-Shiman SL, Kleinman K, Goldmann D, et al. Antibiotic-Resistant Streptococcus pneumoniae in the Heptavalent Pneumococcal Conjugate Vaccine Era: Predictors of Carriage in a Multicommunity Sample. Pediatrics. 2003;112: 862–869. doi:10.1542/peds.112.4.862

40. Abdullahi O, Nyiro J, Lewa P, Slack M, Scott JAG. The descriptive epidemiology of Streptococcus pneumoniae and Haemophilus influenzae nasopharyngeal carriage in children and adults in Kilifi District, Kenya. Pediatr Infect Dis J. 2008;27: 59–64. doi:10.1097/INF.0b013e31814da70c

41. Saha SK, Baqui AH, Darmstadt GL, Ruhulamin M, Hanif M, Arifeen SE, et al. Comparison of Antibiotic Resistance and Serotype Composition of Carriage and Invasive Pneumococci among Bangladeshi Children: Implications for Treatment Policy and Vaccine Formulation. J Clin Microbiol. 2003;41: 5582–5587. doi:10.1128/JCM.41.12.5582-5587.2003

42. Malley R. Antibody and cell-mediated immunity to Streptococcus pneumoniae. J Mol Med. 2010;88: 135–142. doi:10.1007/s00109-009-0579-4

43. Granat SM, Ollgren J, Herva E, Mia Z, Auranen K, Mäkelä PH. Epidemiological evidence for serotype-independent acquired immunity to pneumococcal carriage. J Infect Dis. 2009;200: 99–106. doi:10.1086/599364

44. Balmer P, Borrow R, Findlow J, Warrington R, Frankland S, Waight P, et al. Age-Stratified Prevalences of Pneumococcal-Serotype-Specific Immunoglobulin G in England and Their Relationship to the Serotype-Specific Incidence of Invasive Pneumococcal Disease Prior to the Introduction of the Pneumococcal 7-Valent Conjugate Vaccine. Clin Vaccine Immunol. 2007;14: 1442–1450. doi:10.1128/CVI.00264-07

45. Lipsitch M, Whitney CG, Zell E, Kaijalainen T, Dagan R, Malley R. Are Anticapsular Antibodies the Primary Mechanism of Protection against Invasive Pneumococcal Disease? PLOS Med. 2005;2: e15. doi:10.1371/journal.pmed.0020015

46. Laine C, Mwangi T, Thompson CM, Obiero J, Lipsitch M, Scott JAG. Age-Specific Immunoglobulin G (IgG) and IgA to Pneumococcal Protein Antigens in a Population in Coastal Kenya. Infect Immun. 2004;72: 3331–3335. doi:10.1128/IAI.72.6.3331-3335.2004

47. Elberse KEM, de Greeff SC, Wattimena N, Chew W, Schot CS, van de Pol JE, et al. Seroprevalence of IgG antibodies against 13 vaccine Streptococcus pneumoniae

serotypes in the Netherlands. Vaccine. 2011;29: 1029–1035. doi:10.1016/j.vaccine.2010.11.054

48. Bogaert D, Sluijter M, Toom NL, Mitchell TJ, Goessens WHF, Clarke SC, et al. Dynamics of pneumococcal colonization in healthy Dutch children. Microbiology. 2006;152: 377–385. doi:10.1099/mic.0.28394-0

49. Park IH, Pritchard DG, Cartee R, Brandao A, Brandileone MCC, Nahm MH. Discovery of a New Capsular Serotype (6C) within Serogroup 6 of Streptococcus pneumoniae. J Clin Microbiol. 2007;45: 1225–1233. doi:10.1128/JCM.02199-06

50. Weinberger DM, Harboe ZB, Sanders EAM, Ndiritu M, Klugman KP, Rückinger S, et al. Association of Serotype with Risk of Death Due to Pneumococcal Pneumonia: A Meta-Analysis. Clin Infect Dis. 2010;51: 692–699. doi:10.1086/655828

51. Henriques-Normark B, Blomberg C, Dagerhamn J, Bättig P, Normark S. The rise and fall of bacterial clones: Streptococcus pneumoniae. Nat Rev Microbiol. 2008;6: 827–837. doi:10.1038/nrmicro2011

52. Gupta S, Maiden MCJ. Exploring the evolution of diversity in pathogen populations. Trends Microbiol. 2001;9: 181–185. doi:10.1016/S0966-842X(01)01986-2

53. Lipsitch M, O'Hagan JJ. Patterns of antigenic diversity and the mechanisms that maintain them. J R Soc Interface. 2007;4: 787–802. doi:10.1098/rsif.2007.0229

54. Dagan R, Melamed R, Muallem M, Piglansky L, Greenberg D, Abramson O, et al. Reduction of Nasopharyngeal Carriage of Pneumococci during the Second Year of Life by a Heptavalent Conjugate Pneumococcal Vaccine. J Infect Dis. 1996;174: 1271–1278. doi:10.1093/infdis/174.6.1271

55. Obaro SK, Adegbola RA, Tharpe JA, Ades EW, McAdam KPWJ, Carlone G, et al. Pneumococcal surface adhesin A antibody concentration in serum and nasopharyngeal carriage of Streptococcus pneumoniae in young African infants. Vaccine. 2000;19: 411–412. doi:10.1016/S0264-410X(00)00201-2

56. Mbelle N, Huebner RE, Wasas AD, Kimura A, Chang I, Klugman KP. Immunogenicity and Impact on Nasopharyngeal Carriage of a Nonavalent Pneumococcal Conjugate Vaccine. J Infect Dis. 1999;180: 1171–1176. doi:10.1086/315009

57. Millar EV, Watt JP, Bronsdon MA, Dallas J, Reid R, Santosham M, et al. Indirect Effect of 7-Valent Pneumococcal Conjugate Vaccine on Pneumococcal Colonization among Unvaccinated Household Members. Clin Infect Dis. 2008;47: 989–996. doi:10.1086/591966

58. Singleton RJ, Hennessy TW, Bulkow LR, et al. Invasive pneumococcal disease caused by nonvaccine serotypes among alaska native children with high levels of 7-valent pneumococcal conjugate vaccine coverage. JAMA. 2007;297: 1784–1792. doi:10.1001/jama.297.16.1784

59. Chapman KE, Wilson D, Gorton R. Serotype dynamics of invasive pneumococcal disease post-PCV7 and pre-PCV13 introduction in North East England. Epidemiol Infect. 2013;141: 344–352. doi:10.1017/S0950268812000763

60. Sharma D, Baughman W, Holst A, Thomas S, Jackson D, da Gloria Carvalho M, et al. Pneumococcal Carriage and Invasive Disease in Children Before Introduction of the 13-valent Conjugate Vaccine: Comparison With the Era Before 7-valent Conjugate Vaccine. Pediatr Infect Dis J. 2013;32: 196. doi:10.1097/INF.0b013e3182788fdd

61. Stanek RJ, Mufson MA, Norton NB. Routine Pneumococcal Vaccination of Children Provokes New Patterns of Serotypes Causing Invasive Pneumococcal Disease in Adults and Children. Am J Med Sci. 2013;345: 112–120. doi:10.1097/MAJ.0b013e3182517785

62. Lipsitch M, Dykes JK, Johnson SE, Ades EW, King J, Briles DE, et al. Competition among Streptococcus pneumoniae for intranasal colonization in a mouse model. Vaccine. 2000;18: 2895–2901. doi:10.1016/S0264-410X(00)00046-3

63. Lipsitch M, Colijn C, Cohen T, Hanage WP, Fraser C. No coexistence for free: Neutral null models for multistrain pathogens. Epidemics. 2009;1: 2–13. doi:10.1016/j.epidem.2008.07.001

64. Weiser JN. The pneumococcus: why a commensal misbehaves. J Mol Med. 2010;88: 97–102. doi:10.1007/s00109-009-0557-x

65. Weinberger DM, Dagan R, Givon-Lavi N, Regev-Yochay G, Malley R, Lipsitch M. Epidemiologic Evidence for Serotype-Specific Acquired Immunity to Pneumococcal Carriage. J Infect Dis. 2008;197: 1511–1518. doi:10.1086/587941

66. Temime L, Guillemot D, Boëlle PY. Short- and Long-Term Effects of Pneumococcal Conjugate Vaccination of Children on Penicillin Resistance.

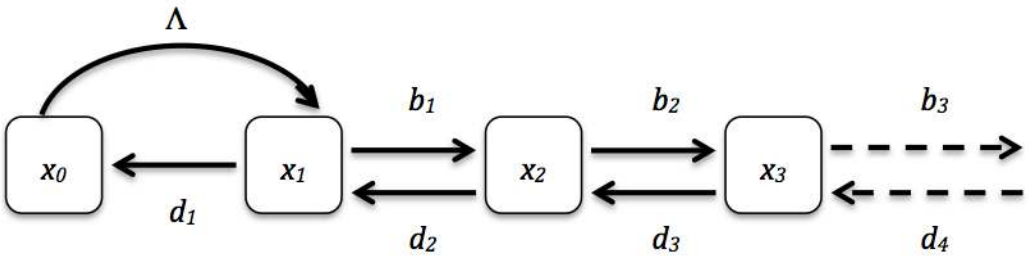
Antimicrob Agents Chemother. 2004;48: 2206–2213. doi:10.1128/AAC.48.6.2206-2213.2004

67. Lavine JS, King AA, Bjørnstad ON. Natural immune boosting in pertussis dynamics and the potential for long-term vaccine failure. Proc Natl Acad Sci. 2011;108: 7259–7264. doi:10.1073/pnas.1014394108

68. Lipsitch M. Interpreting Results from Trials of Pneumococcal Conjugate Vaccines: A Statistical Test for Detecting Vaccine-induced Increases in Carriage of Nonvaccine Serotypes. Am J Epidemiol. 2000;154: 85–92. doi:10.1093/aje/154.1.85

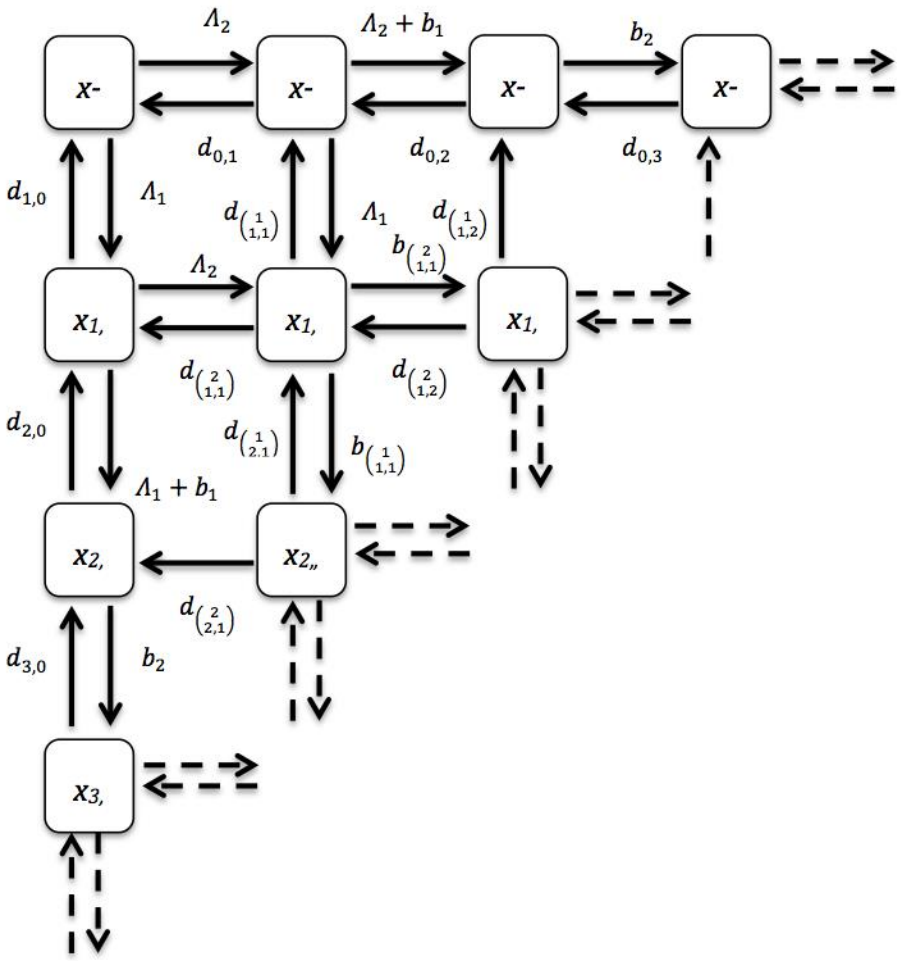
Figures

Figure 1. One-strain dynamics



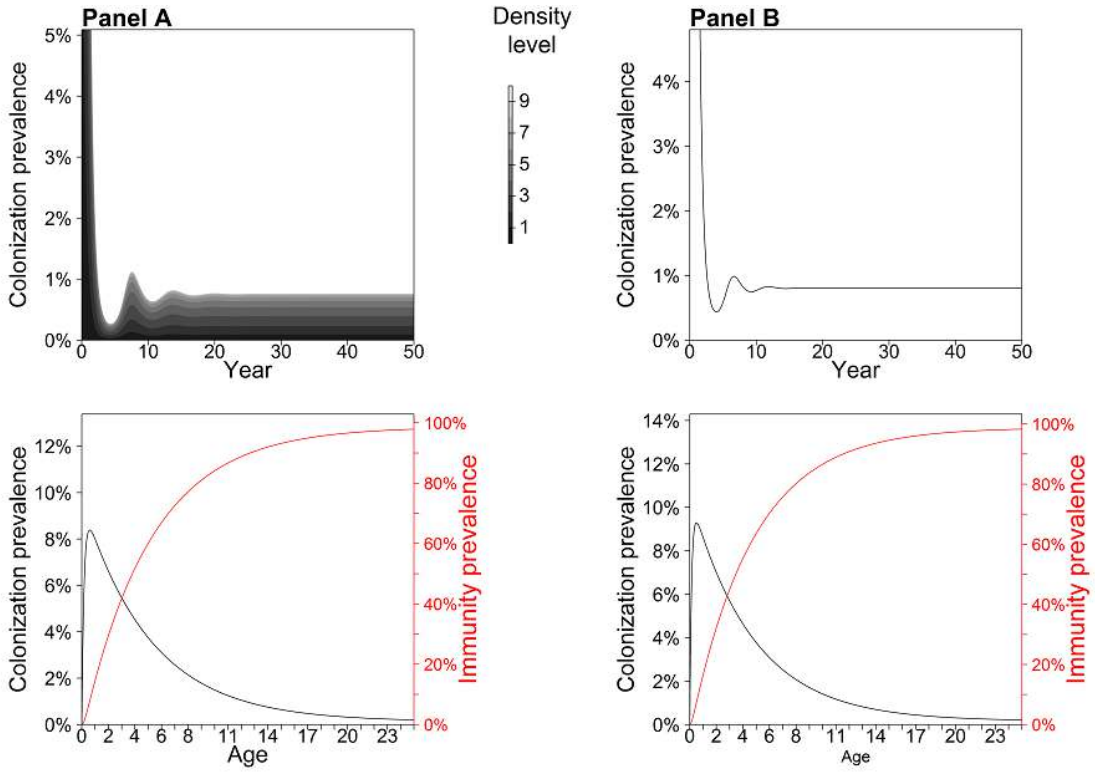
Markov-chain model of one-strain dynamics (***Λ*** is the force of infection; $x_{i=0}$ describes the portion of the population that is not colonized and $x_{i>0}$ describes the population in the categorical level of colonization ***i***; b_i and d_i are the colonization growth and decay rates from level ***i***, respectively).

Figure 2. Two-strain colonization dynamics



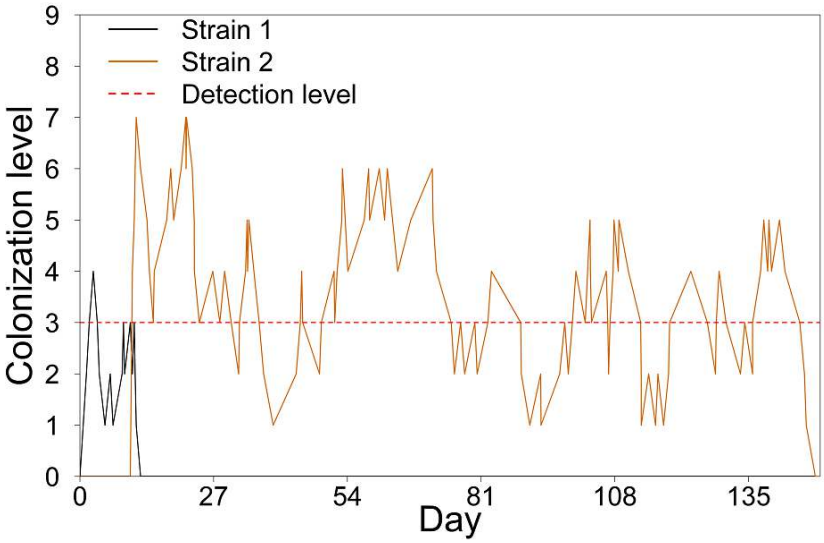
A two-strain Markov-chain model of colonization dynamics ($x_{i,j}$ describes colonization at levels *i* for strain 1 and *j* for the strain 2, Λ_1 and Λ_2 are the force of infection for the strains; and $b_{\binom{s}{q_1,q_2}}$ and $d_{\binom{s}{q_1,q_2}}$ describe growth and decay in strain *s*, respectively).

Figure 3. One-strain model simulations



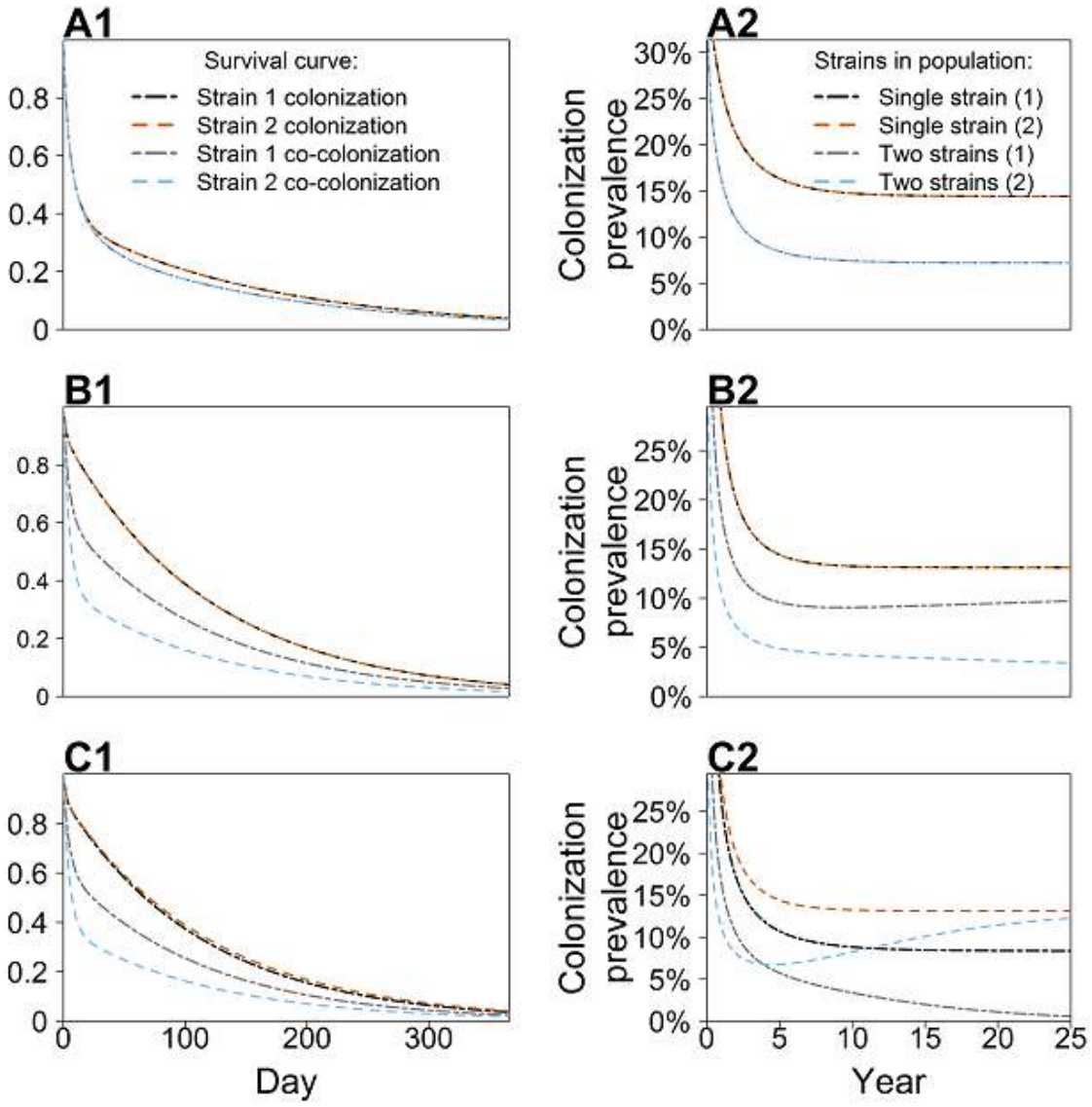
A one-strain model with immunity with multiplicity of colonization, ***M=1***, and a decay function that approximates mean colonization duration at 67 days : (A) the Markov-chain model with 10 colonization levels (***μ = 1/70 years, λ = 0.5, α = 0.135, h = 5, γ = 1, β = 0.1, m = 0.1, ω = 1/180, η = 1/100,000***); (B) a one-strain compartmental model with immunity ($\alpha_{k=0} = 1/duration_{k=0}$, $\alpha_{k=1} = 1/duration_{k=1}$, where $duration_k$ is the approximate duration of colonization under the Markov-chain model, and ***μ, ω*** and **η** are equivalent to that model). Row 1 is the evolution of the model, and row 2 is the distribution of colonization across age groups.

Figure 4. Within-host stochastic colonization simulation



Within-host stochastic simulation of bacterial colonization level over time. The dotted red line represents an artificially set level for detection of colonization.

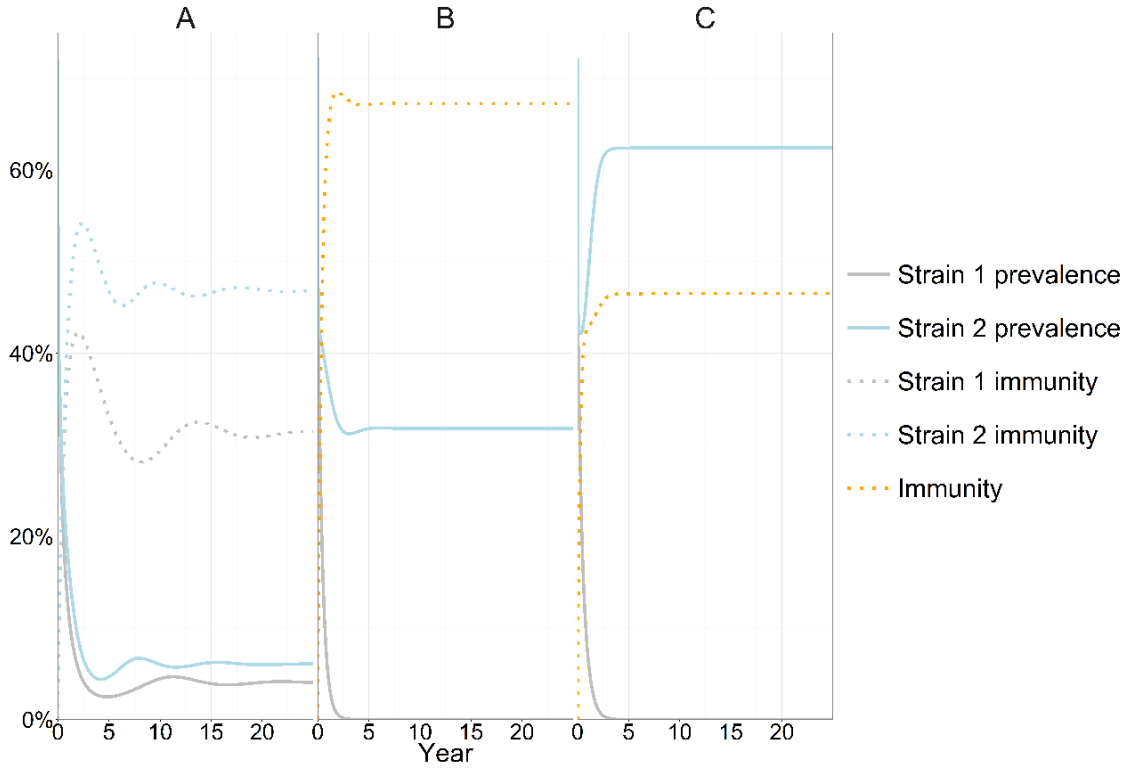
Figure 5. Two-strain model simulations with no immunity



A two-strain model with no immunity. In each scenario we simulate each strain with the other not prevalent in the population, and each strain when the other is also prevalent in the population. Column 1 provides the survival curve for each strain, and column 2 provides the colonization prevalence in the population given the initial abundance of bacteria of each strain. Scenarios: (A) two identical strains with an approximate mean colonization duration of 62 days when there is no multiplicity of colonization and 55 days when there is multiplicity (***M = 2, λ_s = 0.181, α_s = 0.13, γ_s = 1, β_s = 0.002, W = density level***; (B) both strains have an approximated duration of colonization of 106 days, strain 1 is the dominant strain and when the strains co-colonize its duration is approximately 77 days while it is 47 days for strain 2 (***M = 2, λ = (0.5, 0.5), α = (0.06, 0.06), ρ = (1, 1.5), β = (0.004, 0.004), W = density level***); (C) strain 1 is the dominant strain (and clears after approximately

102 days when alone and 71 days when competing with strain 2), but strain 2 clears at a slower rate (it clears after approximately 106 days when alone and 47 days when competing with strain 1) (***M = 2, λ = (0.5, 0.5), α = (0.061, 0.06), ρ = (1, 1.5), β = (0.004, 0.004), W = density level***).

Figure 6. Two-strain model simulations with immunity



A two-strain model with two levels of immunity. Scenarios: (A) strain-dependent immunity (***λ = (0.5, 0.5), α = (0.105, 0.105), ρ = (1, 1), β = (0.015, 0.02), W = density level, $\eta_{s,i}$ (1/180), $\omega_{s,i}$(1/730)***); (B) strain-dependent immunity with increased immunity waxing of strain 1 (same parameters as in A excluding ***$\omega_{s,i}$(2/730)***) ; (C) strain-independent immunity (same parameters as in A)

Supporting Material

1. Model ODEs

1.1. One-Strain Reservoir Dynamics: Markov-Chain Model

The reservoir dynamics are described by a Markov-chain model of the colonizing bacterial quantity levels.

$$\dot{x}_{0,k} = -\Lambda x_{0,k} + d_{1,k}x_{1,k} + \eta_{0,k+1}x_{0,k+1} + \mu\left(1 - x_{0,k}\right)$$

$$\dot{x}_{1,k} = \Lambda x_{0,k} - b_{1,k}x_{1,k} + \left(d_{2,k}x_{2,k} - d_{1,k}x_{1,k}\right) + \left(\omega_{1,k-1}x_{1,k-1} - \omega_{1,k}x_{1,k}\right) + \left(\eta_{1,k+1}x_{1,k+1} - \eta_{1,k}x_{1,k}\right) - \mu x_{1,k}$$

$$\dot{x}_{i>1,k} = \left(b_{i-1,k}x_{i-1,k} - b_{i,k}x_{i,k}\right) + \left(d_{i+1,k}x_{i+1,k} - d_{i,k}x_{i,k}\right) + \left(\omega_{i,k-1}x_{i,k-1} - \omega_{i,k}x_{i,k}\right) + \left(\eta_{i,k+1}x_{i,k+1} - \eta_{i,k}x_{i,k}\right) - \mu x_{i,k}$$

The quantity is described by the level i. Transmission of colonizing bacteria occurs from density level 0 to density level 1. The colonization pressure is

$$\Lambda = \phi_k(\beta, m)\sum_{i>0} W_i x_i$$

where infectiousness (W), describing the rate at which individuals transmit colonizing bacteria, is a function of bacterial densities such that $\frac{dW}{di} > 0$ and $\frac{d^2W}{di^2} \leq 0$. Acquiring colonizing bacteria, ϕ_k, is a function of the potential host's immunity level k:

$$\phi_k(\beta, m) = \frac{\beta + m}{mk}$$

Immunity increases at the rate $\omega_{i,k}$, such that $\frac{d\omega}{di} > 0$ and $\frac{d^2\omega}{di^2} \leq 0$, and $\frac{d\omega}{dk} \leq 0$ and $\frac{d^2\omega}{dk^2} \leq 0$. It wanes at the rate $\eta_{i,k}$, such that $\frac{d\eta}{di} < 0$ and $\frac{d^2\eta}{di^2} \leq 0$, and $\frac{d\eta}{dk} > 0$ and $\frac{d^2\eta}{dk^2} \leq 0$. There is no increase in immunity from $k = K$ or from $i = 0$ and no waning

from $k=0$. The decay function d is increasing in the bacterial quantities, $\frac{dd}{di}>0$ and $\frac{d^2d}{di^2}\leq 0$, and in the immunity level. For simplicity the growth function is held constant, $\frac{db}{di}=0$ and , $\frac{db}{dk}=0$. There is no bacterial growth or decay from the uncolonized state ($b_{0,k}=0$ and $d_{0,k}=0$), and no growth from the capacity level ($b_{L,k}=0$).

1.2. Two-Strain Model without Immunity

The two-strain model can be described by an infinite set of coupled equations describing colonization and infection.

$$\dot{x}_Q=\left(\Lambda_{s=1}x_{q_1-1,q_2}+\Lambda_{s=2}x_{q_1,q_2-1}-\Lambda x_Q\right)+\left(b_{\left(\begin{smallmatrix}1\\ q_1-1,q_2\end{smallmatrix}\right)}x_{q_1-1,q_2}+b_{\left(\begin{smallmatrix}2\\ q_1,q_2-1\end{smallmatrix}\right)}x_{q_1,q_2-1}-b_Q x_Q\right)$$

$$+\left(d_{\left(\begin{smallmatrix}1\\ q_1+1,q_2\end{smallmatrix}\right)}x_{q_1+1,q_2}+d_{\left(\begin{smallmatrix}2\\ q_1,q_2+1\end{smallmatrix}\right)}x_{q_1,q_2+1}-d_Q x_Q\right)+\left(\zeta y_Q-\sigma x_Q\right)-\mu x_Q$$

$$\dot{y}_Q=\left(\Lambda_{s=1}y_{q_1-1,q_2}+\Lambda_{s=2}y_{q_1,q_2-1}-\Lambda y_Q\right)+\left(b_{\left(\begin{smallmatrix}1\\ q_1-1,q_2\end{smallmatrix}\right)}y_{q_1-1,q_2}+b_{\left(\begin{smallmatrix}2\\ q_1,q_2-1\end{smallmatrix}\right)}y_{q_1,q_2-1}-b_Q y_Q\right)$$

$$+\left(d_{\left(\begin{smallmatrix}1\\ q_1+1,q_2\end{smallmatrix}\right)}y_{q_1+1,q_2}+d_{\left(\begin{smallmatrix}2\\ q_1,q_2+1\end{smallmatrix}\right)}y_{q_1,q_2+1}-d_Q y_Q\right)+\left(\sigma x_Q-\zeta y_Q\right)-\mu y_Q$$

where $Q=\{q_1,q_2\}$ and L caps bacterial quantities such that $\sum Q\leq L$. Transmission of colonization of strain s occurs into states x_Q such that $\sum Q<M=2$ and $q_s\geq 1$. Transmission of new bacterial densities into y_q requires that $q_s>1$; the bacterial quantities describe the background colonization and there is no infection without prior colonization. The colonization pressure is $\Lambda=\Lambda_{s=1}+\Lambda_{s=2}$ and the functional form is

$$\Lambda_s = \beta_s \sum_{q_s>0} r_{q_s} x_Q W_Q$$

where $r_{q_s} = \frac{q_s}{\sum Q}$. Growth and decay occur from both strain 1 and strain 2. b_Q and d_Q are total growth and decay from a given state, and the notation $b_{\left(\begin{smallmatrix} s \\ q_1,q_2 \end{smallmatrix}\right)}$ and $d_{\left(\begin{smallmatrix} s \\ q_1,q_2 \end{smallmatrix}\right)}$ describe growth and decay in strain s, respectively. There is no decay from $q_s = 0 \forall s \in S$. We keep b constant; however, competition for resources implies that $\frac{dd_s}{dq_{s'}} > 0$ and $\frac{d^2 d_s}{dq_{s'}^2} \leq 0 \ \forall s' \in S$. To incorporate direct inhibition of one colonizing strain on another, the vector $\mathrm{P} = \{\rho_1, \rho_2\}$ describes the relative dominance of the strains, and $\frac{dd_s}{d\rho_s} > 0$ and $\frac{d^2 d_s}{d\rho_s^2} \leq 0$. We use the following functional form for decay:

$$d_{s,Q}(\alpha_s, \mathrm{P}) = \alpha_s q_s \sum_{s' \in S} \left[\frac{\rho_{s'}}{\rho_s} q_{s'} \right]$$

where α_s is a strain specific rate affecting decay function, and therefore colonization duration, whether another strain is colonizing or not. Births occur into the uncolonized state:

$$\dot{x}_{0,0} = -\Lambda x_{0,0} + d_{1,0} x_{1,0} + d_{0,1} x_{0,1} + \mu(1 - x_{0,0})$$

1.3. Two-Strain Model with Immunity

Immunity adds additional dimensions to the model. Colonized states are modeled according to the following:

$$\dot{x}_{Q,K} = \left(\Lambda_{s=1,K} x_{q_1-1,q_2,K} + \Lambda_{s=2,K} x_{q_1,q_2-1,K} - \Lambda_K x_{Q,K} \right)$$

$$+ \left(b_{\left(\begin{smallmatrix} 1 \\ q_1-1,q_2 \end{smallmatrix}\right),K} x_{q_1-1,q_2,K} + b_{\left(\begin{smallmatrix} 2 \\ q_1,q_2-1 \end{smallmatrix}\right),K} x_{q_1,q_2-1,K} - b_{Q,K} x_{Q,K} \right)$$

$$+\left(d_{\begin{pmatrix}1\\ q_1+1,q_2\end{pmatrix},K}x_{q_1+1,q_2,K}+d_{\begin{pmatrix}2\\ q_1,q_2+1\end{pmatrix},K}x_{q_1,q_2+1,K}-d_{Q,K}x_{Q,K}\right)$$

$$+\sum_{k_v\in K}\left[\omega_{v,Q,k_v-1}x_{v,Q,k_v-1}-\omega_{v,Q,k_v}x_{v,Q,k_v}\right]+\sum_{k_v\in K}\left[\eta_{v,Q,k_v+1}x_{v,Q,k_v+1}-\eta_{v,Q,k_v}x_{v,Q,k_v}\right]$$

$$+\left(\zeta y_{Q,K}-\sigma x_{Q,K}\right)-\mu x_{Q,K}$$

where $K=\{k_1,...,k_v,...,k_V\}$ represents the set of immunity levels to each set of strains v. Given a set v', which contains all strains of the same serotype, $k_{v'}$ represents serotype-dependent immunity and provides protection for each strain $s\in v'$. The set $v''=S$ describes strain-independent, or strain-transcending, immunity. Any other subset of S represents cross immunities. The increasing rate of subset v is ω_{v,q_v,k_v} and its waning rate is η_{v,q_v,k_v}. The former is an increasing function of $q_v>0$ and the latter is a decreasing function of q_v. If τ is a set of all the subsets of strains to which strain s belongs, increases in the colonization pressure of strain s can be written as follows:

$$\Lambda_s=\prod_{v\in\tau}\left[\phi_{k_v}(\beta_s,m_v)\right]\sum_{q_s>0}r_{q_s}W_Q(x_{q_s}+y_{q_s})$$

where $\phi_{k_v}(\beta_s,m_v)=\dfrac{\beta_s+m_v}{m_vk_v}$. The decay function is:

$$d_{s,k_\tau,q_s}(\alpha_s,h_\tau,\mathrm{P})=\alpha_s\prod_{v\in\tau}[h_vk_v]q_s\sum_{s'\in S}\left[\frac{\rho_{s'}}{\rho_s}q_{s'}\right]$$

where h_v is an immunity subset specific inhibition of colonizing bacteria. The infection dynamics (Y) are similar to the two-strain dynamics described in 1.2, incorporating the immunity dynamics described here.

2. Neutrality

2.1 Ecological Neutrality

Taking the reservoir dynamics (not including infection for simplicity) of a two-strain model with no immunity from Appendix 1.2, let $N = \{n_0, n_1, ..., n_l, ..., n_L\}$ be the ecological state variables where $n_l = \sum_{q_1+q_2=l} x_{q_1,q_2}$. Assuming functionally identical strains, we can write the system of equations as follows:

$$\dot{n}_0 = -\left(\beta \sum_{l>0} x_l W_l\right) n_0 + \mu(1 - n_0)$$

$$\dot{n}_1 = \left(\beta \sum_{l>0} x_l W_l\right)(n_0 - n_1) - b_1 n_1 + (d_2 n_2 - d_1 n_1) - \mu n_1$$

$$\dot{n}_{L>i>1} = \left(\beta \sum_{l>0} x_l W_l\right)(n_{i\leq 2} - n_{i<2}) - (b_{i-1} n_{i-1} - b_i n_i) + (d_{i+1} n_{i+1} - d_i n_i) - \mu n_i$$

$$\dot{n}_L = b_{L-1} n_{L-1} - d_L n_L - \mu n_L$$

The system can be written without referring to any given strain.