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Cross-scale dynamics in community and disease ecology: relative timescales shape the community ecology of pathogens

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Abstract. Communities of free-living organisms are shaped by processes operating within and among patches of habitat, whereas pathogen communities are shaped by analogous processes operating within and among hosts. Resource competition (R^*) theory can describe dynamics within patches or hosts, and metacommunity dynamics describe competition–colonization trade-offs, extinction debts, and superinfection. However, models at this broader scale often assume instantaneous competitive exclusion in co-inhabited patches or co-infected hosts. Impacts of more gradual competitive exclusion on the abundance, distribution, and diversity of species are less clear. Here, we nest a general resource competition model within a metacommunity framework and manipulate the relative timescales for processes operating within and among patches/hosts. We focus on superinfection in pathogen communities. We compare cases where transmission depends on infection prevalence vs. the abundance of pathogens within hosts. Surprisingly, slowing the relative pace of competitive exclusion within hosts can decrease infection prevalence of the inferior competitor and increase prevalence of the superior competitor, depending on transmission and virulence. Slower within-host dynamics reduce the abundance of both pathogens within hosts and promote diversity at multiple scales: co-infections within individual hosts and co-occurrence in the host population. These results highlight surprising feedbacks that can emerge across scales and reinforce the rich cross-scale connections between community and disease ecology.

Key words: co-infection; community ecology; competitive exclusion; disease ecology; disturbance; diversity; metacommunity; resource competition; scale; superinfection; timescale; transmission.

Introduction

Ecological dynamics span nested scales of biological organization (Levin 1992). For free-living species they operate within and among patches of habitat. For pathogens, they operate within and among hosts. In metacommunities, the occupancy of species among patches depends on gains via immigration and losses via local extinction (Tilman 1994, Tilman et al. 1994). Yet within each patch, births, deaths, and the local abundance of a species often depend more on resource supply, competition, and predation (Tilman 1982, Grover 1997). In the mid 1990s, canonical theory at both of these scales of organization was applied from community ecology to disease. In the analogy, individual hosts are equivalent to patches. Among hosts, the prevalence of infections depends on gains via transmission—analogous to immigration—and losses via host death—analogous to extinction (May and Nowak 1994, Borer et al. 2016). Yet within each host, the abundance of pathogens may depend on resources, competition between pathogens, or the host immune system (Smith and Holt 1996, Smith 2007, Frost et al. 2008, Wale et al. 2017). These pronounced parallels have promoted the lateral transfer of ideas between community and disease ecology, at both among-patch/host and within-patch/host scales (Kuris and Lafferty 1994, Mihaljevic 2012, Johnson et al. 2015, Seabloom et al. 2015, Borer et al. 2016).

For simplicity, cross-scale models often assume instantaneous competitive exclusion within co-inhabited patches or hosts. Examples include canonical theory for competition–colonization trade-offs and extinction debts in community ecology (Tilman 1994, Tilman et al. 1994) and superinfection in disease ecology and evolutionary epidemiology (May and Nowak 1994). Yet competition frequently occurs on similar timescales to transmission or dispersal. For example, late successional species replace early colonizers in old fields, but competitive exclusion within a patch can last decades (Tilman 1994). Inferior competitors in Florida scrub rely on fire disturbance to colonize empty patches, but can persist in patches with superior competitors between burns

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(Menges and Kimmich 1996). Pathogens compete within co-infected mice (de Roode et al. 2005), zooplankton (Ben-Ami et al. 2008), bees (Klinger et al. 2015), and bacteria (Refardt 2011), but inferior competitors can still be transmitted. Plant pathogens inhibit one another's growth but co-infections remain common (Hood 2003, Halliday et al. 2017). Clearly, competitive exclusion is frequently interrupted by dispersal, disturbance, transmission, or host death. Models that ignore these possibilities may miss important biological outcomes.

Yet impacts of more gradual competitive exclusion on ecological communities are less clear. Cross-scale models in evolutionary epidemiology grapple with separate timescales for processes within and among hosts by tracking ages of infections (Gilchrist and Sasaki 2002, Mideo et al. 2008), sometimes for multiple pathogens (Alizon and van Baalen 2008, Sofonea et al. 2015). These specialized models are often used to study the evolution of virulence, but rarely to ask ecological questions about the distribution, abundance, and diversity of species (Gog et al. 2015, Martcheva et al. 2015). Cross-scale models in community ecology often focus more on spatial heterogeneity (Gross 2008, Olszewski 2012, Haegeman and Loreau 2015) and dispersal limitation (Kneitel and Chase 2004) rather than mismatched timescales (but see Pacala and Rees 1998, Amarasekare and Possingham 2001, Rapti and Caceres 2016). Nevertheless, transient dynamics can transform ecological communities when coupled processes (e.g., within vs. among patches or hosts) operate at mismatched timescales (Hastings 2004). Such impacts have long been hypothesized to maintain species diversity (Huston 1979, Sousa 1979, 1993). General cross-scale models could explore such ecological impacts of similar but separate timescales on communities of free-living species and pathogens alike.

Here, we ask how relative timescales for processes operating within and among patches or hosts shape ecological communities. To promote generality and synthesis, we build on canonical models with shared histories in community ecology, disease ecology, and evolutionary epidemiology. We describe dynamics within patches/hosts with a resource competition model including two competitors and one resource (Tilman 1982, Smith and Holt 1996). Then, we nest this simplified competition module within a metacommunity framework. Critically, we replace the assumption of instantaneous competitive exclusion with simulations of the competition module. This approach allows us to compare cases that approximate the classic assumption of instantaneous competition exclusion (simulating many generations of competition before transmission or dispersal) vs. cases where competition occurs on slower timescales (fewer generations of competition). This approach also allows transient dynamics within patches/hosts to influence metacommunities (Hastings 2004) and enables cross-scale feedbacks that are often absent from epidemiological theory (Mideo et al. 2008).

We focus on the case of superinfection in pathogen communities. In "superinfection", two pathogens coexist among hosts because the superior competitor is more virulent (May and Nowak 1994). We compare scenarios where transmission depends on infection prevalence (Handel and Rohani 2015) vs. the abundance of pathogens within hosts (Ben-Ami et al. 2008), corresponding to density-independent (Smith et al. 1989) or dependent (Matthysen 2005) dispersal of free-living species. Surprisingly, relatively slow dynamics within hosts can decrease infection prevalence of the *inferior* competitor and increase infection prevalence of the *superior* competitor, depending on transmission and virulence. Slower dynamics reduce the abundance of both pathogens within hosts and promote diversity at both scales.

Methods

First, we review canonical models at both scales: "Among hosts: superinfection" and "Within hosts: resource competition." Then we introduce our hierarchical model that tracks dynamics across both scales (overview: Fig. 1; parameters and definitions: Table 1). Finally, we extend our model to consider cases where transmission depends on the abundance of pathogens within hosts instead of the prevalence of infections. We focus the methods and results on pathogen communities but discuss applications to broader community ecology.

Among hosts: superinfection

The superinfection framework is a patch model that attributes changes in infection prevalence to transmission and host death (May and Nowak 1994). The model assumes a constant number of hosts and immediate replacement of hosts after death. The population is divided into the proportions that are healthy (p_0) and infected (p_1). With a single pathogen,

$$\frac{dp_1}{dt} = p_1 p_0 \beta - p_1(d + v) \tag{1}$$

where infected hosts (p_1) transmit pathogens to susceptible hosts (p_0) with a frequency-dependent transmission coefficient (β [proportion of hosts^{-1} · time^{-1}]). Healthy hosts die at a background rate (d [time^{-1}]) which is virulently elevated by infection (v [time^{-1}]). At equilibrium,

$$p_1^* = 1 - \frac{d + v}{\beta}. \tag{2}$$

Thus, equilibrial infection prevalence (p_1^*) decreases with higher host death rate and virulence but increases with higher transmission.

This model is easily expanded to include two or more pathogens that follow a strict competitive hierarchy (May and Nowak 1994, de Roode et al. 2005, Klinger et al. 2015). With two pathogens, the host

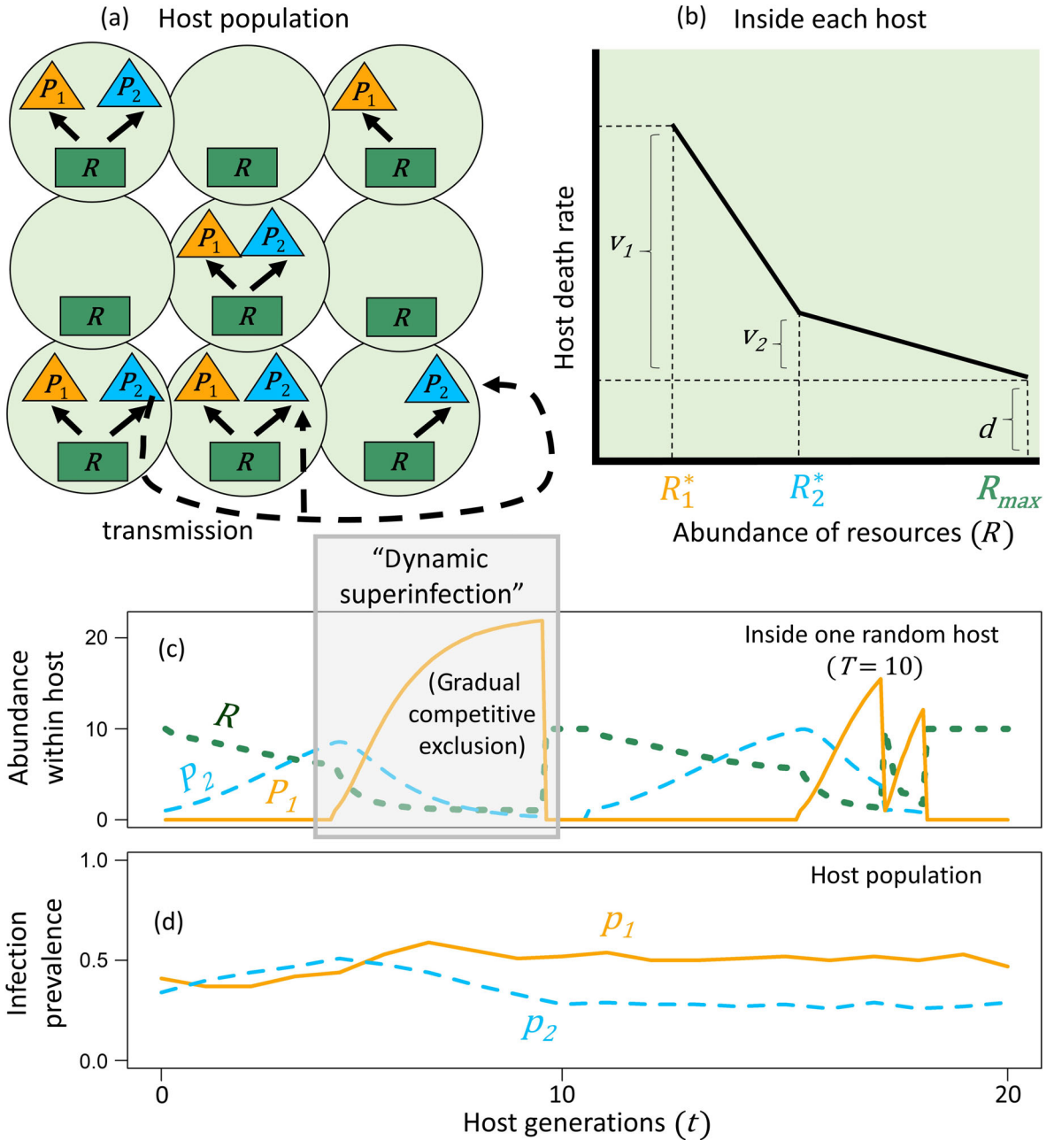

FIG. 1. Conceptual figure illustrating the general hierarchical model. In the analogy between disease and community ecology, patches are equivalent to hosts, pathogens are equivalent to free-living species, transmission is equivalent to dispersal, and host death is equivalent to local extinction. For brevity, this caption focuses on pathogens. (a) Each bubble represents an individual host ($n = 9$). Within each host, pathogens compete for resources (green; R; solid arrows). Co-occurrence within a host is transient, because the superior competitor (orange; P_1) eventually excludes the inferior competitor (blue; P_2). Pathogens are transmitted globally among hosts (dashed arrows). (b) Host death rate increases with resource depletion. At a maximum homeostatic balance R_{max}, hosts die at background rate d. As pathogens deplete resources (moving left along the gradient of resources), they virulently increase death rate. An example simulation tracks (c) abundances of pathogens and resources within one random host and (d) infection prevalence at the scale of the host population. The gray shaded box illustrates dynamic superinfection (i.e., gradual competitive exclusion; see also Appendix S1: Fig. S1). Periodic crashes in pathogen abundance and rebounding resources indicate death of the host and immediate replacement with a new susceptible individual. This simulation features a population of 100 hosts ($n = 100$) and 10 pathogen generations per generation of hosts ($T = 10$; other parameters in Table 1).

TABLE 1. Equilibria, definitions, and parameter values for among-host, within-host, and hierarchical models.

Scale	Symbol	Units	Definition	Value (range)
Among hosts	p_0	Proportion of hosts	Proportion of hosts uninfected	State variable
	p_1	Proportion of hosts	Infection prevalence of superior competitor	State variable
	p_2	Proportion of hosts	Infection prevalence of inferior competitor	State variable
	d	Host generation^{-1}	Background host death rate	0
	v_1	Host generation^{-1}	Virulence of superior competitor	0.3 (0.01–0.6)
	v_2	Host generation^{-1}	Virulence of inferior competitor	0.01
	β	Proportion hosts^{-1} host generation^{-1}	Transmission coefficient	0.5 (0–1)
Within hosts	R	R host^{-1}	Abundance of resources	State variable
	P_1	P_1 host^{-1}	Abundance of superior competitor	State variable
	P_2	P_2 host^{-1}	Abundance of inferior competitor	State variable
	s	R host^{-1} pathogen generation^{-1}	Supply rate of resources	5
	R_{max}	R host^{-1}	Maximum abundance resources	10
	u_1	R^{-1} pathogen generation^{-1}	Reproductive rate of superior competitor	0.1
	u_2	R^{-1} pathogen generation^{-1}	Reproductive rate of inferior competitor	0.02
	m	Pathogen generation^{-1}	Death rate of pathogens	0.1
	q	R pathogen^{-1}	Resource quota of pathogens	2
Hierarchical	T	Pathogen generations host generation^{-1}	Relative pathogen generation time	1, 10, or 100
	n	Number	Number of hosts	1,000
	t	Host generations	Generations of hosts	500

Notes: Equilibria: Among hosts: $p_1^* = 1 - ((d + v_1)/\beta)$; $p_2^* = ((2v_1 + d - v_2)/\beta) - 1$. Within hosts: $R^* = m/u_i$; $P_1^* = (s/mq)(1 - ((m/u_1)/ R_{max}))$; $P_2^* = (s/mq)(1 - ((m/u_2)/R_{max}))$.

population is divided into the proportions that are healthy (p_0), infected by pathogen 1 (p_1), and infected by pathogen 2 (p_2):

$$\frac{dp_1}{dt} = p_1p_0\beta + p_1p_2\beta - p_1(d + v_1) \quad (3)$$

$$\frac{dp_2}{dt} = p_2p_0\beta - p_2p_1\beta - p_2(d + v_2). \quad (4)$$

Here, the superior pathogen 1 can infect both healthy hosts and hosts already infected by pathogen 2, but the inferior pathogen 2 can only infect healthy hosts. In the classic superinfection model, transmission coefficients are assumed equal (i.e., competitive superiority only grants dominance within—not among—hosts). Co-infections are impossible, because the superior competitor instantaneously displaces the inferior competitor via "superinfection" (but see May and Nowak 1995, Alizon 2013). However, pathogens can coexist *among* hosts through a competition–virulence trade-off if stronger competitors are increasingly virulent (May and Nowak 1994). Thus, we assume $v_1 > v_2$. At equilibrium,

$$p_1^* = 1 - \frac{d + v_1}{\beta} \quad (5)$$

$$p_2^* = \frac{2v_1 + d - v_2}{\beta} - 1. \quad (6)$$

Equilibrial prevalence of the superior competitor (p_1^*) is identical to the single-pathogen case (Eq. 2). Thus, prevalence of the superior competitor is not influenced by the presence or virulence of the inferior competitor. If only the inferior competitor is present, its equilibrium also mirrors the single species case (Eq. 2). However, in the equilibrium with both pathogens (Eqs. 5 and 6), prevalence of the inferior competitor (p_2^*) decreases with its own virulence (v_2), increases with virulence of the superior competitor (v_1), and decreases with transmission (β).

Equilibria of this superinfection model (Eqs. 5 and 6) serve as important baselines. Here, we replace the model's assumption of instantaneous competitive exclusion with dynamic competition for resources within hosts (see Within hosts: resource competition).

Within hosts: resource competition

Resource competition theory (Tilman 1982) can apply to pathogens within hosts (Smith and Holt 1996, Griffiths et al. 2014). Resources in hosts can range from key elements (Frost et al. 2008) to organic compounds (Wale et al. 2017). With a single pathogen (P) and resource (R),

$$\frac{dR}{dT} = s\left(1 - \frac{R}{R_{max}}\right) - (RPuq) \quad (7)$$

$$\frac{dP}{dT} = PRu - Pm \quad (8)$$

where resources increase at a supply rate s when rare and plateau at a maximum homeostatic balance maintained

by a host, R_{max}. During infections, resources are depleted by pathogen growth. Pathogens have resource-dependent reproductive rates (u) and resource-independent mortality rates (m). A resource quota (q) represents the number of resources required to "build" each individual pathogen. The internal equilibrium reveals:

$$R^* = \frac{m}{u} \tag{9}$$

$$P^* = \frac{s}{mq}\left(1 - \frac{m/u}{R_{max}}\right). \tag{10}$$

Thus, the equilibrial abundance of resources (R^*; the "minimal resource requirement") increases with pathogen mortality and decreases with pathogen reproductive rate. The equilibrial abundance of pathogens (P^*) increases with resource supply rate. It decreases with mortality of the pathogen and the ratio of its minimal resource requirement to maximum resources.

If a second pathogen is added, the superior competitor (for consistency: P_1) eventually excludes the inferior competitor (P_2) because of the superior competitor's lower minimal resource requirement (Tilman 1982). Note the different notation for among-patch processes (lower case p denotes infection prevalence across the host population) vs. within-patch processes (capital P denotes pathogen abundance within a host). With two pathogens,

$$\frac{dR}{dT} = s\left(1 - \frac{R}{R_{max}}\right) - (RP_1u_1q) - (RP_2u_2q) \tag{11}$$

$$\frac{dP_1}{dT} = P_1Ru_1 - P_1m \tag{12}$$

$$\frac{dP_2}{dT} = P_2Ru_2 - P_2m \tag{13}$$

where the pathogens differ only in their reproductive rates, and $u_1 > u_2$. Thus, the minimal resource requirement of P_1 is lower than that of P_2 ($R_1^* R_2^*$), and P_1 excludes P_2 at equilibrium.

Equilibria of this resource competition model (Eqs. 9 and 10) serve as additional important baselines. However, in the hierarchical model, competition does not necessarily proceed to these equilibria. Instead, we refer to the gradual competitive exclusion of the inferior competitor as "dynamic superinfection" (Appendix S1: Fig. S1). The resulting transient co-occurrence within hosts can trigger feedbacks across scales that alter pathogen metacommunity dynamics.

Hierarchical model

We nested the resource competition model ("Within hosts: resource competition") inside a discrete approximation of the superinfection patch model ("Among hosts: superinfection"). All simulations were run in R version 3.4.0 (R Development Core Team 2017; Data S1). In the discrete superinfection model, we tracked a host population of 1,000 patches (n = 1,000) for 500 host generations (t = 500). Populations of 1,000 were large enough to minimize effects of stochasticity but small enough for computational tractability. Each host began with maximum resources (R_{max} = 10) and a 5% chance of infection by each pathogen (initial abundance 0 or 1).

The hierarchical model requires two distinct timescales representing the relative generation times for pathogens and hosts. We follow the same case-sensitive notation that we established for the prevalence vs. abundance of pathogens. Lower-case t represents host generations (the timescale over which infection prevalences [ps] can change). During each discrete step of t, hosts can die, be replaced, transmit, or become infected. At each of these steps of t, we simulated the competition model (Eqs. 11–13) within each host from times 0–T using the R package deSolve (Soetaert et al. 2010). Thus, capital T represents the number of pathogen generations per generation of hosts (the timescale over which pathogen abundances [Ps] can change). In other words, T is a scaling parameter that converts between timescales for pathogens and hosts. We varied T from 1 to 100 to compare a range of relative timescales. When T = 1, within- and among-host dynamics occur on the same timescale. Similar timescales represent pathogens and hosts with similar generation times, or scenarios where transmission or host death frequently interrupt competition within hosts (Ben-Ami et al. 2008, Refardt 2011, Auld et al. 2014, Klinger et al. 2015). At the other extreme, when T = 100, pathogen-generation time is much faster than transmission or host death, as classically assumed (May and Nowak 1994).

We followed each period of competition with a single discrete host generation with probabilistic host death and/or transmission. We assumed that host death rate increased as pathogens depleted resources within the host. This assumption differs from most evolutionary epidemiology theory, because virulence here is a dynamic consequence of resource depletion rather than a fixed property of a pathogen strain. A piecewise linear function allows independent manipulation of virulence of both competitors. The first relationship (right segment in Fig. 1b) represents virulence of the inferior competitor (P_2) as it depletes resources from the homeostatic maximum (R_{max}) to its minimal resource requirement (R_2^*). Its slope (s) and intercept (b) are:

$$s_2 = \frac{-v_2}{R_{max} - R_2^*} \text{ and } b_2 = d - s_2R_{max}. \tag{14}$$

The second relationship (left line segment in Fig. 1b) represents virulence of the superior competitor (P_1) as it depletes resources further toward its minimal resource requirement (R_1^*):

$$s_1 = \frac{v_2 - v_1}{R_2^* - R_1^*} \text{ and } b_1 = d + v_2 - s_1 R_2^*. \quad (15)$$

The probability of death for each host was drawn from a binomial distribution with probability

$$1 - \exp(-f(R)) \quad (16)$$

where $f(R)$ is the resource–death function. We replaced dead hosts with new susceptible individuals as in May and Nowak (1994), by resetting resources to the homeostatic maximum.

Each individual host infected with pathogen species i transmitted with probability

$$1 - \exp(-\beta(1 - p_i)) \quad (17)$$

where p_i is the current infection prevalence of pathogen i. We assumed identical probabilities of transmission from singly and co-infected hosts and independent transmission of each pathogen from co-infected hosts. Each successfully transmitting host infected a new random host that was previously uninfected by pathogen i (abundance changed from 0 to 1). If the pool of transmitted pathogens was larger than the number of uninfected hosts, all hosts became infected. All of these assumptions mimic the classic superinfection model (Eqs. 3 and 4).

We examined how altering the relative timescales for dynamics within vs. among hosts shaped pathogen metacommunities. After T generations of pathogen competition at each host generation t, we recorded infection prevalence of each pathogen (the proportion of hosts where pathogen abundance exceeded one), the proportion of hosts infected by both pathogens (co-infections), and the mean abundance of pathogens and resources in singly and co-infected hosts. We approximated equilibria of the hierarchical model by averaging over the final 100 (out of 500) host generations to remove effects of initial conditions. We then averaged results over 100 such approximations. We compared dynamics across gradients of virulence of the superior competitor (v_1: Fig. 2) and the transmission coefficient (β: Fig. 3) for both pathogens together (Figs. 2, 3; sensitivity analysis in Appendix S1: Fig. S5) and independently (Appendix S1: Figs. S2–S4). In all cases, contours highlight the impact of altering relative timescales.

Extension of the hierarchical model: abundance-dependent transmission

We extended our hierarchical framework to consider cases where transmission depends on the abundance of pathogens instead of the prevalence of infections. The simulations described above mimic dynamics of the classic superinfection model; transmission in Eq. 17 mimics the frequency-dependent transmission of Eq. 1. However, in this extension, each pathogen individual (across all hosts) transmits with probability

$$1 - \exp(-\beta). \quad (18)$$

Note that in this case the transmission coefficient β takes units of "per pathogen per host generation" instead of "per proportion of hosts per host generation." The pool of successfully transmitted pathogens is then distributed across all hosts, including those already infected.

Results

Much faster dynamics within hosts

As expected, when pathogens undergo many generations of competition between each generation of hosts (T = 100), the hierarchical model approximates equilibrial dynamics of the classic superinfection (Eqs. 5 and 6) and resource competition models (Eqs. 9 and 10). This result is consistent across gradients of virulence (Fig. 2) and transmission (Fig. 3). Each pathogen grows to its equilibrial abundance P^* and depletes resources to its minimal resource requirement R^* (Figs. 2a and 3a). Prevalence of the superior competitor decreases with its virulence (Fig. 2b), increases with transmission (Fig. 3b), and is unaffected by the presence of the inferior competitor (compare to Figs. S2b and S3b, respectively). Prevalence of the inferior competitor depends on the presence of the superior competitor. When alone, the inferior competitor's prevalence increases with transmission (Fig. 3b; Appendix S1: Fig. S4d). When present, the superior competitor reduces prevalence of the inferior competitor via superinfection (Figs. 2b and 3b). These results are all well known (Tilman 1982, May and Nowak 1994).

More interesting results arise when pathogens undergo fewer generations per generation of hosts (T = 10 or 1). Slowing the relative generation time of pathogens dramatically shifts the abundance of pathogens within hosts, prevalence of infections in the host population, and diversity at both scales. We focus first on behavior of the superior competitor.

Similar timescales: superior competitor

Slower relative pathogen-generation time generally decreases the abundance of the superior competitor within hosts (below P_1^*), but increases its prevalence in the host population (above p_1^*). However, both of these impacts fade with lower virulence (Fig. 2c, d). If background host mortality is zero and the pathogen is not virulent, then all infections eventually approach their within-host equilibria. In other words, if hosts never die, the relative generation times of pathogens and hosts are irrelevant. In contrast, when host mortality and resource exploitation occur on similar timescales, host death frequently interrupts infections before pathogens deplete

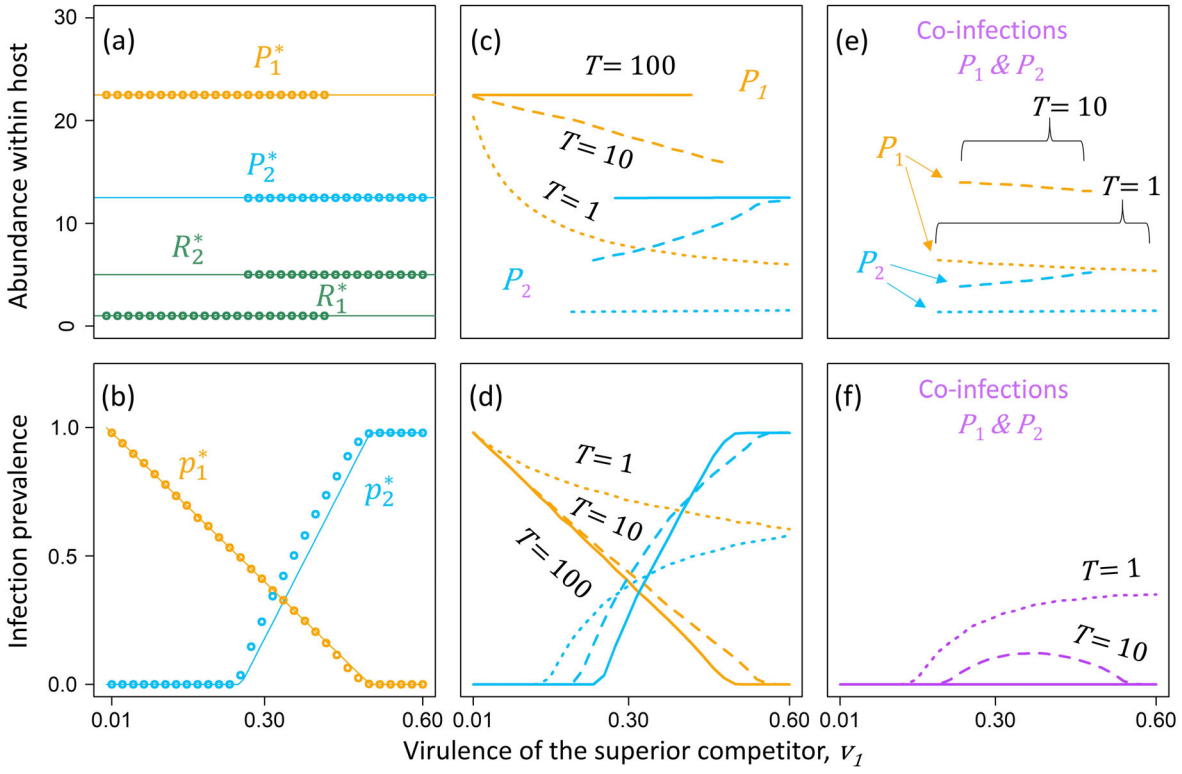

FIG. 2. Abundance and prevalence of two competing pathogens over a gradient of virulence of the superior competitor. (a), (b) Simulations of the hierarchical model (points) approximate analytical equilibria (lines) when pathogens undergo many generations ($T = 100$) between each generation of hosts. (a) The superior competitor (orange; P_1) and inferior competitor (blue; P_2) both reach their maximum abundances and deplete resources (green; R) to their minimal resource requirements in hosts that they infect (regardless of virulence). (b) Higher virulence decreases prevalence of the superior competitor and allows higher prevalence of the inferior competitor. (c), (d) Contours decrease the number of pathogen generations per generation of hosts (solid: $T = 100$; dashed: $T = 10$; dotted: $T = 1$). Competition and virulence jointly determine the impact of slower within-host dynamics on (c) pathogen abundance; (d) infection prevalence; and (e), (f) co-infections. In short, slower dynamics reduce abundance of the superior competitor but increase its prevalence, especially as its virulence increases. These changes have cascading impacts on the inferior competitor and co-infections (explained more extensively in Results). Parameter values are listed in Table 1. Single-species cases shown in the appendix (superior: Fig. S2; inferior: Fig. S4).

resources to their minimal resource requirement (R^*). The reason that these slower dynamics also elevate infection prevalence stems from the resource–death relationship (Fig. 1b). When pathogens cannot deplete resources as far, host death rate remains relatively low. In other words, the superior competitor behaves like a less virulent pathogen. In turn, lower virulence increases the prevalence of infection in the host population (Eq. 2). Hereafter, we refer to this cross-scale feedback as the "exploitation–virulence pathway." In summary, slower within-host dynamics reduce the mean abundance of pathogens, fewer pathogens allow more resources, more resources reduce virulence, and lower virulence increases infection prevalence.

The magnitude of these changes in abundance and prevalence increased exponentially as the relative pace of within-host dynamics slowed. Decreasing pathogen generations per generation of hosts from $T = 100$ to $T = 10$ induced relatively small differences. Decreasing it further from $T = 10$ to $T = 1$ elicited more dramatic responses. These results reflect nonlinear dynamics of the resource competition module. Population growth of the pathogen slowed as it approached its within-host carrying capacity (Fig. 1; Appendix S1: Fig. S1). Thus, the most substantial changes in pathogen abundance occurred in the first few pathogen generations. Consequently, slower within-host dynamics exerted especially large impacts on the pathogen metacommunity, because transmission or host death could interrupt these first few critical pathogen generations.

Similar timescales: inferior competitor

Slowing relative pathogen-generation time has more complicated effects on the inferior competitor, because it responds to (1) the exploitation–virulence pathway (described above), (2) changes in prevalence of the superior competitor, and (3) dynamic superinfection (i.e., gradual competitive exclusion of the inferior competitor). The relative balance of these three forces changes along the

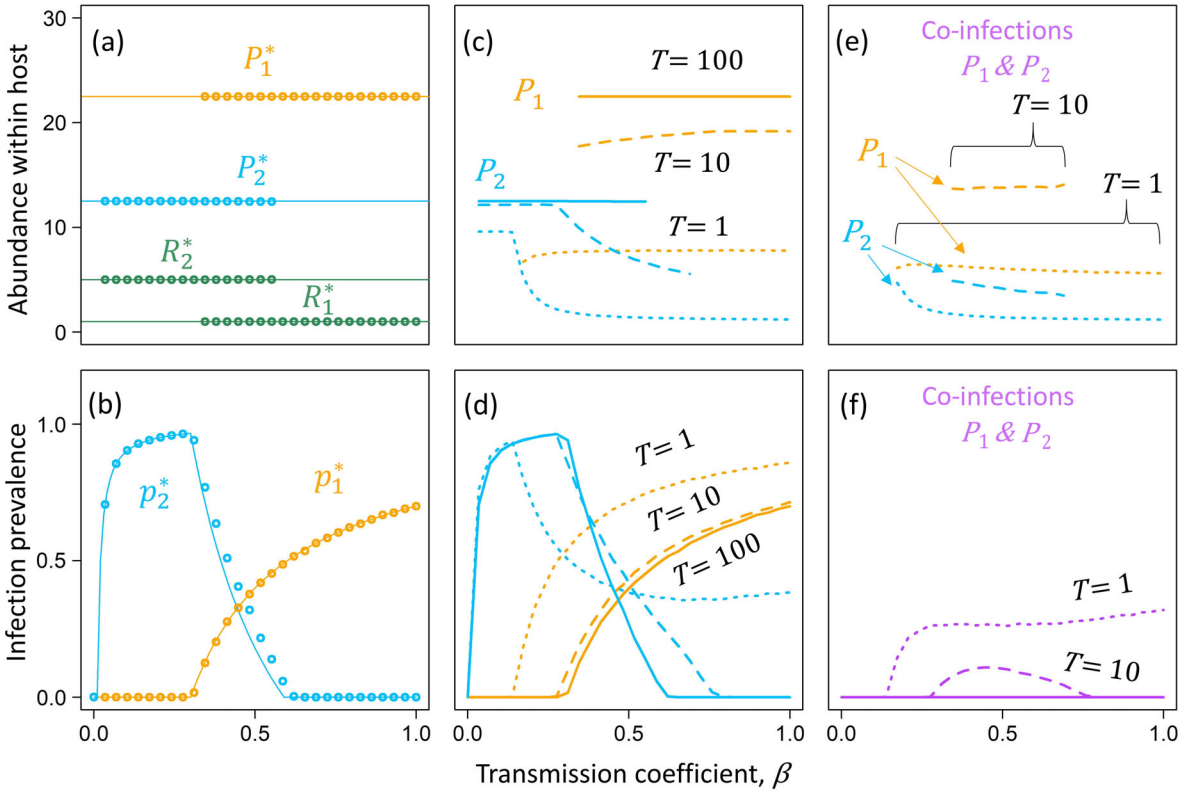

FIG. 3. Abundance and prevalence of two competing pathogens over a gradient of the transmission coefficient. (a), (b) Simulations of the hierarchical model (points) approximate analytical equilibria (lines) when pathogens undergo many generations (T = 100) between each generation of hosts. (a) The superior competitor (orange; P_1) and inferior competitor (blue; P_2) both reach their maximum abundances and deplete resources (green; R) to their minimal resource requirements in hosts they infect (regardless of transmission). (b) Higher transmission allows the superior competitor to invade and increase in prevalence. Prevalence of the inferior competitor increases (before the superior competitor invades) and then decreases (after the superior competitor invades) with transmission. (c), (d) Contours decrease the number of pathogen generations per generation of hosts (solid: T = 100; dashed: T = 10; dotted: T = 1). Competition and transmission jointly determine the impact of slower within-host dynamics on (c) pathogen abundance; (d) infection prevalence; and (e), (f) co-infections. In short, slower within-host dynamics always reduce the abundance of pathogens within hosts and increase prevalence of the superior competitor. Changes in prevalence of the inferior competitor and co-infections reflect altered prevalence and abundance of the superior competitor as well as relaxed competition within hosts (explained more extensively in Results). Parameter values are listed in Table 1. Single-species cases shown in the appendix (superior: Fig. S2; inferior: Fig. S4).

gradient of the transmission coefficient (Fig. 3). First, low transmission excludes the superior competitor. In this range, slower pathogen-generation time only impacts the inferior competitor through exploitation–virulence. As with the superior competitor, slower dynamics reduce mean abundance of the inferior competitor (below P_2^*; Fig. 3c) and increase its infection prevalence (above p_2^*; Fig. 3d).

Second, however, the superior competitor can invade as the transmission coefficient increases (Fig. 3d). Moreover, slower relative pathogen-generation time allows the superior competitor to invade at lower transmission coefficients. Consequently, the inferior competitor suffers from superinfection across a broader range of transmission. In this range, abundance of the inferior competitor continues to decrease further below the drop associated with exploitation–virulence (Fig. 3c). Its infection prevalence also begins to decline and quickly drops (below p_2^*; Fig. 3d). Graphically, slower pathogen-generation time shifts peak infection prevalence left along the transmission axis (Fig. 3d). Thus, slower dynamics (T = 10 or 1) first increase and then decrease prevalence of the inferior competitor relative to cases where pathogens underwent many more generations of competition between each generation of hosts (T = 100).

A third important outcome also emerges—co-occurrence within hosts and elevated infection prevalence of both pathogens—because slower within-host dynamics relax the negative effect of superinfection on the inferior competitor. In other words, without instantaneous exclusion, the inferior competitor persists in transient co-infections (Fig. 1). With high transmission and slow relative pathogen-generation time, prevalence of the inferior competitor declines more gradually than when within-host dynamics are faster (Fig. 3d). This decline is gradual because the inferior competitor persists in hosts

that become co-infected. Faster within-host dynamics would have eliminated the inferior competitor from co-infected hosts via superinfection. Instead, infection prevalence of *both* pathogens is higher (above respective p^*s) because of a lag time between resource depletion and competitive exclusion (dynamic superinfection; see Fig. 1; Appendix S1: Fig. S1). The relative balance of these same three forces—(1) exploitation–virulence, (2) altered prevalence of the superior competitor, and (3) dynamic superinfection—also explain how slower within-host dynamics affect the inferior competitor across the gradient of virulence of the superior competitor (Fig. 2).

Similar timescales: co-infections

Slower within-host dynamics promote persistent co-infections via transient competitive exclusion (Figs. 2f, 3f). Across a broad range of conditions, pathogens not only coexist among hosts in the metacommunity via the competition–virulence trade-off, but also transiently co-occur within individual hosts via dynamic superinfection. The abundance of both pathogens in co-infected hosts is lower than in corresponding single infections (Fig. 2e, f), because co-infections are more recent. Older co-infections (with more abundant pathogens) eventually become single infections via competitive exclusion. Mean resources in co-infected hosts fall below the minimal resource requirement of the inferior competitor (R_2^*; not shown), indicating that the inferior competitor (P_2) is declining and only persists in co-infections via source–sink dynamics. The prevalence of co-infections, that is, the proportion of hosts infected by both pathogens, peaks at intermediate virulence of the superior competitor (Fig. 2f) and transmission (Fig. 3f) and increases as relative pathogen-generation time decreases (from $T = 10$ to $T = 1$).

Extension of the hierarchical model: abundance-dependent transmission

Feedbacks across scales fundamentally change under scenarios where transmission depends on the abundance of pathogens within hosts (Fig. 4) instead of infection prevalence (Figs. 2, 3). Most notably, the exploitation–virulence pathway disappears. Fewer pathogen generations per generation of hosts still reduce the abundance of the superior competitor within hosts (Fig. 4a). However, when transmission depends on abundance, lower abundance within hosts reduces transmission and *reduces* infection prevalence among hosts (Fig. 4b). Because the superior competitor is less prevalent, the inferior competitor reaches *higher* prevalence (Fig. 4b). Co-infections occur over a much narrower range of transmission (Fig. 4c, d) compared to frequency-dependent transmission (Fig. 3e, f). Co-infections are less common in the host population because the superior competitor has gained an additional advantage over the inferior competitor. Not only does it benefit from a lower minimal resource requirement, but it also benefits from a greater probability of transmission—by virtue of its faster reproductive rate and higher within-host abundances.

Discussion

We combined canonical frameworks from community and disease ecology to ask how relative timescales for nested processes shape ecological communities. At a fine scale, resource competition can describe the abundance of free-living species within patches (Tilman 1982) or pathogens within hosts (Smith and Holt 1996). At a broader scale, metacommunity dynamics can describe competition–colonization trade-offs (Tilman 1994), extinction debts (Tilman et al. 1994), and superinfection (May and Nowak 1994). Yet models at this broader scale often assume instantaneous competitive exclusion within co-infected hosts or co-inhabited patches. We relaxed this biologically improbable assumption by nesting resource competition dynamics within each patch or host. We focused on superinfection in pathogen communities and manipulated the relative rate of competitive exclusion by altering the number of generations of pathogen competition per generation of hosts (T). Relatively fast dynamics within hosts ($T = 100$) recreated patterns consistent with classic theory. Slower dynamics ($T = 1$ or 10) decreased the abundances of pathogens within hosts, especially with higher virulence. Slower dynamics increased prevalence of the superior competition via "exploitation–virulence" (with frequency-dependent transmission). Prevalence of the inferior competitor increased or decreased, depending on the balance of exploitation virulence, prevalence of the superior competitor, and "dynamic superinfection." Finally, slower dynamics within hosts promoted diversity at both scales.

The cross-scale framework synthesized here could apply broadly to biological systems that encompass nested scales of organization (Levin 1992), ranging from cells to landscapes (Borer et al. 2016). Regular disturbance, host death, dispersal, or transmission frequently prevent dynamics within patches or hosts from proceeding to competitive exclusion. Examples include pathogens that infect short-lived hosts (Ben-Ami et al. 2008, Refardt 2011, Auld et al. 2014, Klinger et al. 2015) or exclude one another relatively slowly (Hood 2003, de Roode et al. 2005, Halliday et al. 2017), disturbance in intertidal communities (Sousa 1979), perturbation of microbiomes (Christian et al. 2015), and succession in grasslands (Tilman 1994, Menges and Kimmich 1996, Seabloom and Richards 2003), wetlands (Daleo et al. 2014), and forests (Turner et al. 1997). One major difference between free-living and pathogen examples is that pathogens can cause extreme disturbance by killing their hosts. However, infections can also modify host environments in less extreme ways. Here, for example, pathogens reduced resources within hosts and often inhibited additional infections. In other words, pathogens acted as

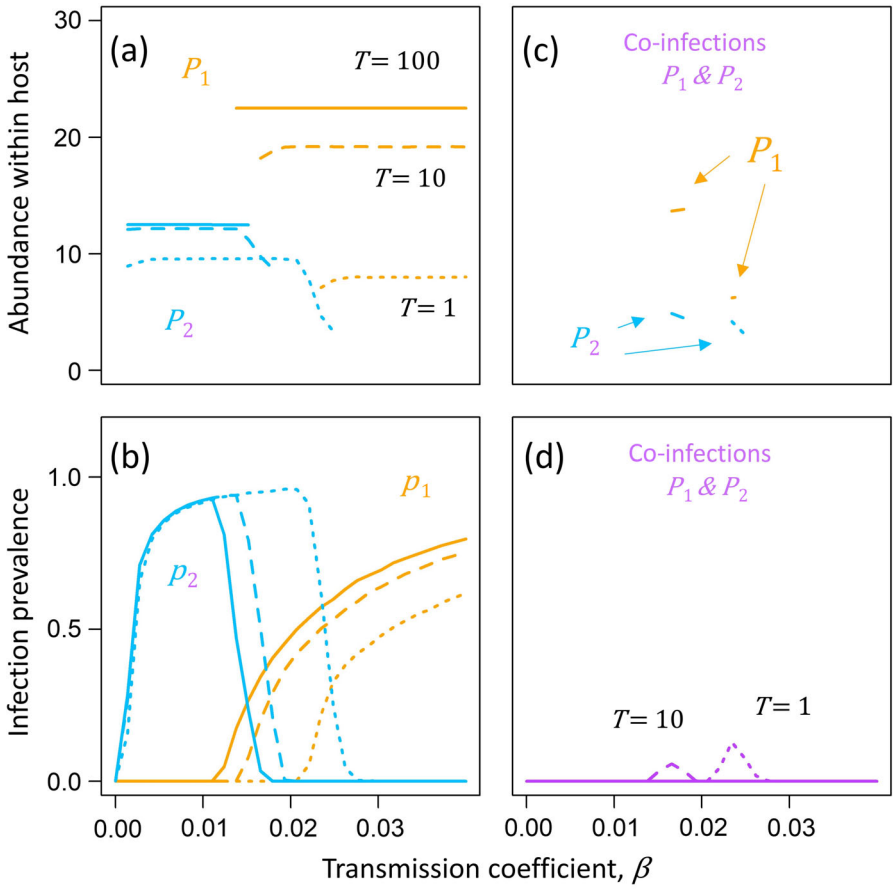

FIG. 4. Abundance-dependent transmission: Two competing pathogens over a gradient of the transmission coefficient. In this model extension, transmission depends on the abundance of pathogens instead of infection prevalence (all parameters other than the transmission coefficient match Fig. 3). Contours decrease the number of pathogen generations per generation of hosts (solid: T = 100; dashed: T = 10; dotted: T = 1). (a) Fewer pathogen generations reduce the abundance of both the superior competitor (orange) and the inferior competitor (blue) within hosts, as in the case of prevalence-dependent transmission. (b) However, fewer pathogen generations *decrease* infection prevalence of the superior competitor (compare to Fig. 3d) and increase infection prevalence of the inferior competitor over most of the gradient of the transmission coefficient. (c) The abundance of both pathogens is lower in co-infections than single infections, and co-infections are restricted to a narrow range of the transmission coefficient. (d) The prevalence of co-infection is lower than the case of prevalence-dependent transmission (compare to Fig. 3f).

ecosystem engineers and induced biotic resistance. Broadly, dispersal into both hosts and patches likely interacts with dynamic resource exploitation and competition to shape metacommunities. Key differences across systems likely include the relative pace of within-patch dynamics (e.g., succession of trees vs. turnover of microbiomes), the frequency of disturbance (e.g., fire for succession; host death for pathogens), and constraints on transmission or dispersal (e.g., frequency vs. abundance–dependence).

Cross-scale feedbacks induced surprising changes in the distribution and abundance of species. We had expected that gradual—vs. instantaneous—competitive exclusion would benefit the inferior competitor but have little impact on the superior competitor. In fact, with the classic assumption of frequency-dependent transmission, slower within-host dynamics consistently increased prevalence of the *superior* competitor and often decreased prevalence of the *inferior* competitor. These surprises emanated from the cross-scale "exploitation–virulence pathway". When within-host dynamics were relatively slow, the superior competitor achieved lower abundances, depleted resources less fiercely, induced less host mortality, and infected a larger proportion of the host population. In turn, the superior competitor excluded the inferior competitor from more hosts (at least with relatively low transmission or high virulence) and reduced its mean abundance in co-infections. Although such feedbacks are rare in epidemiological models (Mideo et al. 2008), they arose here because we viewed virulence as a dynamic consequence of resource exploitation rather than a fixed trait of a pathogen strain (Alizon and van Baalen 2008, Sofonea et al. 2015). When we slowed the relative pace of dynamics within hosts, this form of exploitation–

virulence triggered cross-scale feedbacks that altered the pathogen metacommunity.

Our results point to the need for more empirical studies to characterize dispersal and transmission across scales. We had expected that when transmission depended on the abundance of pathogens rather than infection prevalence, the superior competitor would benefit more, because it reached higher abundances in hosts. Actually, with these conditions, relatively slow dynamics *decreased* prevalence of the superior competitor and consequently *increased* prevalence of the inferior competitor. These outcomes arose because slower dynamics also penalized transmission. Thus, slower within-host dynamics have opposite effects on prevalence of the superior competitor when assuming frequency-dependent vs. abundance-dependent transmission. For pathogens, frequency dependence could reflect vectored or sexually transmitted diseases (Antonovics et al. 1995), whereas abundance–dependence could apply to directly or environmentally transmitted pathogens (Ben-Ami et al. 2008, Halliday et al. 2017). By analogy, dispersal of free-living species can also depend on their frequency across a landscape (Smith et al. 1989) or abundance within a patch (Matthysen 2005). Because metacommunity dynamics were sensitive to these assumptions, data on transmission and dispersal seem especially critical for guiding cross-scale theory (Kneitel and Chase 2004, Matthysen 2005, Gog et al. 2015, Handel and Rohani 2015, Sullivan et al. 2018).

Relatively slow competitive exclusion promoted diversity at both scales. One of the oldest challenges in community ecology is to explain the maintenance of species diversity (Huston 1979, Sousa 1979) including the diversity of parasites (Sousa 1993) and pathogens within hosts (Seabloom et al. 2015). However, in resource competition theory, conditions that allow multiple species to coexist are quite restrictive (Tilman 1982, Grover 1997, but see Olszewski 2012). In contrast, evolutionary epidemiologists focus more on evolutionarily stable strategies of pathogen traits rather than their diversity. By definition, evolutionarily stable strategies cannot be invaded (but see Claessen and deRoos 1995, Caraco et al. 2006, Alizon and van Baalen 2008). Here, the inferior competitor frequently occurred in co-infected hosts (co-inhabited patches), even when resources had been depleted below its minimal resource requirement. In these cases, pathogens transiently co-occurred within any given host, but consistently co-occurred across the host population via source–sink dynamics (Mouquet and Loreau 2003, Hastings 2004, Leibold and Chase 2018). This increase in pathogen diversity arose from periodic host death and gradual competitive exclusion. Such relaxed negative interactions among pathogens infuse transient dynamics into resource competition theory, recapitulate the intermediate disturbance hypothesis (Sousa 1979) to explain the nonequilibrium maintenance of species diversity (Huston 1979, Olszewski 2012), and compromise models of superinfection and co-infection used in evolutionary epidemiology (Alizon 2013).

Applications of this hierarchical model to empirical data seem potentially feasible. Fitting nested models to pathogen communities is notoriously difficult, because such models often require many parameters and obtaining sufficient information about the interactions within hosts is challenging (but see Lello et al. 2004, Mideo et al. 2011). Here, we described dynamics within hosts with a simplistic competition module (Tilman 1982). Indeed, pathogens frequently interact in co-infected hosts via resource competition (Griffiths et al. 2014). The first step toward parameterizing our model would be to ask how common co-infections are in nature (Sousa 1993, Seabloom et al. 2015). If common, the second step would be to determine experimentally how quickly pathogens displace one another in sequential infections (Hood 2003, Ben-Ami et al. 2008, Klinger et al. 2015, Halliday et al. 2017). Together, this information could suggest, at least phenomenologically, the relative pace of dynamics within vs. among hosts. Then, different shapes could describe the probability of host death over the course of single or multiple infections. Finally, the competition model featured here could easily be replaced with other community modules (Grover 1997) that include multiple resources or "predators" representing host immune function (Smith and Holt 1996, Alizon and van Baalen 2008). Such relatively simple, flexible hierarchical models could help address the emerging paradox that co-infections are common in nature (Lello et al. 2004, Seabloom et al. 2015), but that pathogens frequently compete within co-infected hosts (de Roode et al. 2005, Auld et al. 2014, Griffiths et al. 2014, Klinger et al. 2015, Halliday et al. 2017).

In the mid 1990s, theory from community ecology was applied to disease at multiple, nested scales of biological organization. With both fields currently asking questions across scales, the time is ripe to revisit these historical connections. The model presented here highlights how the relative pace of dynamics operating within vs. among patches or hosts shapes fundamental ecological properties, including the distribution, abundance, and diversity of species. Flexibility to incorporate variation in timescales is likely to remain a key ingredient for general cross-scale theory and its applications for metacommunities of free-living species and pathogens alike.

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Supporting Information

Additional supporting information may be found in the online version of this article at http://onlinelibrary.wiley.com/doi/10.1002/ecy.2836/suppinfo

Data Availability

Data are available on the Dryad Digital Repository: https://doi.org/10.5061/dryad.rd435pq