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Quantifying mechanisms of coexistence in disease ecology

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Abstract

Pathogen coexistence depends on ecological processes operating at both within and between-host scales, making it difficult to quantify which processes may promote or prevent coexistence. Here, we propose that adapting modern coexistence theory—traditionally applied in plant communities—to pathogen systems provides an exciting approach for examining mechanisms of coexistence operating across different spatial scales. We first overview modern coexistence theory and its mechanistic decomposition; we subsequently adapt the framework to quantify how spatial variation in pathogen density, host resources and immunity, and their interaction may promote pathogen coexistence. We apply this derivation to an example two pathogen, multiscale model comparing two scenarios with generalist and strain-specific immunity: one with demographic equivalency among pathogens and one with demographic trade-offs among pathogens. We then show how host–pathogen feedbacks generate spatial heterogeneity that promote pathogen coexistence and decompose those mechanisms to quantify how each spatial heterogeneity contributes to that coexistence. Specifically, coexistence of demographically equivalent pathogens occurs due to spatial variation in host resources, immune responses, and pathogen aggregation. With a competition–colonization trade-off, the superior colonizer requires spatial heterogeneity to coexist, whereas the superior competitor does not. Finally, we suggest ways forward for linking theory and empirical tests of coexistence in disease systems.

KEYWORDS
coexistence theory, ecosystem engineer, host immunity, metacommunity, pathogen diversity, spatial heterogeneity, variation-dependent mechanisms

INTRODUCTION

Pathogen communities consist of multiple pathogen species, or even different genetic strains of the same species, co-occurring both within individual hosts and across host populations (Dobson et al., 2008). The diversity of coexisting pathogens impacts dynamics such as host pathology (Johnson & Hoverman, 2012; Katzelnick et al., 2017; Thomas et al., 2003), pathogen transmission (Ferguson et al., 1999; Rohani et al., 1998), and pathogen emergence (Alizon et al., 2013). In human epidemiology, understanding the mechanisms that facilitate strain diversity has tangible implications for public health, such as predicting the efficacy of vaccinations if strain replacement occurs (Matthijnssens et al., 2009) or understanding how pathogen competition may interact with vaccination strategies (Zinder et al., 2013). Therefore, for decades disease ecologists and epidemiologists have sought a

better understanding of which ecological mechanisms promote or hinder the coexistence of pathogens in plant, wildlife, and human systems (Ferguson et al., 2003; Takala & Plowe, 2009; Thompson et al., 2010). To do this, epidemiologists often build competing mathematical models that include different mechanisms. Comparing the models' predictions to observed patterns of pathogen strain diversity can help reveal which mechanisms are important (Lipsitch et al., 2009). Yet even with these sophisticated methods, reliably quantifying the relative contributions of multiple mechanisms to coexistence dynamics has been frustratingly elusive.

Part of the problem is that pathogen coexistence depends on a complex interplay of ecological processes operating within individual hosts and across the host population, and we need methods that can quantify the main and interactive effects of each mechanism. Within hosts, pathogens interact with different components of a host's immune response; these immunological host–pathogen interactions are considered the pathogen's "immunological niche" (Lloyd-Smith, 2013). The degree to which these immunological niches overlap can alter outcomes of pathogen coexistence. For example, pathogen infection may compromise host immune responses, creating facilitative effects that promote coinfection (Beldomenico & Begon, 2010; Rynkiewicz et al., 2015). Intracellular pathogens infecting vertebrates may elicit a specific immune response profile called T-helper type 1 (Th1) responses (Ezenwa & Jolles, 2011). Upregulation of Th1 immunity results in a decreased capacity to mount Th2 immune profiles that target extracellular parasites, thereby increasing host susceptibility to coinfection (Pedersen & Fenton, 2007). Alternatively, pathogens may elicit negative interactions with one another by competing for limited resources within hosts (Cressler et al., 2014), or by causing a general host immune response that targets similar pathogens, a phenomenon referred to as cross-immunity (Cobey & Lipsitch, 2013; Fenton & Perkins, 2010; Gog & Grenfell, 2002). Cross-immunity is predicted to promote the differentiation of pathogens into distinct immunological niches to minimize these negative interactions (Cobey & Lipsitch, 2013; Gog & Grenfell, 2002), and has been shown to promote competitive exclusion of antigenically similar strains in systems such as influenza (Ferguson et al., 2003; Koelle et al., 2006) and dengue (Cummings et al., 2009; Recker et al., 2009). Furthermore, spatial and temporal heterogeneities in host behavior and contact networks can modulate interactions between pathogens or alter the number of hosts available for infection and pathogen spread (Buckee et al., 2004; Rohani et al., 1998). In addition, heterogeneity in host transmission rates has been shown to promote long-term coexistence of different viral strains in a baculovirus system (Fleming-Davies et al., 2015).

METACOMMUNITIES, MODERN COEXISTENCE THEORY, AND DISEASE SYSTEMS

Each of these processes in isolation may alter the maintenance of pathogen diversity. However, multiple ecological mechanisms at different spatial scales are likely to be operating simultaneously, complicating efforts to identify the most salient mechanisms that maintain pathogen coexistence or promote exclusion. Furthermore, these processes may interact in a manner that yields emergent dynamics that cannot be predicted by studying each process in isolation. Consequently, recent work emphasizes incorporating methods from community ecology—a discipline with a wide breadth of conceptual and analytical tools for investigating multiscale species interactions—to study multipathogen assemblages, coexistence, and the maintenance of diversity (Collinge & Ray, 2006; Johnson et al., 2015; Lloyd-Smith, 2013).

Metacommunity theory in particular has received significant attention in recent years due to parallel processes that operate within metacommunities and disease systems (Mihaljevic, 2012; Seabloom et al., 2015). Metacommunity theory posits that species inhabit environmental patches that are linked by migration (Leibold et al., 2004). The community composition at both local and regional levels depends on an interplay of niche-based processes operating within patches and dispersal-based processes operating between patches (Leibold et al., 2004; Leibold & Chase, 2017). By treating hosts as patches, and disease transmission as species dispersal, metacommunity theory provides a conceptual framework that incorporates both within- and between-host processes in regulating pathogen coexistence or exclusion, dynamics of known importance, but that are often considered separately (Lloyd-Smith et al., 2005; VanderWaal & Ezenwa, 2016).

Moving forward, we argue that the integration of metacommunity theory with modern coexistence theory (MCT; Chesson, 2000b) provides a promising method of quantifying how spatial structure across scales may promote or hinder coexistence (Shoemaker & Melbourne, 2016), regardless of underlying model assumptions or system specifics. In MCT, species are said to stably coexist if each species exhibits a positive growth rate when rare (GRWR) in the system, a condition referred to as the mutual invasibility criterion (Chesson, 2000b; Box 1). The contribution of spatially or temporally fluctuating mechanisms to the GRWR can be quantified, or decomposed, by analytically removing variation in the mechanism of interest and comparing observed growth rates with and without the variation present (Chesson, 2000b). Until recently, MCT decompositions have primarily been used to study a limited set of coexistence mechanisms in

BOX 1 Overview of mechanistic decomposition in pathogen model

In modern coexistence theory (MCT), stable coexistence occurs when each pathogen exhibits a positive growth rate when rare (GRWR), while all other pathogens are at equilibrium in the system. To calculate the average GRWR ($\overline{r}_j$) for each pathogen when rare (termed the invader), we simulate a disease system with only one pathogen (termed the resident) and let it reach equilibrium in abundance and spatial distribution (Figure 1a). We then introduce the invader at low density and spatial equilibrium in each time step, $t_{k,0}$, calculate its GRWR by simulating the model one time step forward ($t_{k,1}$, Figure 1b), and average these GRWR over time steps, t_n. We alternate the roles of resident and invader, allowing us to calculate GRWR for both pathogens. In order for coexistence to occur, $\overline{r}_j$ must be >0 for both pathogens (Figure 1c).

The overall GRWR for each pathogen as the invader can be partitioned into variation-independent and dependent mechanisms. To do so, the GRWR calculation is repeated after removing variation in one or more ecological mechanisms from the system. For each of these calculations, the invader GRWR, $\overline{r}_i$, is compared with the resident growth rate, $\overline{r}_r$. Although the resident's overall growth rate is 0 (given it is at its equilibrium) the invader–resident comparison is necessary, as a given mechanism can impact the growth rate of the invader, resident, or both. For two sources of variation (here generically labeled A and B), the contribution to the overall GRWR when all variation is removed from the system is represented by Δ_i^0. Δ_i^A represents the contribution from variation in A, Δ_i^B represents the contribution from variation in B, and Δ_i^{AB} represents the interactive effect from simultaneous variation in both A and B after accounting for each main effect (Δ_i^A and Δ_i^B) (Figure 1d,e). The sum total of these contributions is the overall GRWR:

$$\overline{r}_i - \overline{r}_r = \Delta_i^0 + \Delta_i^A + \Delta_i^B + \Delta_i^{AB}. \quad (1)$$

annual grassland communities (Barabás et al., 2018; Hallett et al., 2019) as extending MCT to different biological systems required deriving novel, complex analytical solutions for each coexistence mechanism. This was often impossible in more complex models, such as those used to understand pathogen dynamics (Ellner et al., 2019).

Therefore, applications of MCT to disease systems, and even other free-living systems in community ecology, have predominantly focused on using a broader, conceptual MCT framework that circumvents the need for deriving separate analytical solutions for each new coexistence mechanism, but does not incorporate variation-dependent mechanisms of coexistence. Under this conceptual approach to MCT decompositions, mechanisms are categorized as either stabilizing (i.e., increasing niche differentiation) or equalizing (i.e., reducing fitness differences; Adler et al., 2007; Chesson, 2000a; Levine et al., 2008; Mordecai et al., 2015). For example, Cobey and Lipsitch (2012) reproduced observed *Streptococcus pneumoniae* serotype diversity by modeling both stabilizing and equalizing components of host immune responses to *S. pneumoniae* infection. Clay et al. (2019) used a zooplankton pathogen system to examine how priority effects alter coexistence, depending on whether the priority effects favored first- or second-arrival pathogens, respectively. Additionally, using the barley and cereal yellow dwarf virus system, Mordecai et al. (2015) showed how pathogens' abilities to coinfect plant hosts stabilized coexistence, but ultimately required vector generalist–specialist trade-offs to offset competitive interactions. Both Clay et al. (2019) and Mordecai et al. (2015) used phase diagrams to identify whether pathogens subsisted individually or coexisted over a range of model parameters, and subsequently inferred how different ecological mechanisms promoted or inhibited coexistence by comparing phase diagrams with and without that mechanism present in the system (Clay et al., 2019; Mordecai et al., 2015).

Such uses of the stabilizing/equalizing MCT framework successfully highlight the crucial role different ecological mechanisms have on pathogen coexistence. However, applications of MCT to disease systems have yet to incorporate a full, variation-dependent decomposition of coexistence, which provides a quantitative framework for understanding how spatial and temporal heterogeneity can promote coexistence (Chesson, 2000a, 2000b). More comprehensive integration of MCT and its decomposition framework with disease ecology will provide insight into how heterogeneity scales to alter pathogen coexistence or competitive exclusion.

Recent developments in MCT (Ellner et al., 2019) now allow for more general decompositions of coexistence

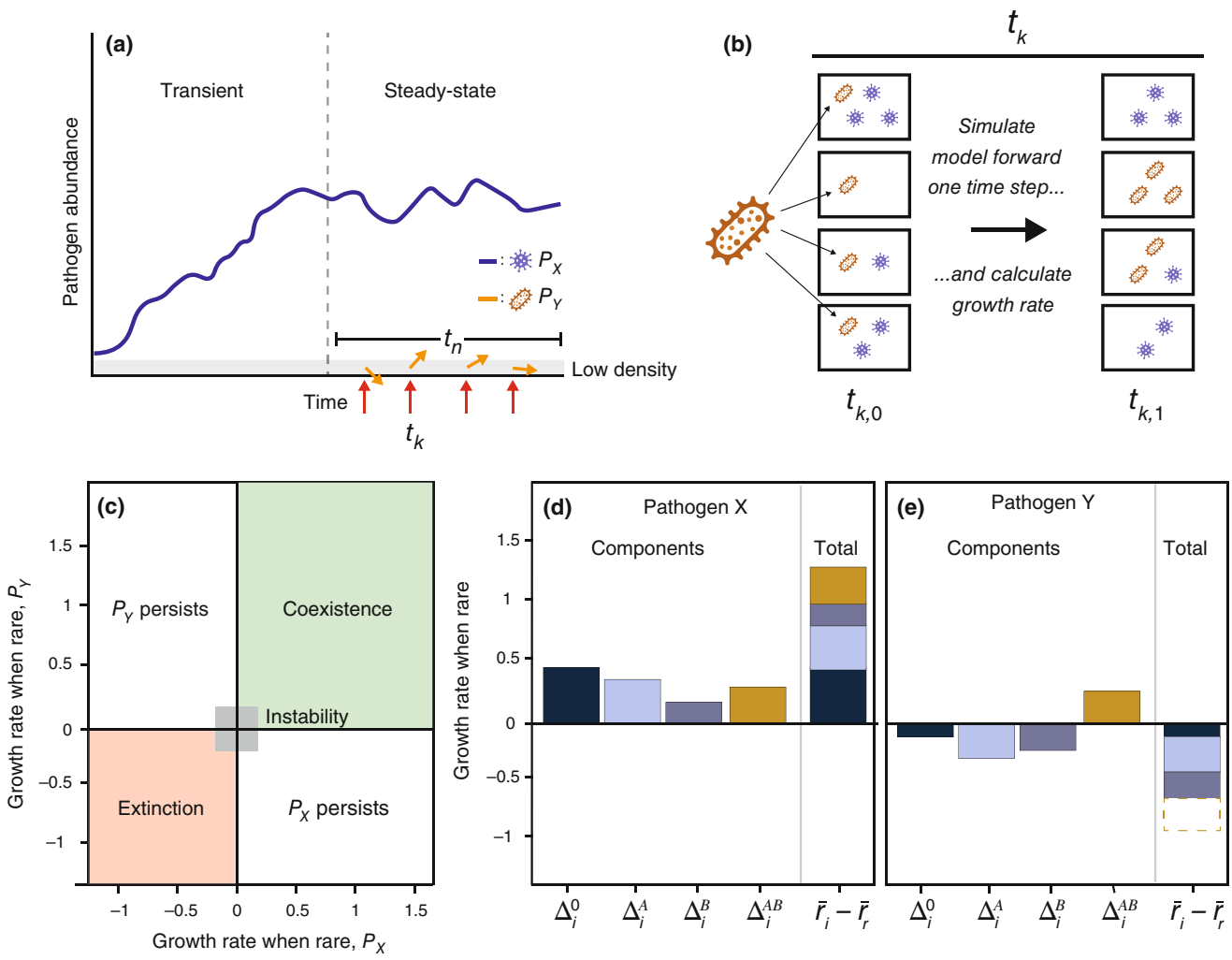

FIGURE 1 Decomposition workflow. (a) We allow a resident pathogen to reach steady-state equilibrium and introduce the invading pathogen at low density for each time point, t_k, in a time range, t_n, that captures all steady-state dynamics. (b) For each t_k, we introduce the invading pathogen into hosts ($t_{k,0}$), simulate the model forward one time step ($t_{k,1}$), and calculate invader growth rate when rare (GRWR). (c) If all pathogens exhibit a positive GRWR, stable coexistence occurs, whereas a negative GRWR indicates competitive exclusion. (d, e) We decompose the GRWR, $\bar{r}_i - \bar{r}_r$, for each pathogen into its mechanistic components, where Δ^0 represents GRWR without variation in either mechanism, Δ^A represents GRWR with variation in mechanism A, Δ^B represents GRWR with variation in mechanism B, and Δ^{AB} represents the interactive effect from variation in both A and B. Each mechanism can promote either coexistence (positive values) or exclusion (negative values).

(or exclusion) mechanisms across model formalizations and do not require complex analytical derivations for each new mechanism, relying instead on simulation methods to decompose GRWR. By incorporating the approach initially developed by Ellner et al. (2019) with pathogen models, MCT can move beyond the stabilizing/equalizing framework previously applied in pathogen systems and provide simultaneous information on how variation-dependent and independent mechanisms contribute to pathogen coexistence, facilitating comparisons between free-living and pathogen systems.

Here, we argue for and provide a case-study analysis extending these recent developments in MCT to pathogen communities, introducing a method with which to evaluate the relative importance of metacommunity stability structure for pathogen coexistence. We provide an overview of the mechanistic decomposition process in the context of a pathogenic, nonfree-living system and decompose the spatial mechanisms of pathogen coexistence and diversity maintenance. Using a general disease model with both within- and between-host components (outlined in Box 2), we highlight the unique, quantitative insights gained from applying MCT's decomposition methods to nonfree-living systems that exhibit host–pathogen (or species–environment) feedbacks. Our decomposition analysis and its revelations of

BOX 2 Overview of disease model

Within-host dynamics, generalist immunity

Within-host infection dynamics are based on a series of Lotka–Volterra predator–prey models modified for pathogen systems; the model includes resource competition and immune system memory (Cressler et al., 2014; Fenton et al., 2006; Fenton & Perkins, 2010). Pathogens consume a common resource within hosts and are removed from the system via immune cells that respond identically to each pathogen, regardless of which pathogen elicited the production of the immune cells (i.e., generalist immunity). Pathogen abundance also stimulates the production of memory cells that provide long-lasting protection to pathogen recolonization by decaying at a significantly lower rate than immune cells. These within-host dynamics for focal pathogen x and secondary pathogen y are modeled by the following equations. Note that we have not included the equations for pathogen y for brevity, as they are derived by switching the notation for the focal x and secondary y pathogens:

$$\frac{dR}{dt} = \theta\left(1 - \frac{R}{R_{max}}\right) - \delta_x P_x R - \delta_y P_y R \tag{2}$$

$$\frac{dP_x}{dt} = \alpha_x \delta_x P_x R - \beta_x I_x P_x - \beta_y I_y P_x \tag{3}$$

$$\frac{dI_x}{dt} = \varepsilon\beta_x I_x P_x + \varepsilon\beta_y I_y P_x + \phi\left(M_x + M_y\right)P_x - \gamma I_x \tag{4}$$

$$\frac{dM_x}{dt} = \rho I_x + \rho I_y - \mu M_x. \tag{5}$$

Equation (2) describes the resource dynamics, R within each host. The host's resource replenishes at rate θ to its carrying capacity, R_{max}. Host resource is consumed by each pathogen population at the rate of δ_x and δ_y. Pathogen population dynamics, P_x, depend on the rate of resource consumption and a resource conversion factor, α_x, which represents the number of pathogens produced for each unit of resource consumed. P_x is removed from the host via an immune response, I_x, at rate β_x and I_y, at rate β_y. The immune response, I_x (Equation 4), depends on the conversion factor ε, which models the number of immune cells produced for each pathogen removed. Immune cells decay at rate γ. The immune response is further stimulated via M_x and M_y memory cells originating from previous infections at rate ϕ. Memory cell M_x dynamics are described by Equation (5), where ρ represents the rate of production and μ is the decay rate, with $\mu \ll \gamma$. We allow pathogen clearance to occur by computationally setting pathogen abundance to 0 when abundances fall below 0.01.

Strain-specific immunity

The above equations are modified such that:

$$\frac{dR}{dt} = \theta\left(1 - \frac{R}{R_{max}}\right) - \delta_x P_x R - \delta_y P_y R \tag{6}$$

$$\frac{dP_x}{dt} = \alpha_x \delta_x P_x R - \beta_x I_x P_x \tag{7}$$

$$\frac{dI_x}{dt} = \varepsilon\beta_x I_x P_x + \sigma_x M_x P_x + \tau M_y P_x - \gamma I_x \tag{8}$$

$$\frac{dM_x}{dt} = \rho I_x + \mu M_x. \tag{9}$$

The immune response is stimulated via memory cells at rate σ_x originating from previous P_x infections (referred to as strain-specific immunity) and rate τ by memory cells originating from previous P_y infections (referred to as cross-immunity). The value of σ relative to τ represents the degree of cross-immunity between P_x and P_y, where $\sigma = \tau$ signifies complete cross-immunity and $\tau = 0$ represents no cross-immunity. Additionally, in this case, memory cell production M_x only depends on immune cells I_x.

Between-host dynamics

Between-host transmission is determined using an individual-based model that describes host contact, pathogen transmission, and host demographics (Grimm et al., 2006). Model simulations were conducted with 1000 hosts and run for 2000 time steps. Abundance of R, P_x, P_y, I_x, I_y, M_x, and M_y are tracked for each host, with initial conditions set at $R = R_{\max}$, $I_x = 1$, $I_y = 1$, $M_x = 0$, and $M_y = 0$. We seed the system by inoculating 100 pathogens per strain into 10 individual hosts. The model then proceeds in four stages that occur at each time step:

First, we determine host contacts. We calculate the number of contacts in a time step for each host via a Poisson distribution defined by an expected number of contacts κ. The identity of each contact is determined by sampling without replacement from all hosts, regardless of infection status, and is unidirectional. Therefore, κ represents the average total number of individual contacts, regardless of host identity. Second, we determine pathogen transmission for each host during each contact event, depending on pathogen load. We used a logit function to determine the probability a transmission event occurs based on that respective pathogen's load in the contacting host (e.g., for P_x, the probability of transmission would be determined by the inverse logit of $\omega_i + \omega_c P_x$). Upon successful transmission, the amount of pathogen transmitted from an infected host to a contacted host is calculated using a binomial distribution with trials equal to the successfully invading pathogen's load and probability υ. The abundance of pathogen transmitted to the new host is subtracted from the infecting host. Third, within-host dynamics are resolved for each host following Equations (2–5) or (6–9), where each time step in the individual-based model corresponds to one time step in the within-host Lotka–Volterra model. Fourth, we simulate host demography (e.g., births and deaths) by selecting individuals from a Bernoulli distribution with mortality probability η that is independent of host pathogen or immune load. Hosts that are lost due to mortality are immediately replaced by the same number of new hosts with no pathogen load or immune memory, thereby keeping the total host population constant through time (Keeling & Rohani, 2011). Newly introduced hosts are immediately susceptible to infection. An overview of the infection model is in Appendix S1: Figure S1, parameters are in Tables S1 and S2, and a sensitivity analysis is shown in Figure S3.

the mechanisms that facilitate pathogen coexistence illustrate that MCT is a powerful analytical framework under which to study the role of temporal and spatial heterogeneities on the structuring of pathogen communities (Figure 1).

PERFORMING MECHANISTIC DECOMPOSITIONS IN A DISEASE SYSTEM

Pathogens coexist if they meet the mutual invasibility criterion, requiring that each pathogen in the system exhibits positive GRWR (Box 1; Chesson, 2000b). To calculate the average GRWR for each pathogen ($\bar{r}_j$, where here the overbar denotes the spatial average for pathogen species j), we follow simulation approaches from MCT. We first simulate dynamics of only one pathogen (termed the resident) and let it reach its steady-state equilibrium (Figure 1). Over a given duration of the resident's spatio-temporal steady-state equilibrium, t_n, we then reintroduce the other pathogen (termed the invader) into the system at each time step at a low density such that the steady-state dynamics of the resident pathogen are not altered. We introduce this invader over enough time steps to capture all steady-state dynamics (i.e., during the last 100 time steps of our model simulation).

Following previous spatial MCT methods, the invading pathogen is introduced into the host metacommunity at its observed spatial equilibrium (Chesson, 2000a; Shoemaker & Melbourne, 2016). To calculate invader spatial equilibrium, for each given time t_k during t_n, we introduce the invading pathogen at low abundance (0.5% of average pathogen abundance across the last 100 time

steps) into all hosts ($t_{k,0}$) and run the model forward one time step ($t_{k,1}$), where k denotes the time step for GR calculations. We then divide the invading pathogen abundance in each host by the overall invading pathogen abundance in the population and then multiply that proportion by the total initial invader abundance; this ensures that total invader abundance is constant but density across hosts is updated. We reset all variables to their original states at $t_{k,0}$. We then reintroduce the invading pathogen using the updated invader abundances and continue this process until the invader's spatial equilibrium is reached. Next, the infection model is then run one more step and the growth rates for both the invader and resident are calculated to determine GRWR. This entire process is then repeated for t_{k+1}, t_{k+2}, ... t_n. The average GRWR, $\overline{r}_j$, over t_n is therefore given by:

$$r_j(\lambda(t_k), \nu(t_k)) = \ln \frac{\sum_{a=1}^{N} P_{j,t_{k,1}}}{\sum_{a=1}^{N} P_{j,t_{k,0}}}, j = x, y \tag{10}$$

$$\overline{r}_j = \frac{1}{n} \sum_{k=1}^{n} r_j(\lambda(t_k), \nu(t_k)) \tag{11}$$

where λ and ν are varying pathogen fitness and density, respectively, N is the total number of hosts, n is the total number of time steps over which the resident is at steady-state equilibrium and the decompositions are calculated, and j denotes pathogens x or y, respectively.

After calculating $\overline{r}_j$, we partition growth rates into mutually exclusive variation-independent and dependent mechanisms. These mechanisms parse why coexistence versus competitive exclusion occurs, examining components that are inherently linked and have cascading effects in ecological systems. For example, one could ask how important are average differences in growth rates between species versus how important is heterogeneity in pathogen spatial distributions across hosts. To decompose these mechanisms for coexistence, we simulate the infection model while removing variation in one or more mechanisms, and then recalculating population growth rates. Here, we focus on spatial variation; we define variation-dependent mechanisms to include two spatial coexistence mechanisms and their interaction: (1) spatial variation in pathogen fitness (i.e., host resources, immune cells, and memory cells, represented by λ), (2) spatial variation in pathogen density (i.e., variation in density across hosts, represented by ν), and (3) the interactive effect of the variation-dependent mechanisms, analogous to the fitness–density covariance term from Chesson's traditional spatial decomposition (Chesson, 2000a; Shoemaker & Melbourne, 2016; Snyder et al., 2005). To determine each mechanism's contribution to $\overline{r}_j$ in our model, we first remove all variation in pathogen fitness and density by equally distributing host resources (R), resident pathogen abundance (P), immune cells (I), and memory cells (M) across all hosts for each time step, t_k, and calculating GRWR with no variation-dependent mechanisms:

$$\varepsilon_j^0 = r_j(\overline{\lambda}, \overline{\nu}). \tag{12}$$

We then reintroduce spatial variation in either pathogen fitness, λ (R, I, M; Equation 13) or density, ν (P; Equation 14) and subtract out the contribution of ε_j^0 to determine each mechanism's main effect:

$$\varepsilon_j^{\lambda}(\lambda) = r_j(\lambda, \overline{\nu}) - \varepsilon_j^0 \tag{13}$$

$$\varepsilon_j^{\nu}(\nu) = r_j(\overline{\lambda}, \nu) - \varepsilon_j^0 \tag{14}$$

Finally, we calculate the interaction of λ and ν, which represents the additional contribution to the GRWR when both fitness and abundance are allowed to vary simultaneously:

$$\varepsilon_j^{\lambda\nu}(\lambda, \nu) = r_j(\lambda, \nu) - \left[\varepsilon_j^0 + \varepsilon_j^{\lambda} + \varepsilon_j^{\nu}\right] \tag{15}$$

We rearrange Equation (15), calculating the decomposition for each timestep t_k in t_n. Averaging over each time step yields:

$$\overline{r}_j = \overline{\varepsilon}_j^0 + \overline{\varepsilon}_j^{\lambda} + \overline{\varepsilon}_j^{\nu} + \overline{\varepsilon}_j^{\lambda\nu} \tag{16}$$

where the overbar denotes the average strength of each mechanism. However, to fully capture the effect of a given mechanism on coexistence, we must assess growth rates for both the resident, $\overline{r}_r$, and the invader, $\overline{r}_i$. As the resident pathogen is at steady-state equilibrium and the invader is at a sufficiently low density to not alter the resident's overall growth rate, $\overline{r}_r$ is ~0. However, the invader–resident comparison is still necessary as the importance of each mechanism for the resident (the epsilon terms) may not be zero; rather their total contribution will sum to zero (Ellner et al., 2019; Hallett et al., 2019). Therefore, we make invader–resident comparisons for Equations (10–15) and coexistence is calculated as:

$$\overline{r}_i = \overline{r}_i - \overline{r}_r = \Delta_i^0 + \Delta_i^{\lambda} + \Delta_i^{\nu} + \Delta_i^{\lambda\nu}. \tag{17}$$

where $\Delta_i^X = \varepsilon_i^X - \varepsilon_r^X$ for each mechanism X. Each component of the decomposition can be interpreted as follows:

1. Δ_i^0: growth rate when pathogen fitness (as defined by the abundance of host resources, R, and host immune components, I and M) and pathogen abundance, P, are evenly distributed across all hosts. This term represents the growth rate with no variation, i.e., when all spatial variation in pathogen fitness and abundance is removed.
2. Δ_i^λ: growth rate when pathogen fitness is allowed to spatially vary while pathogen abundance is evenly distributed across all hosts. Different sources of spatial variation in pathogen fitness could be evaluated by this term, such as variation in host contacts or nutritional status. In our model, this term represents the growth rate when the invading pathogen encounters a host population in which another pathogen is endemic and produces long-lasting host immunity, with spatially varying resources available for the invader's growth.
3. Δ_i^ν: growth rate when pathogen abundance is allowed to spatially vary while pathogen fitness is evenly distributed across all hosts. In our model, this term represents the growth rate when the invading pathogen encounters a host community in which long-lasting immunity elicited by an endemic pathogen is evenly distributed across all hosts, but the endemic pathogen abundance varies spatially.
4. $\Delta_i^{\lambda\nu}$: interactive effect of spatially varying pathogen fitness and pathogen abundance. This term represents the contribution of spatial variation in pathogen fitness and abundance to the growth rate beyond their separate effects.

MECHANISMS OF PATHOGEN COEXISTENCE

Following the method of decomposition outlined above, we assessed the impact of spatial variation in pathogen fitness and density under two classic infection scenarios, highlighting the utility of MCT for interpreting disease dynamics: (1) a scenario in which both pathogens are demographically equivalent, and (2) a competition–colonization (virulence–transmission) trade-off scenario. For both scenarios, we examine pathogen coexistence under general immunity versus strain-specific immunity (Box 2). In the demographically equivalent scenario, both pathogens are parameterized identically (Appendix S1: Tables S1 and S2; Hubbell, 2001; Leibold et al., 2004). Matching classic competition–colonization models (May & Nowak, 1994; Tilman, 1994), in Scenario 2, all hosts (i.e., patches) are identical and the superior competitor (P_x) outcompetes the superior colonizer (P_y), while the superior colonizer has a baseline transmission probability ($\omega_{i,y}$) greater than that of the superior competitor (Appendix S1: Tables S1 and S2). However, deviating from the classic model and following recent extensions of the competition–colonization trade-off (Shoemaker & Melbourne, 2016; Strauss et al., 2019), the superior competitor exhibits a host resource consumption (δ) greater than that of the superior colonizer, causing competitive exclusion to not be instantaneous in our model, but rather a transient period occurs in which the superior colonizer decreases in abundance until competitive exclusion is reached. These two scenarios highlight insights gained by adapting MCT decompositions to disease ecology, focusing on classic disease models with analogs in the community ecology literature (Leibold et al., 2004; Shoemaker & Melbourne, 2016).

All pathogens exhibited positive GRWR in both demographically equivalent and competition–colonization trade-off scenarios (Figures 2 and 3), resulting in coexistence of both pathogens. However, by decomposing coexistence into its constitutive variation-independent and -dependent mechanisms, we observe that the relative contribution of different mechanisms strongly varied between the infection scenarios, highlighting the different aspects of spatial variation that can promote coexistence in disease communities.

Scenario 1: Demographic equivalence

In the demographically equivalent scenario with generalist immunity (Figure 2a,b), both pathogens were able to coexist due to spatial variation in pathogen fitness (Δ^λ), density (Δ^ν), and the interactive effect from simultaneous variation in fitness and density ($\Delta^{\lambda\nu}$). Pathogens could not invade under averaged, variation-independent conditions (Δ^0), indicating that coexistence only occurs via the spatial (i.e., among-host) variation present in the disease system. Both pathogens exhibited identical GRWR, as expected given their identical parameter values (Hubbell, 2001).

A decomposition of the disease model allows us to break down the mechanisms that produce coexistence of demographically equivalent pathogens under generalist immunity. In our case study, current or previous infections by the resident pathogen elicits long-lasting, generalist immunity in hosts, thereby decreasing the number of hosts with favorable growth conditions for the invader. This spatial variation in host quality yields spatial heterogeneity in the invader's spatial equilibrium, causing the invader to aggregate in hosts with the lowest abundances (or complete absence) of the resident pathogen

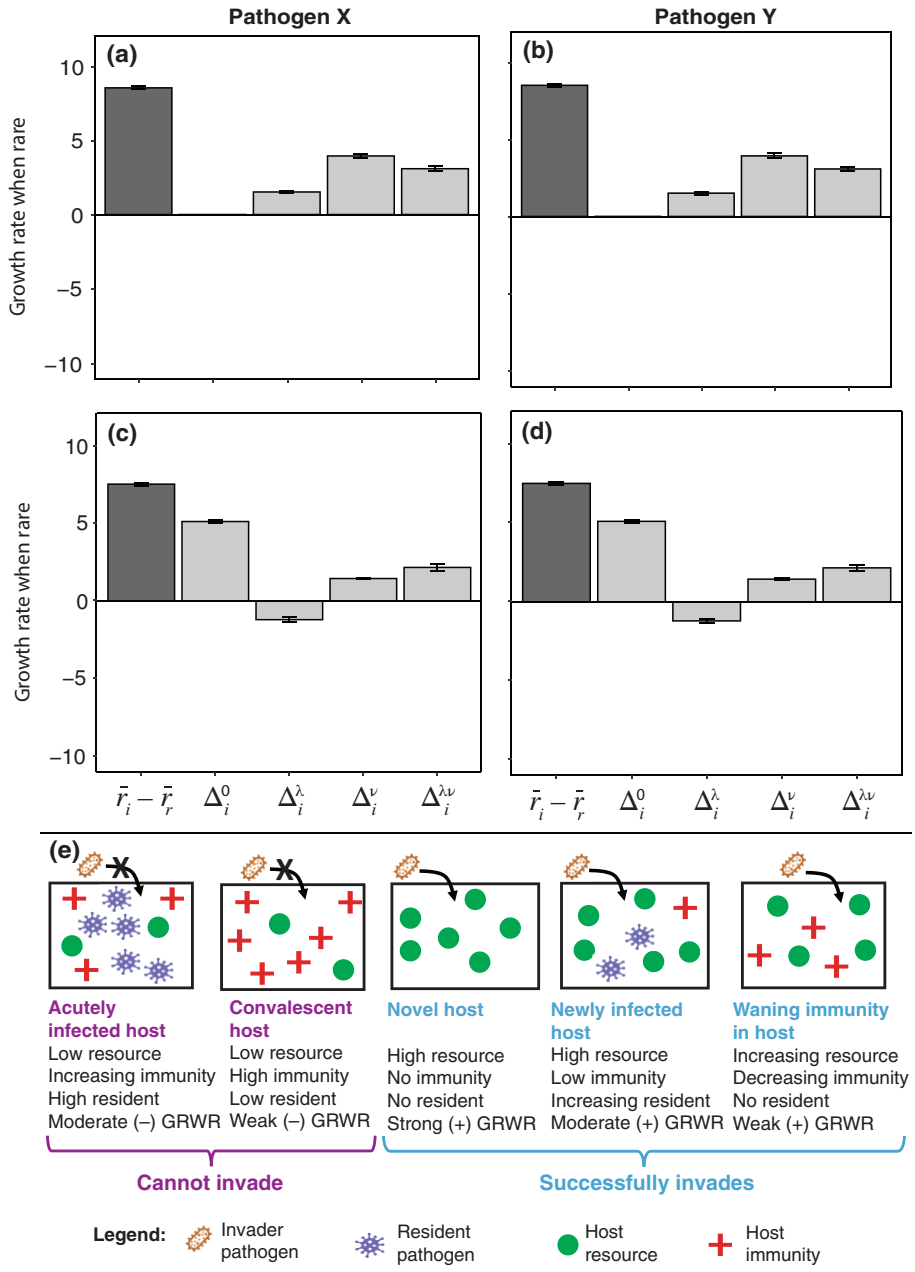

FIGURE 2 Partitioning the contributions of spatial variation in pathogen fitness (λ) and density (ν) on growth rate when rare (GRWR) for demographically equivalent pathogens P_x (first column) and P_y (second column) encountering (a, b) a generalist immune response and (c, d) strain-specific immunity. The dark gray bar ($\bar{r}_i - \bar{r}_r$) is the sum total of all light gray bars (Δ_i^0, Δ_i^λ, Δ_i^ν, $\Delta_i^{\lambda\nu}$). Error bars represent the standard deviation derived from 500 simulations. (e) Visual depiction why GRWR is positive in the demographically equivalent scenario. The invader has a negative GRWR in currently infected and convalescent hosts. However, host demography yields a fraction of hosts uninfected with the resident pathogen, where GRWR is positive. Additionally, invasion can occur in newly infected hosts or hosts with waning immunity.

(Figure 2e). More specifically, the strong positive effects of Δ^λ, Δ^ν, and $\Delta^{\lambda\nu}$ on the invader's GRWR indicate that the invader can coexist by aggregating in hosts with high resource levels, low competition (i.e., few resident pathogens), and low immune response (i.e., either because the resident was only recently infected or because the host has not had recent exposure). Despite pathogens being demographically equivalent and all hosts responding identically to each pathogen, the introduction of host immune memory via infection means that pathogens "engineer" their host/patch environment through time, thereby introducing inherent heterogeneity in host quality for pathogen growth that promotes long-term coexistence. This pattern points to the potential impact of pathogen

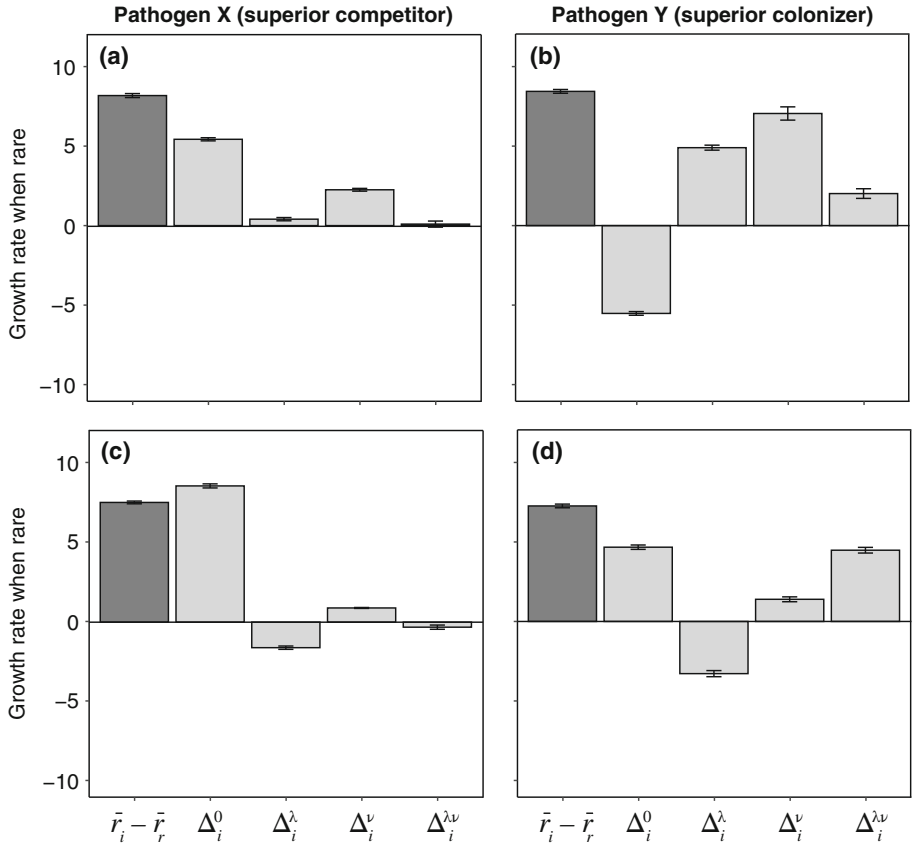

FIGURE 3 Partitioning the contributions of spatial variation in pathogen fitness (λ) and density (ν) on growth rate when rare (GRWR) for pathogens exhibiting a competition–colonization trade-off encountering (a, b) a generalist immune response and (c, d) strain-specific immunity. P_x (first column) is the superior competitor, whereas P_y (second column) is the superior colonizer. The dark gray bar ($\bar{r}_i - \bar{r}_r$) is the sum total of all light gray bars (Δ_i^0, Δ_i^λ, Δ_i^ν, $\Delta_i^{\lambda\nu}$). Error bars represent standard deviation derived from 500 simulations.

aggregation during epidemic emergence of novel pathogens in a host population when there is strong cross-immunity to currently circulating pathogen(s) and suggest that host–pathogen feedbacks that are central to disease ecology can dramatically alter the long-term trajectories of demographically equivalent species.

With strain-specific immunity and demographically equivalent pathogens (Figure 2c,d), both pathogens exhibited positive growth rates under averaged conditions (Δ^0), highlighting that strain-specific immunity can yield coexistence, even without the contribution of spatial variation. Variation in pathogen fitness (Δ^λ) had negative effects on coexistence, whereas variation in density (Δ^ν) and simultaneous variation in fitness and density ($\Delta^{\lambda\nu}$) had positive effects on coexistence. More generally, variation-dependent mechanisms contributed less to overall GRWR relative to variation-independent mechanisms (Δ^0). The invading pathogen's positive growth rate under nonvarying conditions is due to the strain-specific immunity targeting the resident species, providing the invader with a competitive advantage and leading to a positive growth rate.

Scenario 2: Competition–colonization trade-off

The competition–colonization (virulence–transmission) trade-off is a classic trait trade-off that promotes coexistence (May & Nowak, 1994; Tilman, 1994). Congruent with the results of previous work, we found that, under specific parameter conditions, pathogens with differing competitive and colonizing abilities maintained coexistence (Figure 3a,b, please refer to Appendix S1: Figure S2 for decomposition with the superior competitor excluding the superior colonizer).

Our decomposition highlights why coexistence occurs, even under generalist immunity; spatial variation created by host demography and immune responses was required for the superior colonizer to coexist with the superior competitor. In other words, the competition–colonization trade-off relies on spatial variability for coexistence of the superior colonizer with the superior competitor. While the superior competitor (P_x) exhibited a positive growth rate from variation-independent mechanisms (Δ^0), the

superior colonizer (P_y) exhibited a strongly negative variation-independent growth rate. Therefore, in the absence of variation, the superior colonizer is driven toward extinction by the superior competitor under generalist immunity. Only via spatial variation in pathogen fitness (Δ^{λ}), density (Δ^{ν}), and their interaction ($\Delta^{\lambda\nu}$) could the superior colonizer's negative growth rate in the absence of variation be offset, yielding coexistence. Host demography and immunity yielded spatial variation in the superior colonizer's abundances across hosts, including novel hosts not previously infected, allowing the superior colonizer to maintain a positive GRWR (Shoemaker & Melbourne, 2016). Similarly, spatial variation still promotes coexistence of the superior colonizer when it is competitively excluded, but not enough to overcome the strong negative effects of variation-independent mechanisms (Δ^{0}; Appendix S1: Figure S2). In contrast, spatial variation in pathogen fitness and density had positive impacts on the overall GRWR for the superior competitor, but spatial variation was not necessary, as the superior competitor can competitively exclude the superior colonizer regardless of spatial heterogeneity. In other words, the strong positive effect of Δ^{0} is sufficient for the superior competitor to invade from rarity under generalist immunity.

In the competition–colonization trade-off scenario with strain-specific immunity (Figure 3c,d), both the superior competitor (P_x) and superior colonizer (P_y) generally exhibited similar decomposition patterns to the demographically equivalent scenario when encountering strain-specific immunity (Figure 2c,d). Strain-specific immunity overwhelms the impact of spatial coexistence mechanisms in both demographically equivalent and competition–colonization trade-off scenarios. In this case, host immunity drives dynamics while differences in pathogen demography are masked; as such, spatial structure is no longer required for the superior colonizer to coexist (Figure 3d). This result emphasizes that, depending on underlying pathogen and host dynamics, spatial variation can play critical or inconsequential roles in sustaining pathogen coexistence.

INSIGHTS FOR PATHOGEN COMMUNITIES FROM MCT DECOMPOSITIONS

Identifying the ecological mechanisms responsible for pathogen coexistence or competitive exclusion presents unique challenges to disease ecologists due, in large part, to processes simultaneously operating at multiple spatial scales. Application of MCT to disease systems offers a powerful, quantitative framework with which to investigate the role of both within- and between-host variation for pathogen coexistence. Indeed, close parallels between disease and community ecology have yielded advances across fields when tools from one field are adapted for the other, such as metacommunity theory (Mihaljevic, 2012) and the virulence–transmission (competition–colonization) trade-off framework (May & Nowak, 1994; Tilman, 1994). Extending MCT decompositions from their historical focus on free-living systems (Chesson, 2000b; Hallett et al., 2019) and recent extensions that incorporate plant–soil feedbacks for plant coexistence (Kandlikar et al., 2021; Ke & Wan, 2020) to disease systems and pathogen coexistence can provide unique insights into the critical mechanisms underpinning pathogen community structure. For example, our case study highlights how, in two different pathogen systems (e.g., demographically equivalent and competition–colonization scenarios), the general signatures of pathogen community dynamics might be similar (namely, both pathogens coexist), yet a mechanistic decomposition reveals that internal host dynamics alter the ecological processes responsible for promoting coexistence.

Decomposing GRWR into its constitutive elements provides a common, quantitative metric with which to compare underlying mechanisms of coexistence between disease scenarios, allowing disease ecologists to explore how heterogeneity modulates pathogen dynamics. In our case study, we focus on demographic differences (or lack thereof) between pathogens. However, the applications can be extended to other scenarios to investigate how multiple types and scales of heterogeneities may alter coexistence, including differences across host species, underlying the contact network structure between host individuals, and strain-specific versus generalist immunity. Comparing strain-specific and generalist immunity shows that spatial coexistence mechanisms were critical for promoting coexistence under general immunity, but that strain-specific immunity overwhelmed the impact of spatial coexistence mechanisms. Such strong differences in decompositions highlight how the application of MCT to disease ecology provides a flexible, exciting avenue for future research investigating the role of cross-scale disease dynamics on pathogen communities that could not otherwise be detected.

We generated these observations using a relatively general disease model that incorporates basic elements of an infectious disease system, including immune memory, varying host contacts, and resource competition between pathogens. However, concurrent work in community ecology shows how MCT decompositions can be applied to

more complex systems and can be tested empirically (Ellner et al., 2019; Hallett et al., 2019; please refer to Supplemental Methods for a discussion of empirical applications). For example, the application of MCT in community ecology often focuses on the role of environmental variation on species coexistence. Disease ecologists can use similar approaches to simultaneously investigate the variation in both biotic and abiotic mechanisms, such as seasonal temperature fluctuations or species trade-offs in abiotically varying environments (Altizer et al., 2006; Mordecai et al., 2016). Furthermore, these decomposition methods can be applied to pathogen communities with more than two species (Ellner et al., 2019), albeit with the same potential limitations when applying MCT to free-living communities. As ecological communities become larger, higher order and intransitive interactions between species may violate assumptions of the mutual invasibility criterion (e.g., resident communities must stably exist without the invader species). However, recent advances in coexistence theory more easily allow for extensions to higher diversity communities (Saavedra et al., 2017; Spaak & De Laender, 2020). As such, the flexibility of MCT has the potential to contribute to our understanding of how multiple types of variation—such as host heterogeneities in infection susceptibility, vaccination status, and evolving contact networks—alter pathogen community diversity and coexistence.

CONCLUSIONS

Learning how best to leverage knowledge of underlying pathogen coexistence mechanisms will be an area for active investigation, and recent applications of MCT in free-living communities suggest the applied utility of mechanistic decompositions. For example, in grassland communities, variation in competitive environments, mediated via precipitation patterns, can have a stronger effect on coexistence than direct effects (Hallett et al., 2019). By identifying the impact of variation in different climate conditions on species' GRWR using mechanistic decompositions, conservationists can focus efforts on sustaining low abundance species that are most susceptible to climate variation. We see parallel insights for disease ecology. For example, understanding the importance of temperature variation on vectored-pathogen coexistence might help to predict how pathogen community structures will be altered under changing climate conditions, or how different vaccination strategies might alter spatial variation in pathogen density, and therefore, pathogen coexistence (Dobson & Roberts, 1994; May & Anderson, 1978). Partitioning GRWR has the strong potential to inform these intervention efforts.

AUTHOR CONTRIBUTIONS

Andrew J. Sieben and Lauren G. Shoemaker came up with the conceptual framing of the manuscript, Andrew J. Sieben, Joseph R. Mihaljevic, and Lauren G. Shoemaker jointly developed the models and methods. Andrew J. Sieben conducted the analyses, coded models, and wrote the manuscript, and all authors contributed substantially to revisions.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

All code (Sieben et al., 2022) is novel and can be found in Zenodo at https://doi.org/10.5281/zenodo.6549365.

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REFERENCES

Adler, P. B., J. HilleRisLambers, and J. M. Levine. 2007. "A Niche for Neutrality." *Ecology Letters* 10: 95–104.

Alizon, S., J. C. de Roode, and Y. Michalakis. 2013. "Multiple Infections and the Evolution of Virulence." *Ecology Letters* 16: 556–67.

Altizer, S., A. Dobson, P. Hosseini, P. Hudson, M. Pascual, and P. Rohani. 2006. "Seasonality and the Dynamics of Infectious Diseases." *Ecology Letters* 9: 467–84.

Barabás, G., R. D'Andrea, and S. M. Stump. 2018. "Chesson's Coexistence Theory." *Ecological Monographs* 88: 277–303.

Beldomenico, P. M., and M. Begon. 2010. "Disease Spread, Susceptibility and Infection Intensity: Vicious Circles?" *Trends in Ecology and Evolution* 25: 21–7.

Buckee, C. O., K. Koelle, M. J. Mustard, and S. Gupta. 2004. "The Effects of Host Contact Network Structure on Pathogen Diversity and Strain Structure." *Proceedings of the National Academy of Sciences* 101: 10839–44.

Chesson, P. 2000a. "General Theory of Competitive Coexistence in Spatially-Varying Environments." *Theoretical Population Biology* 58: 211–37.

Chesson, P. 2000b. "Mechanisms of Maintenance of Species Diversity." *Annual Review of Ecology and Systematics* 31: 343–66.

Clay, P. A., K. Dhir, V. H. W. Rudolf, and M. A. Duffy. 2019. "Within-Host Priority Effects Systematically Alter Pathogen Coexistence." *American Naturalist* 193: 187–99.

Cobey, S., and M. Lipsitch. 2012. "Niche and Neutral Effects of Acquired Immunity Permit Coexistence of Pneumococcal Serotypes." *Science* 335: 1376–80.

Cobey, S., and M. Lipsitch. 2013. "Pathogen Diversity and Hidden Regimes of Apparent Competition." *American Naturalist* 181: 12–24.

Collinge, S. K., and C. Ray. 2006. *Disease Ecology: Community Structure and Pathogen Dynamics*. Oxford: Oxford University Press.

Cressler, C. E., W. A. Nelson, T. Day, and E. Mccauley. 2014. "Disentangling the Interaction among Host Resources, the Immune System and Pathogens." *Ecology Letters* 17: 284–93.

Cummings, D. A., S. Iamsirithaworn, J. T. Lessler, A. McDermott, R. Prasanthong, A. Nisalak, R. G. Jarman, D. S. Burke, and R. V. Gibbons. 2009. "The Impact of the Demographic Transition on Dengue in Thailand: Insights from a Statistical Analysis and Mathematical Modeling." *PLoS Medicine* 6: e1000139.

Dobson, A., K. D. Lafferty, A. M. Kuris, R. F. Hechinger, and W. Jetz. 2008. "Homage to Linnaeus: How Many Parasites? How Many Hosts?" *Proceedings of the National Academy of Sciences* 105: 11482–9.

Dobson, A., and M. Roberts. 1994. "The Population Dynamics of Parasitic Helminth Communities." *Parasitology* 109(Suppl): S97–108.

Ellner, S. P., R. E. Snyder, P. B. Adler, and G. Hooker. 2019. "An Expanded Modern Coexistence Theory for Empirical Applications." *Ecology Letters* 22: 3–18.

Ezenwa, V. O., and A. E. Jolles. 2011. "From Host Immunity to Pathogen Invasion: The Effects of Helminth Coinfection on the Dynamics of Microparasites." *Integrative and Comparative Biology* 51: 540–51.

Fenton, A., J. Lello, and M. B. Bonsall. 2006. "Pathogen Responses to Host Immunity: The Impact of Time Delays and Memory on the Evolution of Virulence." *Proceedings of the Royal Society B: Biological Sciences* 273: 2083–90.

Fenton, A., and S. E. Perkins. 2010. "Applying Predator-Prey Theory to Modelling Immune-Mediated, within-Host Interspecific Parasite Interactions." *Parasitology* 137: 1027–38.

Ferguson, N., R. Anderson, and S. Gupta. 1999. "The Effect of Antibody-Dependent Enhancement on the Transmission Dynamics and Persistence of Multiple-Strain Pathogens." *Proceedings of the National Academy of Sciences* 96: 790–4.

Ferguson, N. M., A. P. Galvani, and R. M. Bush. 2003. "Ecological and immunological determinants of influenza evolution." *Nature* 422: 428–33.

Fleming-Davies, A. E., V. Dukic, V. Andreasen, and G. Dwyer. 2015. "Effects of Host Heterogeneity on Pathogen Diversity and Evolution." *Ecology Letters* 18: 1252–61.

Gog, J. R., and B. T. Grenfell. 2002. "Dynamics and Selection of Many-Strain Pathogens." *Proceedings of the National Academy of Sciences* 99: 17209–14.

Grimm, V., U. Berger, F. Bastiansen, S. Eliassen, V. Ginot, J. Giske, J. Goss-Custard, et al. 2006. "A Standard Protocol for Describing Individual-Based and Agent-Based Models." *Ecological Modelling* 198: 115–26.

Hallett, L. M., L. G. Shoemaker, C. T. White, and K. N. Suding. 2019. "Rainfall Variability Maintains Grass-Forb Species Coexistence." *Ecology Letters* 22: 1658–67.

Hubbell, S. P. 2001. *The Unified Neutral Theory of Biodiversity and Biogeography*. Princeton, NJ: Princeton University Press.

Johnson, P. T., J. C. De Roode, and A. Fenton. 2015. "Why Infectious Disease Research Needs Community Ecology." *Science* 349: 1259504.

Johnson, P. T., and J. T. Hoverman. 2012. "Parasite Diversity and Coinfection Determine Pathogen Infection Success and Host Fitness." *Proceedings of the National Academy of Sciences* 109: 9006–11.

Kandlikar, G. S., X. Yan, J. M. Levine, and N. J. Kraft. 2021. "Soil Microbes Generate Stronger Fitness Differences than Stabilization among California Annual Plants." *The American Naturalist* 197: E30–9.

Katzelnick, L. C., L. Gresh, M. E. Halloran, J. C. Mercado, G. Kuan, A. Gordon, A. Balmaseda, and E. Harris. 2017. "Antibody-Dependent Enhancement of Severe Dengue Disease in Humans." *Science* 358: 929–32.

Ke, P.-J., and J. Wan. 2020. "Effects of Soil Microbes on Plant Competition: A Perspective from Modern Coexistence Theory." *Ecological Monographs* 90: e01391.

Keeling, M. J., and P. Rohani. 2011. *Modeling Infectious Diseases in Humans and Animals*. Princeton, NJ: Princeton University Press.

Koelle, K., S. Cobey, B. Grenfell, and M. Pascual. 2006. "Epochal Evolution Shapes the Phylodynamics of Interpandemic Influenza A (H3N2) in Humans." *Science* 314: 1898–903.

Leibold, M. A., and J. M. Chase. 2017. *Metacommunity Ecology*. Princeton, NJ: Princeton University Press.

Leibold, M. A., M. Holyoak, N. Mouquet, P. Amarasekare, J. M. Chase, M. F. Hoopes, R. D. Holt, et al. 2004. "The Metacommunity Concept: A Framework for Multi-Scale Community Ecology." *Ecology Letters* 7: 601–13.

Levine, J. M., P. B. Adler, and J. HilleRisLambers. 2008. "On Testing the Role of Niche Differences in Stabilizing Coexistence." *Functional Ecology* 22: 934–6.

Lipsitch, M., C. Colijn, T. Cohen, W. P. Hanage, and C. Fraser. 2009. "No Coexistence for Free: Neutral Null Models for Multistrain Pathogens." *Epidemics* 1: 2–13.

Lloyd-Smith, J. O. 2013. "Vacated Niches, Competitive Release and the Community Ecology of Pathogen Eradication." *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences* 368: 20120150.

Lloyd-Smith, J. O., S. J. Schreiber, P. E. Kopp, and W. M. Getz. 2005. "Superspreading and the Effect of Individual Variation on Disease Emergence." *Nature* 438: 355–9.

Matthijnssens, J., J. Bilcke, M. Ciarlet, V. Martella, K. Bányai, M. Rahman, M. Zeller, P. Beutels, P. Van Damme, and M. Van Ranst. 2009. "Rotavirus Disease and Vaccination: Impact on Genotype Diversity." *Future Microbiology* 4: 1303–16.

May, R. M., and R. M. Anderson. 1978. "Regulation and Stability of Host-Parasite Population Interactions: II. Destabilizing Processes." *The Journal of Animal Ecology* 47: 249.

May, R. M., and M. A. Nowak. 1994. "Superinfection, Metapopulation Dynamics, and the Evolution of Diversity." *Journal of Theoretical Biology* 170: 95–114.

Mihaljevic, J. R. 2012. "Linking Metacommunity Theory and Symbiont Evolutionary Ecology." *Trends in Ecology and Evolution* 27: 323–9.

Mordecai, E. A., K. Gross, and C. E. Mitchell. 2015. "Within-Host Niche Differences and Fitness Trade-Offs Promote Coexistence of Plant Viruses." *American Naturalist* 187: E13–26.

Mordecai, E. A., A. G. Jaramillo, J. E. Ashford, R. F. Hechinger, and K. D. Lafferty. 2016. "The Role of Competition–Colonization Tradeoffs and Spatial Heterogeneity in Promoting Trematode Coexistence." *Ecology* 97: 1484–96.

Pedersen, A. B., and A. Fenton. 2007. "Emphasizing the Ecology in Parasite Community Ecology." *Trends in Ecology and Evolution* 22: 133–9.

Recker, M., K. B. Blyuss, C. P. Simmons, T. T. Hien, B. Wills, J. Farrar, and S. Gupta. 2009. "Immunological Serotype Interactions and their Effect on the Epidemiological Pattern of Dengue." *Proceedings of the Royal Society B: Biological Sciences* 276: 2541–8.

Rohani, P., D. J. Earn, B. Finkenstadt, and B. T. Grenfell. 1998. "Population Dynamic Interference among Childhood Diseases." *Proceedings of the Royal Society B: Biological Sciences* 265: 2033–41.

Rynkiewicz, E. C., A. B. Pedersen, and A. Fenton. 2015. "An Ecosystem Approach to Understanding and Managing within-Host Parasite Community Dynamics." *Trends in Parasitology* 31: 212–21.

Saavedra, S., R. P. Rohr, J. Bascompte, O. Godoy, N. J. Kraft, and J. M. Levine. 2017. "A Structural Approach for Understanding Multispecies Coexistence." *Ecological Monographs* 87: 470–86.

Seabloom, E. W., E. T. Borer, K. Gross, A. E. Kendig, C. Lacroix, C. E. Mitchell, E. A. Mordecai, and A. G. Power. 2015. "The Community Ecology of Pathogens: Coinfection, Coexistence and Community Composition." *Ecology Letters* 18: 401–15.

Shoemaker, L. G., and B. A. Melbourne. 2016. "Linking Metacommunity Paradigms to Spatial Coexistence Mechanisms." *Ecology* 97: 2436–46.

Sieben, A. J., J. R. Mihaljevic, and L. G. Shoemaker. 2022. "Quantifying Pathogen Coexistence." Zenodo, Software. https://doi.org/10.5281/zenodo.6549365.

Snyder, R. E., E. T. Borer, and P. Chesson. 2005. "Examining the Relative Importance of Spatial and Nonspatial Coexistence Mechanisms." *The American Naturalist* 166: E75–94.

Spaak, J. W., and F. De Laender. 2020. "Intuitive and Broadly Applicable Definitions of Niche and Fitness Differences." *Ecology Letters* 23: 1117–28.

Strauss, A. T., L. G. Shoemaker, E. W. Seabloom, and E. T. Borer. 2019. "Cross-Scale Dynamics in Community and Disease Ecology: Relative Timescales Shape the Community Ecology of Pathogens." *Ecology* 100: e02836.

Takala, S. L., and C. V. Plowe. 2009. "Genetic Diversity and Malaria Vaccine Design, Testing and Efficacy: Preventing and Overcoming 'Vaccine Resistant Malaria'." *Parasite Immunology* 31: 560–73.

Thomas, M. B., E. L. Watson, and P. Valverde-Garcia. 2003. "Mixed Infections and Insect-Pathogen Interactions." *Ecology Letters* 6: 183–8.

Thompson, R. C., A. J. Lymbery, and A. Smith. 2010. "Parasites, Emerging Disease and Wildlife Conservation." *International Journal for Parasitology* 40: 1163–70.

Tilman, D. 1994. "Competition and Biodiversity in Spatially Structured Habitats." *Ecology* 75: 2–16.

VanderWaal, K. L., and V. O. Ezenwa. 2016. "Heterogeneity in Pathogen Transmission: Mechanisms and Methodology." *Functional Ecology* 30: 1606–22.

Zinder, D., T. Bedford, S. Gupta, and M. Pascual. 2013. "The Roles of Competition and Mutation in Shaping Antigenic and Genetic Diversity in Influenza." *PLoS Pathogens* 9: e1003104.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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