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How direct competition shapes coexistence and vaccine effects in multi-strain pathogen systems

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HIGHLIGHTS

- We study how direct competition at co-colonization shapes multi-strain coexistence.
- We consider neutral and non-neutral models varying symmetry assumptions for clone interactions.
- The nested models are applied to pneumococcus prevalence data post-vaccination in Portugal.
- Our framework co-estimates transmission, competition and vaccine efficacy parameters.

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ABSTRACT

We describe an integrated modeling framework for understanding strain coexistence in polymorphic pathogen systems. Previous studies have debated the utility of neutral formulations and focused on cross-immunity between strains as a major stabilizing mechanism. Here we convey that direct competition for colonization mediates stable coexistence only when competitive abilities amongst pathogen clones satisfy certain pairwise asymmetries. We illustrate our ideas with nested SIS models of single and dual colonization, applied to polymorphic pneumococcal bacteria. By fitting the models to cross-sectional prevalence data from Portugal (before and after the introduction of a seven-valent pneumococcal conjugate vaccine), we are able to not only statistically compare neutral and non-neutral epidemiological formulations, but also estimate vaccine efficacy, transmission and competition parameters simultaneously. Our study highlights that the response of polymorphic pathogen populations to interventions holds crucial information about strain interactions, which can be extracted by suitable nested modeling.

1. Introduction

Ecological communities are shaped by multiple forces, the most prominent being competition for shared resources among their members (Begon et al., 2009). Inter- and intra-specific interactions occur over a range of scales and are central to explain how populations structure and diversify. While classical competition theory predicts competitive exclusion of species with similar phenotypes, another observation is that species diversity may result from multiple processes acting at different levels, and that similarities in competitive abilities can facilitate coexistence (Bengtsson et al., 1994). One of the central debates in ecology has been precisely to disentangle the mechanisms of coexistence: whether coexistence of different species results from adaptation to environmental heterogeneity (Gause, 1934), the niche view, or from a balance between immigration, speciation and extinction (MacArthur, 1967), the neutral view. Although recent years have seen increasing efforts to connect these two views, showing for example that niche and neutral models predict equivalent species abundance distributions in high-diversity ecological communities (Chisholm and Pacala, 2010), or invoking stochasticity in community assembly processes (Tilman, 2004), the discussion is still ongoing. The mathematical quest for explaining factors generating and maintaining polymorphism in populations is old (Kimura,

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1984), encompassing biological traits from altruistic behaviour (Eshel, 1977) to pathogen virulence (Levin and Pimentel, 1981; Nowak and May, 1994) and antigenic determinants (Dietz, 1979; Lipsitch and O'Hagan, 2007).

In particular, multi-strain pathogen systems have attracted special attention in the debate of neutral vs. niche mechanisms, e.g. in *Streptococcus pneumoniae* bacteria (Cobey and Lipsitch, 2012), dengue viruses (Mier-y Teran-Romero et al., 2013), and human papillomavirus (Murall et al., 2014). Considering mathematical equilibria, analytical approaches have focused on stringent criteria for the stable coexistence of multiple strains at the population level, when this appears at odds with competitive exclusion. Detailed models have attempted to characterize transmission, clearance and immune interaction parameters at the level of individual pathogen types, combined with mechanisms that reduce competition and re-establish stable coexistence steady states. The most prominent stabilizing mechanism invoked in multi-strain systems has been cross-immunity acting between different strains (Dietz, 1979; Mato, 1983; Bremermann and Thieme, 1989; Gupta et al., 1994).

In this paper, we explore an alternative mechanism, namely direct competition at co-colonization with two pathogen clones, which has also been studied, but less extensively (Lipsitch, 1997). We show that direct competition at co-colonization (or co-infection) does not stabilize coexistence of two pathogen clones unless competitive abilities are asymmetric in specific ways. We illustrate this view on a prominent polymorphic pathogen system: pneumococcal bacteria, frequent colonizers of the human nasopharynx, that display a wide variety of antigenic serotypes defined by their polysaccharide capsule (Bentley et al., 2006). Serotype prevalence varies widely between and within countries (O'Brien, 2008; Imöhl et al., 2010; Hung et al., 2013), and the reasons underlying this variation are not well understood. The extent and features of co-colonization in pneumococcus are receiving increasing attention in recent years, thanks to advances in molecular detection methods (Brugger et al., 2009). Existing estimates go up to 20% (Rivera-Olivero et al., 2009; Auranen et al., 2010; Brugger et al., 2010), with data on multiple carriage of different serotypes emerging rapidly (Valente et al., 2012; Ercibengoa et al., 2012). Described mechanisms of direct competition among pneumococci include bacteriocin secretion (Dawid et al., 2007) and competence-mediated fratricide (Guiral et al., 2005). Other mechanisms that can potentially confer an advantage to a strain in co-colonization include the capsular biosynthetic cost (Hathaway et al., 2012; Weinberger et al., 2009), resistance to opsonophagocytic killing (Nelson et al., 2007) and phage lysogeny (Carrolo et al., 2010), although these comprise indirect competition mechanisms.

To control pneumococcal disease, multivalent conjugate vaccines have been introduced since 2001 in many countries. The seven-valent pneumococcal conjugate vaccine (PCV7) was the first of such vaccines, conferring protection against 7 serotypes: 4,6 B, 9 V, 14, 18 C, 19 F and 23 F. This led to a decline of vaccine type (VT) carriage and disease, but a rising prevalence of non-vaccine serotypes (Weinberger et al., 2011), with relatively stable overall carriage and accessory genome composition at the population level (Croucher et al., 2013). A recent study in day care attendees in Portugal (Valente et al., 2012) detected a significant decrease in simultaneous carriage of multiple serotypes, and attributed this finding to a greater competitive ability of non-vaccine types (NVT), although this is yet to be confirmed. More recently, a 13-valent vaccine (PCV13), that protects against additional serotypes has been released, and research into next-generation vaccines is ongoing. The competitive underpinning of serotype coexistence and serotype replacement in pneumococcus (Weinberger et al., 2011), following vaccination with conjugate vaccines, has been a matter of intense investigation in recent years. Mathematical models have been used to estimate various parameters of interest, such as pathogen transmission rate, serotype-specific immune parameters, and to compute the vaccine impact (Cobey and Lipsitch, 2012; Flasche et al., 2013; Nurhonen et al., 2013; Bottomley et al., 2013).

In this study, contrary to the recent trend of including serotype-specific detail in complex, often individual-based, models for pneumococcus dynamics, we adopt more classical mathematical formulations, which are amenable to analytical treatment, and provide insight into coexistence, competition and vaccination effects. We consider both a neutral and non-neutral epidemiological model for serotype coexistence. The neutral model assumes symmetric interacting clones, under the broad premise of ecological equivalence (Chave, 2004; Hubbell, 2006), while the non-neutral formulation assumes fixed asymmetric trait values for competitive abilities at co-colonization. This approach goes in the same spirit of Lipsitch et al. (2009), advocating for the adoption of neutral null models as a starting point, to be followed by non-neutral formulations that include explicitly specific stabilizing mechanisms, in order to avoid hidden factors that may induce stable coexistence "for free".

We opted to embrace this dual perspective on multi-type pathogens. Using a nested modeling framework that interpolates between symmetric and asymmetric competition at co-colonization, we study the behavior of a neutral and non-neutral formulation for coexistence of multiple strains. The models are inspired by and fitted to a pneumococcus dataset from a study following PCV7 vaccination in Portugal (Valente et al., 2012), but are easily applicable to other similar data on comparable polymorphic pathogens. On the theoretical side, our results underscore the utility of the symmetry approximation in capturing the dynamics of multi-type pathogens. On the methodological side, we provide a new approach for estimating competition coefficients and vaccine efficacy using cross-sectional data pre- and post-vaccination, integrated with an epidemiological framework. By testing two seemingly opposing ecological theories on the same data set, we examine more closely the detectability of niche effects in certain epidemiological scenarios that describe summary measures at the population level.

2. Colonization model for pneumococcus among day-care children

Pneumococcus transmission is known to occur mainly in young children attending day-care, thus we model a closed system of transmission, implicitly assuming the contribution of contacts between this age group and older age groups is minimal (Hoti et al., 2009; Pessoa et al., 2013). Using a susceptible-infected-susceptible (SIS) deterministic model, we track the proportions of hosts in 6 compartments: susceptible hosts, S, hosts colonized by one vaccine serotype I_V, or one non-vaccine serotype, I_N, and co-colonized hosts I_{VV}, I_{NN}, and I_{VN} with two vaccine serotypes, two non-vaccine serotypes or one of each, respectively. In this formulation, individual serotypes enter the system only by way of a reduced number of higher-level entities, in this case, VT and NVT groupings. The pre-vaccine dynamics are formalized by the equations below:

$$\frac{dS}{dt} = \mu - S(\lambda_V + \lambda_N) + \gamma(1-S) - \mu S$$

$$\frac{dI_V}{dt} = S\lambda_V - I_V(k_{VV}\lambda_V + k_{VN}\lambda_N) - (\gamma+\mu)I_V$$

$$\frac{dI_N}{dt} = S\lambda_N - I_N(k_{NN}\lambda_N + k_{NV}\lambda_V) - (\gamma+\mu)I_N$$