CHAPTER 13

Theories of diversity in disease ecology

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13.1 Introduction

Organisms engaged in parasitic and pathogenic interactions with their hosts represent fundamentally important components of ecosystems. After decades of study, an appreciation has been cultivated for the role of pathogens in regulating host population dynamics (Hudson et al. 1998), shaping host behavior (Rohr et al. 2009; Perkins et al. 2016) and evolution (Best et al. 2008; Boots et al. 2012), facilitating exotic species invasions (Mitchell and Power 2003; Torchin and Mitchell 2004), increasing food web connectance (Lafferty et al. 2006a; Lafferty et al. 2006b), and influencing ecosystem biomass and functioning (Kuris et al. 2008). From an applied point of view, parasites and pathogens are the source of numerous challenges to conservation and human health, with the magnitude of those challenges expected to grow as numerous forms of global change continue their worrisome trends (Lafferty 2009; Martin et al. 2010; Rohr et al. 2011).

Despite the prominent role that parasites and pathogens play in all corners of ecosystems and their considerable entanglement throughout them, the treatment of parasitic and pathogenic interactions in ecological theory has largely been relegated to the study of interactions between a single parasite or pathogen and a single host. This view is perfectly adequate in many systems. In humans, for example, a number of pathogens that were once zoonotic have now adapted to exclusively circulate among humans (Wolfe et al. 2007). Many of these and other pathogens exhibit strain diversity (e.g., plasmodium and pneumococcus), yet others can, for all intents and purposes, be considered as a single strain in ecological analyses due to the essentially uniform immune response that genetic variants elicit from their hosts (e.g., measles and smallpox viruses) (Lipsitch and O'Hagan 2007). Moreover, this body of theory focused on single-pathogen, single-host systems has led to numerous fundamental advances in population ecology. Many works—including a canonical book (Anderson and May 1992) and a chapter in the third edition of *Theoretical Ecology: Principles and Applications* (Grenfell and Keeling 2007)—have developed, reviewed, and synthesized this body of work exquisitely.

Many parasites and pathogens cannot possibly be understood from a single-host, single-pathogen perspective, however. For every pathogen that has transitioned to exclusive transmission in humans, there are at least as many that circulate in one or more animal species or in animals and humans (Taylor et al. 2001; Wolfe et al. 2007). This diversity of hosts is significant in large part because of heterogeneities among hosts in their susceptibility and infectiousness to a given pathogen (Kilpatrick et al. 2006). Compounding those heterogeneities

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is the structure of contacts between hosts of the same and different species (Paull et al. 2012; Vazquez-Prokopec et al. 2016). In terms of pathogen diversity, it is not uncommon for pathogens to occur as multiple strains, each of which may elicit an immune response from its host that is more effective against itself than other strains (Gupta et al. 1996; Cobey and Lipsitch 2012; Bedford et al. 2015). These strains may interact in other ways, as well. They can engage in exploitative or interference competition, as can pathogens of completely different types (Pedersen and Fenton 2007). Pathogens can also engage in facilitation by temporarily suppressing a host's immune defenses (Mina et al. 2015).

The goal of this chapter is to survey prominent themes in theoretical research on host and pathogen diversity to date. Specifically, we draw attention to theory on the relationship between host diversity and disease and theory on the coexistence of diverse, interacting pathogens. Although there are many valuable contributions to the theory of host and pathogen diversity that do not fall cleanly into either of these two categories, we have chosen to focus on these areas due to the fact that they have received disproportionate attention in disease ecology research. For example, one topic that we have largely ignored that has a great deal of relevance to questions of diversity in host-pathogen interactions is evolution (Levin et al. 1999; Gandon et al. 2001; Grenfell et al. 2004; de Roode et al. 2005). We do, however, describe some important extensions and applications of the two bodies of theory on which we focus, and we comment on potential synergies between and future directions for these two bodies of theory.

Theories related to host and pathogen diversity have been presented in excellent reviews and syntheses before (Rohani et al. 2006; Pedersen and Fenton 2007; Civitello et al. 2015a; Seabloom et al. 2015), but we find it rare for theoretical work related to host and pathogen diversity to be presented alongside one another (Dobson 1990; Holt and Dobson 2006; Keeling and Rohani 2011). By doing so here, and with a focus on both theoretical advances and empirical evidence in support of those advances, we hope to facilitate crosstalk between these areas of research and to provide an accessible entry point for the more general reader of this volume.

13.2 Host diversity

Hypotheses regarding relationships between host diversity and disease have potentially important public health, management, and policy implications because they imply that changes to biodiversity, whether natural and anthropogenic, could increase or decrease human and wildlife diseases. Thus, understanding when, where, and how host diversity affects disease is important because it can facilitate predicting and mitigating disease outbreaks and can influence policy decisions for both biodiversity conservation and public health. Nevertheless, the disease ecology community has become polarized by disagreement over the question of whether host diversity reduces or increases infectious disease risk (Randolph and Dobson 2012; Lafferty and Wood 2013; Ostfeld 2013; Ostfeld and Keesing 2013; Salkeld et al. 2013; Wood and Lafferty 2013; Wood et al. 2014; Civitello et al. 2015a; Civitello et al. 2015b; Salkeld et al. 2015; Levi et al. 2016; Wood et al. 2016; Ostfeld and Keesing 2017; Wilcox 2017).

There are two competing hypotheses regarding the relationship between diversity and disease, the dilution and amplification effect hypotheses. The dilution effect hypothesis proposes that host diversity can reduce the per-host abundance of a particular pathogen and thus reduces the risk of infectious disease caused by that pathogen (Van Buskirk and Ostfeld 1995; Keesing et al. 2010). Consequently, the dilution effect predicts that loss of host diversity should increase infectious disease burden, with the implication that biodiversity conservation (defined as preserving functioning ecosystems with predominantly native species) might reduce infectious diseases. A meta-analysis revealed that much of the published research supports the dilution effect hypothesis (Civitello et al. 2015a). In contrast, some studies support alternatives to the dilution effect (Dunn 2010; Dunn et al. 2010; Randolph and Dobson 2012; Lafferty and Wood 2013; Wood and Lafferty 2013; Young et al. 2013; Wood et al. 2014, 2016), such as no relationship, a highly context-dependent relationship, or an amplification effect—defined by Keesing et al. (2006) as the opposite of the dilution effect, or a positive relationship between

host diversity and risk of a particular infectious disease in that host community. Here, we outline the theory for various relationships between host diversity and disease, as well as evidence in support of and against these relationships.

13.2.1 The basics of host diversity–infectious disease theory

Intuitively, host diversity is unlikely to affect pathogens of humans if they rarely interact with non-human hosts or are well controlled in some settings by sanitation, drugs, or vaccines (Wood et al. 2017). Examples include directly-transmitted, specialist pathogens of humans without free-living stages, intermediate hosts, or vectors, such as HIV and the causative agents of human tuberculosis, measles, non-pandemic influenza, and pneumonia (Wood et al. 2017). In contrast, multi-host, wildlife, and zoonotic pathogens, and pathogens with complex life cycles, free-living infectious stages, or generalist vectors are most likely to respond to changes to overall biodiversity. Examples include West Nile virus, hantavirus, and the causative agents of Chagas disease and leptospirosis (Dizney and Ruedas 2009; Suzan et al. 2009; Derne et al. 2011; Kilpatrick 2011; das Chagas Xavier et al. 2012; Gottdenker et al. 2012; Luis et al. 2018). Nevertheless, some of these expectations will need to be re-evaluated as disease ecologists better understand how host diversity (a) regulates the density of susceptible hosts that might then pass directly-transmitted pathogens amongst themselves (Keesing et al. 2006; Strauss et al. 2015; Luis et al. 2018) and (b) influences microbiota that protect against infectious diseases (e.g., Keesing et al. 2010; Johnson et al. 2015; Knutie et al. 2017).

For pathogens that are responsive to host diversity, theory suggests that if the dilution effect occurs, then relationships between host diversity and disease must be non-linear (Figure 13.1). This is because pathogens cannot exist where host richness equals zero given that pathogens rely on hosts for their survival (Ostfeld and Keesing 2000b; Ostfeld et al. 2009; Lafferty and Wood 2013; Wood and Lafferty 2013; Kilpatrick et al. 2017). Thus, pathogen abundance must initially increase at low levels of host richness before higher levels of richness could theoretically cause a dilution effect (Figure 13.1). For this reason, most dilution effect research has focused on how biodiversity reductions in relatively pristine communities affect disease risk (Van Buskirk and Ostfeld 1995; Schmidt and Ostfeld 2001; Keesing et al. 2006; Ostfeld and Keesing 2012; Levi et al. 2016). In other words, they have focused on the disassembly rather than the assembly of communities. Importantly, the more left-skewed or asymptotic relationships between host diversity and disease are, the more amplification effects should predominate, whereas the more right-skewed they are, the more dilution should predominate (Wood et al. 2016, see Figure 13.1). Additionally, if most communities fall in the right or left portions of unimodal diversity-disease curves, then dilution or amplification, respectively, will be most common, regardless of the direction of the skew (Figure 13.1).

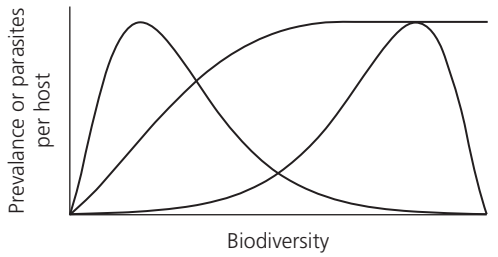

Figure 13.1 Hypothetical relationships between biodiversity and disease risk. The right-skewed distribution suggests that dilution might occur more frequently, but less intensely than amplification, because the relationship is moderately negative over a greater portion of the biodiversity gradient than it is strongly positive. The left-skewed distribution suggests that amplification might occur more frequently but less intensely than dilution, because the relationship is moderately positive over a greater portion of the biodiversity gradient than it is strongly negative. An asymptotic distribution suggests that amplification becomes increasingly moderate with biodiversity. In addition to the shape of biodiversity-disease relationships, the frequency with which each biodiversity level occurs in the environment will also affect the likelihood and intensity of dilution and amplification. These hypothetical curves underscore the importance of documenting the shape of biodiversity-disease relationships, which has rarely been accomplished empirically.

13.2.2 Mechanisms for host diversity–infectious disease interactions

Many of the proposed mechanisms for dilution and amplification include community assembly processes (LoGiudice et al. 2003; Ostfeld and LoGiudice 2003; Keesing and Ostfeld 2015), and thus it is important to cover some basic concepts regarding community assembly and disassembly. Communities are often dichotomized into those that exhibit substitutive assembly, whereby increases in diversity are associated with replacements of individuals because of competition (usually due to a fixed carry capacity for the community), and those that exhibit additive assembly, whereby total density or biomass increases with diversity (Joseph et al. 2013; Mihaljevic et al. 2014). In reality, this is a false dichotomy because theory suggests that all systems should assemble in both an additive and substitutive manner (Mihaljevic et al. 2014). For example, if we start with a system absent of species, then assembly must be additive because species will fill these unoccupied niches and thus will not compete. However, if we assume that niches are not endless, then as open niches are filled and species richness increases, so too do the chances that any new species added to the community will compete with an existing species. Hence, at the inflection point of the species richness versus abundance curve, all communities should shift from additive to substitutive assembly (Mihaljevic et al. 2014). What matters to dilution and amplification mechanisms discussed next is where communities fall on their species richness versus abundance curve.

When communities assemble additively, amplification likely occurs because additional host species will increase the total number of hosts, thus facilitating density-dependent pathogen transmission (Dobson 2004; Rudolf and Antonovics 2005). In contrast, some processes can cause either amplification or dilution. For example, when community assembly is additive, amplification or dilution can occur when competent hosts or non-competent hosts, respectively, are added to communities via the sampling effect—the idea that more diverse communities are more likely to contain a host species that either strongly increases or decreases disease (e.g., Halliday et al. 2017). However, sampling effects might be less about diversity per se than about species composition or the presence/absence of particular species. In contrast to the sampling effect, the niche complementarity hypothesis depends more directly on diversity per se. It is the notion that coexisting species should often fill different functional roles in a community and thus as diversity increases, regardless of composition, an ecosystem service, such as disease control, should increase (Cardinale et al. 2012; Becker et al. 2014; Rohr et al. 2015; Frainer et al. 2018). The shape of relationships between host diversity and disease will affect whether sampling effects cause amplification or dilution. Right-skewed relationships have more space for scenarios where sampling effects promote dilution and left-skewed relationships have more space to promote amplification.

Dilution is generally expected to occur more frequently when communities reach substitutive assembly, where additional host species must be substituted for individual hosts already present in the community and thus increasing richness does not increase host densities. Given that host densities tend to be relatively constant at this stage of assembly, the frequency of hosts that vary in their competency to transmit pathogens can thus change as new hosts are added. Using a multi-host model, Mihaljevic et al. (2014) considered density- and frequency-dependent pathogen transmission modes crossed with purely additive, purely substitutive, or a saturating host community abundance-richness relationship (starting additive and shifting to substitutive). Importantly, their model revealed that pathogens with frequency-dependent transmission generally show dilution regardless of whether host assembly was additive or substitutive, consistent with other theory supporting the notion that frequency-dependent transmission increases the likelihood of dilution (Dobson 2004; Rudolf and Antonovics 2005; Faust et al. 2017). However, when transmission was density dependent, amplification predominated when communities assembled additively and dilution predominated when they assembled substitutively; thus, the relationship between host richness and disease risk was hump-shaped for the more realistic scenario of a saturating host

community abundance-richness relationship—where communities start assembling additively and shift to substitutive assembly as niches fill. Given this theory, if communities are at a substitutive stage of assembly or experience frequency-dependent transmission, dilution seems likely. The biological mechanism often proposed for these patterns is based on the following assumptions: i) either pathogens should experience greater selection to infect abundant than rare hosts or abundant hosts likely make considerable investments into reproduction, growth, and/or dispersal at the expense of defenses against pathogens, or both occur, ii) abundant hosts are more likely to colonize and less likely to be extirpated from ecosystems, and iii) rare hosts displace common hosts when host diversity is high (Ostfeld and Keesing 2000b; Previtali et al. 2012). If these assumptions are true, then abundant and widespread hosts would regularly be amplifying hosts, while hosts with greater diluting potential would be added to communities as biodiversity increases or would be lost from communities when they become fragmented or disturbed (Joseph et al. 2013; Mihaljevic et al. 2014; Johnson et al. 2015; Levi et al. 2016). Under these scenarios, natural community disassembly would regularly cause increases in disease risk.

13.2.3 Evidence in support of proposed mechanisms for host diversity–infectious disease interactions

Several of the assumptions behind the theory for the dilution effect have empirical and observational support (Johnson et al. 2013a; Venesky et al. 2014; Rohr et al. 2015; Liu et al. 2018). For example, a combination of mesocosm experiments and field surveys demonstrated that the most abundant and widespread amphibian hosts are also the most competent hosts for a particular trematode species, supporting the notion that community assembly and disassembly processes function in a manner consistent with the dilution effect for this pathogen (Johnson et al. 2013a). Community (dis)assembly processes also support dilution effects documented for Lyme disease (Ostfeld and Keesing 2000a; LoGiudice et al. 2003; Ostfeld and LoGiudice 2003; Keesing et al. 2010), and in a recent study, when plant communities were (dis)assembled randomly, dilution was not observed, but when they (dis)assembled naturally, host diversity significantly reduced disease, again highlighting the potential importance of natural assembly processes (Liu et al. 2018). Several other studies support the notion that widespread hosts with "fast-paced" life histories are more susceptible to pathogens when controlling for exposure (Johnson et al. 2012; Han et al. 2015; Sears et al. 2015). This suggests that rare species have an advantage because they are infected less frequently given the same exposure as abundant species, a concept supported in many plant-pathogen systems. For example, Parker et al. (2015) coupled an experiment on forty-four host plant species, with a database on 210 host genera and 212 fungal pathogens, and showed that abundant and phylogenetically common plant species have more infectious disease than rare plant species, particularly those that are phylogenetically distant from common species.

Importantly, this advantage of rarity is also a mechanism for the associational resistance, crop rotation, and Red Queen hypotheses, classic and well-established concepts in plant-herbivore and disease biology, all of which are based on the assumption that communities are in the substitutive portions of their diversity-abundance curves (Lively and Dybdahl 2000; Barbosa et al. 2009; Lively 2010). The associational resistance hypothesis is the well-supported idea that plant host diversity reduces herbivory (Barbosa et al. 2009), in many cases from insects, such as aphids, that have long-term intimate relationships with their host plant (i.e., they are pathogens; Raffel et al. 2008). Whereas the associational resistance hypothesis focuses on the advantages of variation in plant host species in space, crop rotation highlights the value of increasing host plant diversity temporally to reduce pathogen accumulation (Mordecai 2011). The Red Queen hypothesis incorporates a within-species dilution effect (Clay et al. 2008; Ostfeld and Keesing 2012), positing that as a genotype gets more abundant, it faces greater parasitism pressures (Lively and Dybdahl 2000; Lively 2010) so that as the diversity of genotypes within a species increases, per capita disease risk generally declines (e.g., "Red Queen Communities"; Clay et al. 2008).

These examples highlight several mechanisms by which biodiversity can protect against disease both within and among species (see also Civitello et al. 2015a).

13.2.4 Application of theory on host diversity to disease management

Importantly, community assembly theory and field observations suggest that low-diversity communities are a nested subset of their higher-diversity counterparts (Johnson et al. 2013a). This is an example of how diversity and species composition can be correlated (Keesing et al. 2010), a correlation that can make it challenging to disentangle composition from diversity. However, this correlation can also make it easier to manage diseases than if diversity and composition were related to one another idiosyncratically, because managing diversity will by default result in the management of composition (Keesing et al. 2010). As an example, top predators are often added to communities late during community assembly and are often lost from communities first because of their rarity and need for large plots of intact land or water. Owing to these traits, much of the theory behind relationships between host diversity and disease suggests that top predators are frequently diluting species. However, top predator species cannot be added to or sustained in a community without first ensuring that there is an ample abundance and diversity of their prey species, and thus, the nested nature of assembly processes can make it difficult to manage single species or species composition without managing biodiversity.

Both diversity-disease interactions and conservation generally occur at local to regional scales (Kilpatrick et al. 2017) and thus the dependence of dilution and amplification effects on scale can influence the effectiveness of management (Lafferty and Wood 2013; Wood and Lafferty 2013; Kilpatrick et al. 2017). There are several ways in which scale might influence the relationship between biodiversity and disease. Theory suggests that relationships between biodiversity and infectious disease might be strongest at local scales and weaken at larger scales (Johnson et al. 2015) because species interactions that affect dilution and amplification occur at relatively small spatial scales, whereas abiotic factors like climate tend to predominate as drivers of biological patterns at larger spatial scales (Levin 1992; McGill 2010). Cohen et al. (2016) found support for this hypothesis in amphibian chytrid fungus, West Nile virus, and the bacterium that causes Lyme disease. At large spatial scales, the distribution of pathogens was strongly influenced by climate and human population density, whereas at smaller spatial scales, host richness was a significant predictor of disease prevalence (Cohen et al. 2016). It is also possible that the diluting capacity of a non-competent host might be most observable at small scales where encounter reduction (reducing encounter rate or duration between infected and susceptible individuals; Keesing et al. 2006) can occur, while the amplifying effect of a competent host might be most observable at larger temporal and spatial scales necessary to support definitive hosts and full lifecycle completion of the pathogen (Buck and Perkins 2018). Understanding the scales at which dilution and amplification predominate will be necessary to effectively employ manipulations of biodiversity as a disease management tool.

Whether biodiversity conservation is an effective management tool for protecting against newly introduced pathogens will likely depend on the mechanisms for dilution. Theory suggests that abundant hosts, which are more likely to colonize and less likely to be extirpated from ecosystems, amplify disease risk because: i) pathogens should experience greater selection to infect abundant than rare hosts, ii) abundant hosts make considerable investments into reproduction, growth, and/or at the expense of defenses against pathogens (i.e., trade-offs), or iii) both (Ostfeld and Keesing 2000b; Previtali et al. 2012). However, few studies have attempted to quantify the contribution of these two mechanisms to host competence. If abundant hosts are competent predominantly because pathogens experience greater selection pressure to infect abundant than rare hosts, then biodiversity conservation might not be very effective at preventing outbreaks of novel pathogens because they would be naïve to most of the hosts they encounter and thus would not have experienced selection to infect them yet. In contrast, if abundant hosts are competent predominantly because they invest

little in pathogen defenses, then an evolutionary history between a host and pathogen would be less necessary for dilution and thus biodiversity conservation could theoretically be effective at preventing colonization and outbreaks of novel pathogens. Hence, understanding the mechanisms for disease dilution will be crucial for determining whether biodiversity conservation will be effective at managing the hazards and risk of disease emergence (Luis et al. 2013; Hosseini et al. 2017).

13.3 Pathogen diversity

Whereas research on host diversity and infectious disease has revolved around polarizing debate about dilution and amplification, research on pathogen diversity and infectious disease has been somewhat more diffuse. One major focus though has been investigation of interactions among pathogens and their role in mediating a variety of outcomes in multi-pathogen systems: coexistence and competitive displacement, as well as cycling and turnover. An understanding of the conditions under which each of these outcomes occurs in a given system is of great significance, because changes in the factors that promote these outcomes—which can result from introduction of new pathogens, changes in host communities, application of interventions, or evolution—can shift a system's trajectory from one outcome to another. Thus, an ecological understanding of these regimes may hold important clues to how to successfully eradicate certain pathogens and how to prevent the emergence of others.

This body of theory has been developed primarily under two alternative scenarios: a single pathogen with multiple strains or multiple pathogens with a single strain each. Although there can be important differences between pathogen assemblages that fall into these different categories (e.g., the former may involve frequent genetic exchange, whereas the latter does not), there are many similarities among processes that shape these assemblages (Seabloom et al. 2015). These similarities are not surprising given more general similarities between processes shaping ecological and population genetic diversity (Vellend 2010). Accordingly, we draw from examples of theoretical work on pathogen diversity under both scenarios, and from work that ranges from generic to specific in its emphasis on a particular system.

13.3.1 A community ecology framework for pathogen coexistence

In a general sense, coexistence mechanisms in multi-pathogen systems can be organized around three themes (Bashey 2015). First, pathogen coexistence can be explained through niche differentiation, which involves more intense competition among like than unlike pathogens. Two forms of competitive interactions among pathogens that must be sufficiently weak to allow for co-existence (Rohani et al. 2006) include cross-reactive immunity, which involves one infection eliciting a host immune response that inhibits another (Figure 13.2c), and ecological interference, which involves pathogens reducing host availability for other pathogens through mechanisms unrelated to immunity (Rohani et al. 1998, 2003, and Figure 13.2a). At the same time, pathogens can sometimes facilitate one another through host immunosuppression (Mina et al. 2015). Second, competition-colonization trade-offs can contribute to the maintenance of pathogen diversity, provided that pathogens exhibit variation in traits related to within-host and between-host processes and that variation in those traits is negatively correlated (Hochberg and Holt 1990). The spatially discrete nature of hosts and the necessity of continual colonization of new hosts for pathogen persistence ensure that opportunities for pathogens specializing in competition or colonization are always available. Third, temporal and spatial heterogeneities in the environment experienced by pathogens can promote their coexistence under certain conditions. For example, storage effects occur when pathogens that vary in their responses to a heterogeneous environment transform their success under favorable conditions into persistence under unfavorable conditions through some form of buffering (Chesson 2000). This buffering can be achieved in a variety of ways, including by retreating to an alternative transmission mode when conditions under their primary transmission mode become unfavorable (Roche et al. 2014).

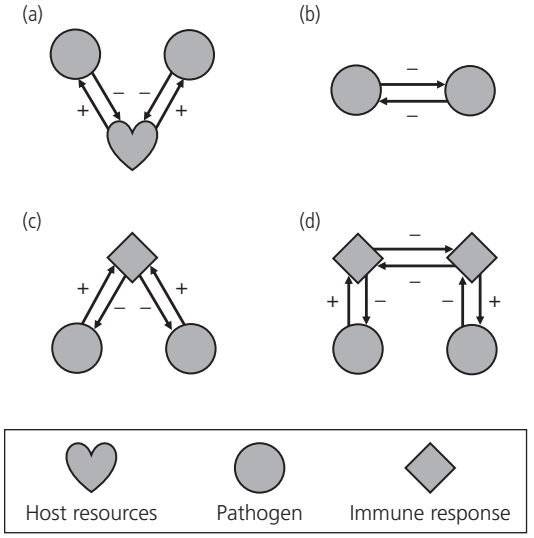

Figure 13.2 Different forms of pathogen interaction. Pathogen interactions can occur either during coinfection of a single host organism by two or more pathogens, or non-concurrently following infection by the first pathogen. (a) Exploitative competition can occur during coinfection when two or more pathogens compete for the same limited host resource. It can also occur non-concurrently if one pathogen kills hosts that can no longer be infected by other pathogens. (b) Interference competition most often occurs between pathogens coinfecting a single tissue type within a host. (c) Apparent competition can occur during coinfection when two or more pathogens stimulate a similar and sufficiently broad immune response. It can also occur non-concurrently when adaptive immunity developed in response to one pathogen is cross-reactive to a subsequent pathogen. (d) Facilitative interactions are also possible, such as when an immune response elicited by one pathogen inhibits a different immune response to another pathogen.

Given how difficult it can be to empirically measure any of several coexistence mechanisms that might be operating, realistic models of pathogen communities offer a valuable tool for gaining insight about the relative contributions of different mechanisms to coexistence in a given system (Mordecai et al. 2016). At the same time, it is critical to develop null models that do not result in coexistence as an artefact of a model's structure or as a result of an unintentionally impactful assumption (Lipsitch et al. 2009). To avoid that, an appreciation for past theoretical research that has established general conditions for coexistence of interacting pathogens is essential.

13.3.2 A diverse web of interactions among pathogens

Mechanisms for pathogen coexistence are usually modulated in one way or another by within-host interactions. Like other organisms, pathogens are known to engage in three major forms of competition: exploitative, interference, and apparent (Mideo 2009, and Figure 13.2a-c). These competitive interactions span what some have portrayed as three "trophic levels," corresponding to host resources (producers), pathogens (consumers), and host immune responses (predators) (Pedersen and Fenton 2007; Graham 2008). Focusing on simultaneous coinfections in humans, Griffiths et al. (2014) found that exploitative competition for host resources shared by two or more pathogens was the most common form of interaction. As an example, multiple species of malaria pathogens and helminths consume red blood cells, in some cases depleting them to such an extent that reductions in the density of competing pathogens result (Budischak et al. 2018). Interference competition between pathogens is also known to occur, although this appears to occur more commonly among pathogens that are physically co-located within certain host tissues (Griffiths et al. 2014). Interactions among pathogens occupying different host tissues or infecting a host at different points in time more typically take the form of apparent competition (Holt 1977), mediated by host immune responses that apply to some degree to two or more pathogens. For example, immune-mediated apparent competition was surmised among helminths infecting the digestive tracts of wild rabbits, due in part to the fact that pathogens occurring downstream in the digestive tract were able to negatively affect pathogens upstream of them (Lello et al. 2004). Despite widespread appreciation for this diversity of interactions among pathogens, pinpointing the nature of and mechanisms for these interactions can be a challenging undertaking (Fenton et al. 2010).

Among other interactions, the ways that pathogens can interact through host immune systems are quite diverse (Pedersen and Fenton 2007). In the context of pathogens infecting a host concomitantly (i.e., coinfection), interactions among even very phylogenetically distant pathogens are possible.

T-helper (Th) cells, which generate signals to activate different types of immune responses, offer one such example. Two major types of these are Th1 and Th2 cells, which elicit immune responses that are effective against intracellular and intercellular pathogens, respectively (Graham 2002). Because both Th1 and Th2 cells originate from the same pool of naive Th cells, an active immune response to one pathogen can inhibit the development of an immune response to another pathogen that infects the host shortly after the first pathogen, at least in the same tissue (Su et al. 2005; Graham 2008, and see Figure 13.2d). Conversely, pathogens that are combatted effectively with signals emanating from the same type of Th cells can lead to a synergized immune response on coinfecting pathogens (Curry et al. 1995; Page et al. 2005, see Figure 13.2c). Depending on which pathogens are involved in coinfection and the order in which two or more infections occur, coinfection can affect transmission dynamics of either or both pathogens and either dampen or exacerbate heterogeneities in the contributions of individual hosts to transmission (Graham et al. 2007).

Beyond coinfection, pathogens infecting a mammalian host can also interact through adaptive immunity developed in response to previous infections by other pathogens (Figure 13.2c). Although pathogen specificity is a hallmark of adaptive immunity, there are reasons to speculate that cross-reactivity of antibody-based adaptive immunity could be fairly common due to evolutionary advantages of an immune system that responds to pathogens that are similar, but not identical, to ones encountered in the past (Fairlie-Clarke et al. 2009). Regardless of their ultimate cause though, capturing the complexities of potential cross-reactivities among the many pathogens that a host faces is a daunting task for theory (Rohani et al. 2006). Cobey (2014) offered one way to simplify this complexity by proposing that a pathogen's "immunophenotype" be defined in terms of the strength, duration, and breadth of a host's immune response to it. These three dimensions can be made to depend on the abundances of other pathogens and various components of the host's immune system. Notably, the immunophenotype of a pathogen can depend on host species, infection history, and current infection and immunological status (Cobey 2014). One even simpler alternative involves tracking the status of hosts with respect to their immunity to each of many strains rather than their full history of infection (Gog and Swinton 2002; Gog and Grenfell 2002). The major advantage of this approach is that it reduces the dimensionality of the state space considerably, although this comes at the cost of the rather specific assumption that cross-reactive immunity renders some hosts completely immune instead of all or some hosts partially immune. Irrespective of the details, ways to address the complexity of pathogen interactions mediated by host immunity through simplifying, but biologically justifiable, assumptions remain an important goal for theory.

13.3.3 Theoretical results about pathogen coexistence

Theoretical results about pathogen coexistence depend a great deal on the properties of the model being used in the analysis. In the simplest models of ecologically similar pathogens, coexistence is a simple question of whether the strength of cross-reactive immunity is below a certain threshold (Keeling and Rohani 2011). From there, conditions for coexistence can quickly become more complicated. White (1998) showed that even the most basic refinements of assumptions about cross-reactive immunity lead to complications that affect criteria for coexistence. Under a model with susceptible-infectious-recovered compartments (SIR, in which hosts gain permanent immunity), conditions for coexistence were sensitive to assumptions about whether past infection results in reduced susceptibility or reduced transmissibility of a subsequent pathogen (White 1998). This distinction is important, because reduced transmissibility blocks transmission but still allows for population immunity to accrue. Under a model with susceptible-infectious-susceptible compartments (SIS, in which hosts are only immune temporarily), coexistence was enabled by differences in the pathogens' abilities to infect partially or completely susceptible hosts (White 1998). This effectively partitions hosts into two distinct resources that can support the coexistence

of two pathogens specializing on those resources. Coinfection with another pathogen can add an additional dimension to the way in which hosts are partitioned into distinct resources. Although not capable of fully explaining coexistence of *Streptococcus pneumoniae* strains, Cobey and Lipsitch (2013) found that coinfection with *Haemophilus influenzae* promotes *S. pneumoniae* strain coexistence by disrupting the competitive hierarchy of strains that is typical in the absence of *H. influenzae*. Trade-offs in pathogen fitness in different host or vector species can contribute similarly to pathogen coexistence (Mordecai et al. 2016).

The task of explaining pathogen coexistence in real systems can sometimes be much more formidable than explaining the coexistence of two or three pathogens in a simple model. To explain the coexistence of over ninety strains of *S. pneumoniae*, Cobey and Lipsitch (2012) found that two forms of immunity needed to be invoked. Acting alone, an antibody-based form of immunity that was specific to strains to which an individual had been previously exposed was not sufficient to counteract inherent competitive advantages of certain strains, resulting in greater competitive exclusion than has been observed empirically. When a nonspecific form of immunity based on CD4+ Th cells was added to the model, Cobey and Lipsitch (2012) were able to reproduce observed levels of serotype diversity and to better account for other aspects of *S. pneumoniae* epidemiology, as well. Another consideration that can be important for explaining strain coexistence is the potential for pathogen strains to evolve on relatively fast timescales. In such cases, strong cross-reactive immunity can contribute to stable coexistence of a discrete number of strains, provided that pathogen molecules detected by the immune system respond evolutionarily to that form of diversifying selection. Even in the presence of the homogenizing effect of genetic exchange among strains, Gupta et al. (1996) found empirical support for this theoretical result in the form of more discrete structuring of multilocus, antigenic variants of *Neisseria meningitidis* bacteria than would be expected under random multilocus combinations consistent with observed levels of variation at each locus on its own. Relaxing the assumption of homogeneous mixing of host contacts by Gupta et al. (1996) amplifies this tendency of strong cross-reactive immunity to promote coexistence of multiple discrete strains, resulting in even greater strain diversity (Buckee et al. 2004; Buckee et al. 2007).

Negative frequency dependence favoring antigenic variants to which host immunity has deteriorated over time has been shown to result in cyclical dynamics that can maintain pathogen diversity through time (Gupta et al. 1998; Gupta and Galvani 1999; Gomes et al. 2002). While these basic results are clear, additional considerations come into play when models are used to explain cyclical dynamics in real systems. Focusing on the bacteria that cause cholera, Koelle et al. (2006) showed that alternating cycles of dominance by either of two serotypes in Bangladesh could be explained by a simple, two-serotype model with strong, but nonetheless partial, cross-reactive immunity. Interestingly, acknowledgment of two serotypes with partial cross-reactive immunity provides an alternative to their previous explanation of cholera dynamics in this setting, which depended on the assumption that immunity is temporary (Koelle et al. 2005). In other words, partial cross-reactive immunity between two strains with alternating cycles offers a plausible explanation for the appearance of temporary immunity when information about strains is not visible in the data (Koelle et al. 2006). Another pathogen that exhibits strain cycling is dengue, which is transmitted by mosquitoes and is well known for the complex interannual dynamics of its four serotypes that affect humans (Cummings et al. 2004). One hypothesis about dengue serotype cycling that has been advanced is that it is driven by antibody-dependent enhancement (ADE), which could enhance the susceptibility and/or transmissibility of an infection with a second serotype, thereby giving a boost to non-dominant serotypes beyond that afforded by herd immunity against the dominant serotype (Ferguson et al. 1999; Cummings et al. 2005; Recker et al. 2009). Although recent evidence does demonstrate ADE of severe disease (Katzelnick et al. 2017), whether ADE is capable of eliciting the effects necessary to drive serotype cycling remains unclear. A more widely accepted alternative hypothesis is that some combination of temporary cross-reactive immunity and seasonal

transmission account for serotype cycling (Wearing and Rohani 2006; Adams et al. 2006; Reich et al. 2013; ten Bosch et al. 2016).

13.3.4 Application of theories of pathogen diversity to disease management

One notable body of theoretical work on pathogen diversity that is relevant to disease management assumes that strains circulate independently of one another. This "strain theory" of malaria (Gupta et al. 1994; Gupta and Day 1994) is based on the premise that immunity to a single strain of *Plasmodium falciparum* is long-lasting, but immunity to all strains is negligible. A highly significant, but controversial, prediction of strain theory is that the R_0 for any given strain is relatively low and, thus, intervention coverage thresholds required for eradication are significantly higher if *P. falciparum* is conceptualized as a single- rather than a multi-strain pathogen (Gupta et al. 1994). Given that R_0 estimates for malaria that do not account for strain structure can often be in the range of fifty to a hundred or more (Smith et al. 2007), strain theory makes eradication seem vastly more achievable (Gupta et al. 1994). One critique of this prediction (Dye et al. 1996) used results from a field trial of insecticide-treated bednets that showed little impact on prevalence in humans to argue that intervention coverage would need to be in excess of 96% to achieve eradication, which is far higher than Gupta et al. (1994) envisioned. In response, Gupta and Snow (1996) provided an alternative interpretation of the trial data that is compatible with predictions from strain theory. Recent extensions of strain theory (Artzy-Randrup et al. 2012; He et al. 2018) have used agent-based models to place more emphasis on the highly polygenic nature of *P. falciparum* antigenic repertoires and the important complication that *P. falciparum* undergoes extensive recombination, which raises questions about what the concept of a strain even means for this pathogen (McKenzie et al. 2008).

Another body of theoretical work involving multiple pathogen strains that has received significant attention is that of vaccine escape, which is a phenomenon whereby strains that are not targeted by a vaccine can increase in prevalence due to competitive release from a target strain that has been reduced by vaccination (McLean 1995). This outcome depends critically though on the strength of cross-reactive immunity and the relative competitive abilities of the target and non-target strains prior to vaccination (Gupta et al. 1997). In addition, McLean (1995) found that low vaccination coverage was one reason why vaccine escape might not be observed in a system that otherwise has potential for it. Looking at coverage from a different perspective, Lipsitch (1997) found that vaccination coverage thresholds for elimination of the target strain were lower for a strain-specific vaccine than for a bivalent vaccine, which would affect both strains. Intuitively, this result follows from the non-target strain contributing to the demise of the target strain via apparent competition through naturally-acquired, cross-reactive immunity, while the non-target strain remains resilient to vaccine-derived immunity. Lipsitch (1997) noted that such a scenario may be compatible with the biology of *H. influenzae*. One pathogen for which strain replacement from vaccine escape has been observed empirically is pneumococcus (Hanage et al. 2010). Others with perceived potential for strain replacement include rotavirus (Pitzer et al. 2011), human papillomavirus (Orlando et al. 2012), malaria (Neafsey et al. 2015), dengue (Rodriguez-Barraquer et al. 2014), and pertussis (Nicoli et al. 2015).

The ecological principle underlying vaccine escape, competitive release, is relevant not only to competing strains but also to distinct pathogens engaged in competition. As an example, Lloyd-Smith (2013) assessed the potential of orthopox viruses besides smallpox virus, especially monkeypox virus, to fill the niche vacated by smallpox virus following its eradication in 1980. Although intensive epidemiological investigations in the early 1980s concluded that monkeypox virus was not quite capable of sustained spread ($R_0 = 0.83$) (Fine et al. 1988), more recent epidemiological trends show clear signatures of competitive release not from smallpox virus itself, but from the smallpox vaccine that is no longer in use and thus protects only an aging, and dwindling, population (Rimoin et al. 2010). It is notable that the only two infectious diseases eradicated to date—smallpox and rinderpest—both appear to have competitors

encroaching on their vacated niches. Rather than discourage efforts to eradicate diseases, the lesson from these examples is that the possibility of competitive release of other pathogens should not come as a surprise. Instead, preparations for this possibility, along with appropriate research and surveillance, should be undertaken during early stages of planning for eradication campaigns (Lloyd-Smith 2013).

13.4 Are theories of host and pathogen diversity ships passing in the night?

The respective bodies of theory on host and pathogen diversity surveyed previously have been developed largely independently of one another. That is, theories of host diversity have mostly asked how host diversity impacts the disease burden associated with a single type of pathogen, and theories of pathogen diversity have mostly asked how diverse pathogens manage to coexist in a single type of host. Here, we explore a few points of interface between these distinct bodies of theory, with the goal of stimulating further developments at this intersection.

One natural question at the interface of host and pathogen diversity is what impact the former has on the latter. Intuitively, host diversity should promote pathogen diversity by expanding the diversity of niches available to pathogens (Hechinger and Lafferty 2005). One way that this can manifest is in terms of the diversity of host immune repertoires, which models have shown can promote strain diversity (Gupta and Galvani 1999). Support for host diversity as a driver of pathogen diversity by way of niche diversity has also been demonstrated in broader pathogen communities (Johnson et al. 2016). Beyond ideas related to niche diversity, factors that affect the persistence of any single pathogen should also affect pathogen diversity, given that the maintenance of diversity requires the persistence of each constituent species. A number of theoretical studies (Holt et al. 2003; Dobson 2004; Fenton et al. 2015) have demonstrated that host species can easily differ in their individual contributions to a pathogen's persistence. In some cases, a single host species may be sufficient to ensure persistence of a pathogen, whereas in other cases pathogen persistence may only be possible in the presence of multiple host species that are each incapable of sustaining the pathogen on their own. In primates, it has been noted that host species with higher population densities tend to harbor more pathogens (Nunn et al. 2003; Altizer et al. 2007). This finding is consistent with theoretical predictions that higher host density should allow for persistence of pathogens with a wider range of threshold densities for persistence (Dobson 1990).

Another important question at the interface of host and pathogen diversity is what the implications of pathogen diversity are for host health. While the effects of host diversity on host health have been investigated intensely, pathogen diversity has more often been examined as its own object of study rather than as a driver of disease. There are exceptions though. In a simple model of antigenic strain diversity, Abu-Rabbad and Ferguson (2005) showed that there is a monotonically increasing relationship between pathogen diversity and overall pathogen prevalence combined across strains. This relationship was modulated critically though by the strength of cross-reactive immunity, with more intense cross-reactive immunity resulting in lower prevalence. Empirical investigations of the relationship between pathogen diversity and host disease have yielded somewhat different results. An empirical study (Johnson and Hoverman 2012) of six trematode pathogens in an amphibian host found that the relationship between pathogen diversity and host disease depended on whether pathogen communities assembled additively or substitutively, mirroring results about the relationship between host diversity and disease. Specifically, additive assembly increased disease severity, whereas substitutive assembly decreased disease severity in cases where the prevalence of a more virulent pathogen was reduced by increased pathogen diversity (Johnson and Hoverman 2012). In two studies (Johnson et al. 2013b; Rottstock et al. 2014) in which host disease was examined across naturally occurring variation in host and pathogen diversity, greater pathogen diversity was negatively associated with disease, which is more consistent with the notion that pathogen community assembly is substitutive in those systems. In theoretical work going forward, considering pathogen diversity and

the dynamic nature thereof may, at a minimum, provide greater insight into the mechanisms underlying relationships between host diversity and disease.

Relationships between host and pathogen diversity are also sensitive to other players in ecological communities. In particular, predators of pathogens offer an additional potential mechanism by which overall biodiversity can mitigate disease risk. Predation on pathogens and parasitized hosts can be an important but overlooked limit on pathogens; for example, comprising an estimated 44% of trophic links in the well-studied Carpinteria Salt Marsh food web (Lafferty et al. 2006b), though most of these links led to pathogen transmission rather than pathogen loss. In one study, increasing tadpole diversity was associated with reduced chytrid fungal loads per frog, and the degree to which tadpole species filter-fed; thus, removing chytrid zoospores from the water was associated positively with their ability to reduce chytrid infections in both transmission experiments and field surveys (Venesky et al. 2014). In another study, the diversity of predators of multiple species of trematode cercariae was associated negatively with trematode infections per host in the field (Rohr et al. 2015). This study used both experiments and mathematical models to demonstrate that the degree to which a species preferred to consume pathogens over hosts determined how strongly that species could dilute disease through pathogen-encounter-reduction mechanisms (Rohr et al. 2015). Many effects of predator diversity on pathogens might actually be species composition effects, but they are good examples for where a sampling effect in diverse communities could tend to increase the chance that pathogen feeders might occur.

13.5 Diversifying the use of theory to address questions of diversity in disease ecology

Theories on host and pathogen diversity in disease ecology have developed over the past three to four decades and have done much to extend understanding of infectious disease dynamics beyond the single-host, single-pathogen paradigm that preceded it, and still dominates. Many key advances in the theory of multi-host and/or multi-pathogen systems have been underpinned by theoretical developments in community ecology more broadly. In reference to host diversity, community assembly theory has played an important role in clarifying the conditions under which diseases in some host communities are subject to dilution effects and others to amplification effects. In reference to pathogen diversity, modern coexistence theory has been helpful for many who seek to understand what impact each of the very many possible interactions among pathogens have on their mutual persistence. We now turn our attention to questions about the future. What underutilized elements of ecological theory will underlie future advances in our understanding of multi-host and/or multi-pathogen systems? What new theoretical capabilities are needed to meet the most formidable challenges ahead?

One feature of current theory that we find strikingly pervasive is the focus on long-term, equilibrium behavior. As a starting point, using models with stable equilibrium properties to analyze something as inherently complex as a multi-host and/or multi-pathogen system is perfectly reasonable. At some point though, one must wonder what lies beyond models with those properties. Regarding host diversity, we now know a great deal about how changes in host diversity affect the transmission of pathogens that exhibit long-term persistence, but is there similarly general understanding that can be obtained about how changes in host diversity affect diseases prone to epidemics or that are only beginning to emerge? Troublingly, some of the multi-host diseases of greatest concern to human health—such as Lyme disease, West Nile, and yellow fever—exhibit strongly seasonal epizootics with a great deal of poorly understood interannual variation therein. To assume that we fully understand the role of host diversity in those systems would be naive. Regarding pathogen diversity, we now know a great deal about conditions that permit the long-term coexistence of multiple pathogens that circulate in a well-mixed host population, but do we know the extent to which those conditions apply for strongly-immunizing pathogens that persist only

at the scale of a metapopulation? In systems such as these, coinfection—a key driver of pathogen interactions in many systems—may be much less common (Vogels et al. 2019). As inspiration for how to advance theory in light of these challenges, one nice demonstration by Lourenço and Recker (2013) showed how more realistic representations of transmission dynamics can alter conclusions about pathogen interactions. They used a spatially explicit, agent-based model of dengue virus transmission to show that stochastic amplification of differences among serotypes was sufficient to recreate many of the same patterns that simpler models could explain only by invoking strong interactions among serotypes. Until possibilities such as these are explored in a greater diversity of systems, much of the theory of multi-host and/or multi-pathogen systems will, in our view, remain provisional.

Another theme of current theory that we have noticed is that the variety of pathogen assemblages that are considered in analyses of multi-pathogen systems is somewhat limited. For example, rather than consider all pathogens in a given community, theoretical investigations often focus on a much smaller subset, such as i) hosts known to harbor a particular type of pathogen (e.g., West Nile virus and its many hosts); ii) strains within a single species of pathogen (e.g., dengue virus serotypes); iii) hosts and/or pathogens that all have a similar mode and dynamic of transmission (e.g., pathogens that all have stable, long-term persistence in a shared set of hosts); iv) a small number of different pathogen types with a documented interaction of specific interest (e.g., helminths and malaria pathogens); or v) a system with a tractable number of multiple hosts and multiple pathogens (e.g., barley yellow dwarf viruses of plants). There are important questions to be addressed in each of these situations, but the fact that the current state of theory is limited to these subsets of the full assemblage of hosts and pathogens must be acknowledged. We find these choices to be reminiscent of the "modules" that have been a focus of theory on food webs (Holt 1997). They may well be instructive in many ways, but they are somewhat myopic in their view of true communities of pathogens and their hosts. There are, of course, reasonable arguments for restricting the focus of theory in this way. First, it may be the case that interactions beyond the players in these restricted groupings are so minimal as to be insignificant. After all, the specificity to respond to only certain pathogens, or their close relatives, is a hallmark of adaptive immune responses. At the same time though, immune responses can be much less specific in many host species (Wuerthner et al. 2017), a consideration that could lead to greater connectedness in host-pathogen interaction networks than previously appreciated. Second, the analytical tractability of models involving a large number of types quickly diminishes as diversity exceeds that of the more limited assemblages that have been the focus of much work to date. In addition to ways that some models of strain diversity have addressed this issue (Gog and Grenfell 2002; Cobey and Lipsitch 2012), theory from other areas of ecology, such as food webs (McCann 2011), may offer inspiration for future advancements.

Finally, it is worth reflecting on the range of possibilities for how theory—and, more broadly, mechanistic models with a basis in theory—can be used to enhance understanding and management of host-pathogen systems. Many compartmental models offer the ability to obtain formulas describing how various parameters affect conditions for pathogen persistence, which can then be used to describe the contribution of different host species to transmission, explain pathogen coexistence, or inform strategies for pathogen elimination. Models ranging from simple to complex can be used to simulate system dynamics, informing how different biological mechanisms give rise to different observable patterns or how a system might respond to various perturbations from the environment, evolutionary forces, or interventions. Models can be generic and studied without reference to a particular system, or they can be used to extract signals from data not readily apparent in the data itself. Models can also be used for forecasting, an enterprise that directly interfaces models with data, offers a unique opportunity for model comparison and hypothesis testing, and offers direct value for public health (Du et al. 2017; Johnson et al. 2018; Reich et al. 2019). While there

are notable exemplars involving multi-host and/or multi-pathogen systems for each of these uses of theory, our perception is that progress in many of these areas is much farther along for single-host, single-pathogen systems than for multi-host and/or multi-pathogen systems. As theories of host and pathogen diversity continue to develop, theoretical ecologists may benefit from looking outward from the narrow literature within existing niches in this area, such as the ones we focused on in this review. Doing so may inject humility and spark creativity, leading to the construction of new and exciting theoretical niches in this field.

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