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Dose relationships can exacerbate, mute, or reverse the impact of heterospecific host density on infection prevalence

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Abstract. The likelihood an individual becomes infected depends on the community in which it is embedded. For environmentally transmitted parasites, host community composition can alter host density, the density of parasites that hosts encounter in the environment, and the dose to which hosts are subsequently exposed. While some multi-host theory incorporates some of these factors (e.g., competition among hosts), it does not currently consider the nonlinear relationships between parasite exposure dose and per-propagule infectivity (dose–infectivity relationships), between exposure dose and infected host mortality (dose–mortality relationships), and between exposure dose and parasite propagule excretion (dose–excretion relationships). This makes it difficult to predict the impact of host species on one another's likelihood of infection. To understand the implications of these nonlinear dose relationships for multi-host communities, we first performed a meta-analysis on published dose–infectivity experiments to quantify the proportion of accelerating, linear, or decelerating dose–infectivity relationships; we found that most experiments demonstrated decelerating dose–infectivity relationships. We then explored how dose–infectivity, dose–mortality, and dose–excretion relationships might alter the impact of heterospecific host density on infectious propagule density, infection prevalence, and density of a focal host using two-host, one-parasite models. We found that dose relationships either decreased the magnitude of the impact of heterospecific host density on propagule density and infection prevalence via negative feedback loops (decelerating dose–infectivity relationships, positive dose–mortality relationships, and negative dose–excretion relationships), or increased the magnitude of the impact of heterospecific host density on infection prevalence via positive feedback loops (accelerating dose–infectivity relationships and positive dose–excretion relationships). Further, positive dose–mortality relationships resulted in hosts that traditionally decrease disease (e.g., low competence, strong competitors) increasing infection prevalence, and vice versa. Finally, we found that dose relationships can create positive feedback loops that facilitate friendly competition (i.e., increased heterospecific density has a positive effect on focal host density because the reduction in disease outweighs the negative effects of interspecific competition). This suggests that without taking dose relationships into account, we may incorrectly predict the effect of heterospecific host interactions, and thus host community composition, on environmentally transmitted parasites.

Key words: *amplification; dilution; infection; infection risk; prevalence.*

Introduction

Hosts and their parasites do not exist in isolation. Rather, the likelihood of infection of any individual host (i.e., the probability an individual is infected in a short time interval) depends on the community in which it is embedded, due to direct interspecific competition and cross-species parasite transmission (O'Regan et al. 2015). Competitors can "amplify" (i.e., increase) infection prevalence in a host species if they have high infection "competence," meaning they have high susceptibility to infection and transmission potential (Power and Mitchell 2004). Similarly, competitors can "dilute" (i.e., decrease) infection prevalence in a host species if they have low competence. With low enough competence, competitors can even create "friendly competition," where they increase the density of the host species by lowering infection likelihood, despite competing for resources (Hall et al. 2009). Ultimately, understanding how competitors alter infection likelihood of individual host species will

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allow us to predict the viability of host populations and the risk of spillover to other host species (Luis et al. 2018). However, nonlinear interactions between density dependent disease processes often make it difficult to predict how one host species will impact infection likelihood in heterospecific host species (Searle et al. 2016).

When parasite transmission requires infectious propagules to move through the environment (environmentally transmitted parasites, Box 1), competing host species alter the likelihood of infection by changing the density of parasite propagules within the environment, and thus the dose of propagules that each host encounters. Many virulent parasites transmit via the environment, including waterborne parasites such as cholera and schistosomiasis and orally transmitted parasites such as tapeworms (Wardle and Mcleod 1952, Reidl and Klose 2002, Steinmann et al. 2006). Host species that both compete for resources and become infected by the same pathogen influence the spread of environmentally transmitted parasites in three ways. First, infected individuals excrete parasite propagules into the environment (Wardle and Mcleod 1952), but host species differ in the number of propagules they shed. Second, hosts (and non-host organisms) remove parasite propagules from the environment upon infection, and possibly by consuming them (Burge et al. 2016). Third, competing host species can alter one another's density via interspecific competition, changing the number of individuals available to transmit and remove propagules (Strauss et al. 2015). Altogether, this means that competing host species determine the dose of parasite propagules that each individual contacts, and thus the likelihood of infection for each host species.

Box 1. Defining environmental transmission.

We categorize parasites as environmentally transmitted if they must travel through the environment when transmitting between hosts. We consider "the environment" to be any space that is not in or on a host or vector. In these systems, infected hosts release parasite propagules into the environment. Susceptible hosts come in contact with a *dose* of parasite propagules, based on the density of parasite propagules in the environment, and the rate at which hosts come in contact with those propagules (e.g., in the case of water borne pathogens, propagule dose will increase if propagule density in the water increases, or if the host drinks more water). Susceptible hosts then have some probability of becoming infected based on the dose of propagules they contact.

The likelihood of infection, however, often changes nonlinearly with propagule dose (Fig. 1A, B). As propagule dose increases, the infectivity of each parasite propagule can decrease, leading to a decelerating (antagonistic) dose–infectivity relationship. Alternatively, as propagule dose increases, the infectivity of each parasite propagule can increase, leading to an accelerating (synergistic) dose–infectivity relationship (Regoes et al. 2003). Further, as propagule dose increases, infected host mortality and propagule excretion from infected individuals may change (Ashworth et al. 1996, Dallas and Drake 2014) (Fig. 1C, D). Together, these "dose relationships" (dose–infectivity, dose–mortality, and dose–excretion relationships) make parasite transmission a function of environmental propagule density, which is in turn a function of parasite transmission. This feedback loop may create challenges for predicting how competing host species will influence infection likelihood. To date, however, mechanistic models of multi-host systems typically do not incorporate dose-dependent feedback loops (Bowers and Begon 1991, Begon and Bowers 1994, Greenman and Hudson 2000, Cáceres et al. 2014, Strauss et al. 2015, Searle et al. 2016). Further, while some studies suggest that accelerating dose–infectivity relationships are common (Regoes et al. 2002), we lack a quantitative review of how common accelerating and decelerating dose–infectivity relationships are. By exploring the frequency of different types of dose relationships, and the impact they have on multi-host systems, we may be better able to predict the impact of heterospecific host interactions on infection likelihood in individual host species.

Thus, we sought to answer several basic questions. First, are accelerating, linear, or decelerating dose–infectivity relationships more common in published studies? To answer this question, we conducted a meta-analysis of experimental dose–infectivity experiments and found that parasites usually exhibit decelerating dose–infectivity relationships. Second, we asked whether the impact of competing host species with varying infection competencies on disease in a focal host would depend on the relationship (1) between dose and the infectivity of parasite propagules (dose–infectivity relationships), (2) between dose and host excretion rates of parasite propagules (dose–excretion relationships), or (3) between dose and the mortality rate of infected individuals (dose–mortality relationships). Using two-host, one-parasite models that incorporate the types of dose relationships found in empirical studies, we examined how the effects of interspecific host density on infection prevalence in a focal host were mediated by dose–infectivity, dose–mortality, and dose–excretion relationships. We found dose relationships can increase, decrease, or even reverse the impact of heterospecific host density on infection prevalence. These results indicate that dose dependency is common in host–parasite interactions, and that disease models that do not take these dose

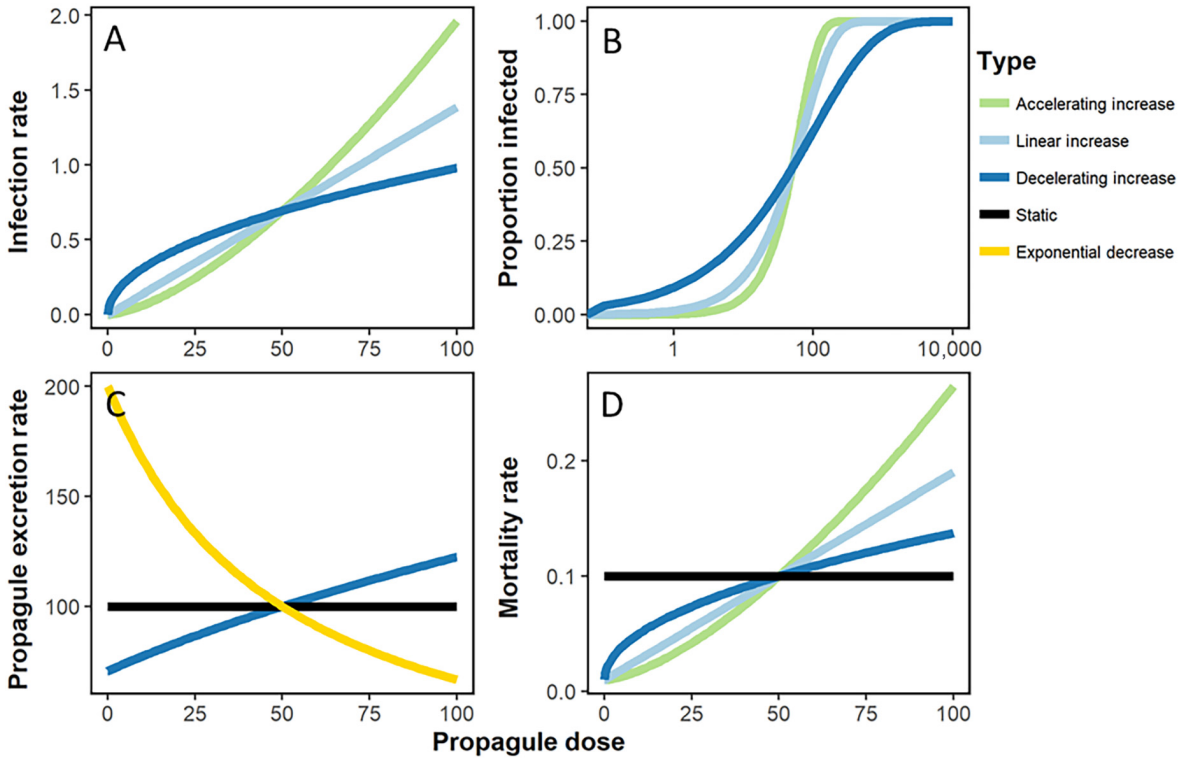

FIG. 1. Dose relationships can take a variety of forms. The *x*-axis shows propagule dose and the *y*-axis shows (A) the infection rate (dose–infectivity relationship), (B) the proportion of individuals becoming infected after exposure to that dose (dose–infectivity relationship, continued), (C) the rate at which parasite propagules are excreted from infectious individuals (dose–excretion relationship), and (D) the mortality rate of infected individuals (dose–mortality relationship). The shape of each dose relationship is described by a shape parameter (k for dose–infectivity relationships, Eq. 1, γ for dose–excretion relationships, Eq. 9, and ρ for dose–mortality relationships, Eq. 10). If k, ρ, or γ is greater than 1, the dose relationship has an accelerating increase. If k, ρ, or γ is equal to 1, the dose relationship has a linear increase. If k, ρ, or γ is between 1 and 0, the dose relationship has a decelerating increase. If k, ρ, or γ is equal to 0, the dose relationship is static. If k, ρ, or γ is less than 0, the dose relationship has an exponential decrease. Lines are shown for parameter values included in model results, based on the literature review results.

relationships into account may result in inaccurate predictions of disease dynamics in dose-dependent systems.

META-ANALYSIS METHODS

Literature review

To find empirical dose–infectivity relationships, we conducted a literature search in Google Scholar using the terms "parasite dose," "pathogen dose," "propagule dose," "bacterial dose," "viral dose," "dose–response relationship," AND "parasite" or "pathogen," or "ID50" AND "prevalence." This search led to underrepresentation of marine systems compared to terrestrial and freshwater systems, so we additionally searched for "dose" combined with well-studied marine parasites. We accepted experimental studies that (1) exposed individual hosts to varying parasite propagule doses/densities, (2) reported the proportion of hosts infected for each propagule dose/density, and (3) found variation in the proportion of hosts infected across propagule doses/densities. Our literature review included host–parasite systems across a variety of habitats, host taxa, and parasite taxa (Table 1). Many experiments exposed hosts to a variety of propagule densities, but were not able to measure contact rate, and thus dose. In these cases, we assumed that dose scaled linearly with propagule density, though this is not always true (Strauss et al. 2019). To avoid biases from model organisms, we only accepted one experiment per combination of host species and parasite species, choosing the experiment with the most dose treatments. We did not include experiments performed on incarcerated people due to ethical concerns. For each host–parasite pair, we recorded the parasite dose used in each treatment, the number of individuals per treatment, the number of individuals successfully infected in each treatment, and the duration of time that individuals were exposed to parasites. Where raw data were not available, we extracted the number of infected individuals from published figures. Finally, we recorded whether dose altered any other aspects of infection, such as host mortality or the number of parasite propagules released from each individual.

TABLE 1. Categories of host–parasite interactions included in the literature review.

Category	No. combinations
Environment	
Freshwater	14
Marine	13
Terrestrial	71
Transmission	
Direct	3
Environmental	86
Vector borne	9
Host taxa	
Ciliate	1
Human	9
Invertebrate	46
Plant	26
Non-human vertebrate	16
Parasite taxa	
Bacteria	13
Fungi	13
Nematode	3
Oomycete	25
Protist	7
Trematode	3
Virus	30
Other	4

Notes: We found 98 host–parasite combinations across 63 studies. We consider "environmental" parasites to be parasites where host contact is not required for transmission, and where parasites are not transmitted via vectors. Parasites in the "other" taxa category include cercozoan, myxozoan, platyzoan, and trypanosome parasites.

Meta-analysis

We conducted an analysis to determine whether dose–infectivity relationships were linear, decelerating, or accelerating. For linear dose–infectivity relationships, dose does not change per-propagule infectivity, and dose changes infection rate in a linear manner. Under decelerating dose–infectivity relationships, the infectivity of individual parasite propagules decreases with increased propagule dose. Thus, as dose increases, propagule infectivity decreases, and the infection rate increases in a concave-down manner. This does not necessarily mean that parasites mechanistically interfere with one another. Rather, this pattern could be the result of nonlinear immune responses in an individual as dose increases. Finally, under accelerating dose–infectivity relationships, the infectivity of individual parasite propagules increases with increased propagule dose. Thus, as dose increases, propagule infectivity increases, and the infection rate increases in a concave-up manner. Accelerating dose–infectivity relationships can be created if a high parasite dose is required to overwhelm host defenses.

To determine whether the dose–infectivity relationships in our literature review were better represented by accelerating, decelerating, or linear relationships, we derived an equation that described the proportion of individuals infected for a given dose of parasites. We model an experiment where N individuals are exposed to parasite propagules at density P. The dose that individuals consume is fP, where f is the parasite contact rate. Parasites are removed from the experiment when they contact individuals, at a rate fPN. We assume that the length of the experiment is sufficiently short such that total host density is constant, infected individuals do not recover from infection, and infected individuals do not release new parasite propagules into the environment. In the model, the changes in susceptible host density (S), infected host density (I), and P are

$$\frac{dS}{dt} = -\beta(fP)^k S \tag{1A}$$

$$\frac{dI}{dt} = \beta(fP)^k S \tag{1B}$$

$$\frac{dP}{dt} = -fNP \tag{1C}$$

where β is per-propagule infectivity, k is the dose shape parameter, and $\beta(fP)^k$ is the host infection rate. For a given study, if $k = 1$, the infection rate increases linearly with dose, if $k < 1$, the infection rate has a decelerating increase with dose, and if $k > 1$, the infection rate has an accelerating increase with dose (Fig. 1A).

We used Bayesian inference to fit Eqs. 1A–1C to the published data from our literature review. For each study, we numerically ran our system of ODEs for the experimental run time. We then estimated the values of β, k, and f most likely to generate the infection prevalence reported in the studies for each dose treatment. We used vaguely informative priors to prevent β and k from going below 0. If parasite dose was instantaneous (e.g., injections), we assumed that hosts contact all parasites instantaneously (see Appendix S1 for details). In cases where parasite densities were reported as dilutions, we relativized all parasite densities so that the lowest parasite density was 100 parasites/volume. This ensured that the parasite density in the experiment was never less than 1. We did not let fP fall below 1, as individuals cannot contact partial propagules. As our main variable of interest was k, we additionally tested whether the posterior estimate for k depended on β and f. While artificially lowering β increased our estimate of k to compensate for the reduced infection rate, and vice-versa, our posterior estimate of k did not depend on f (Appendix S1).

We further tested whether experiments in our meta-analysis best fit a sigmoidal dose–infectivity relationship, where per-propagule infectivity first increases with dose and then decreases. This would match a pattern where a minimal infective dose is necessary to overcome an individual's immune system and establish an infection, but further increases in parasite dose yield diminishing returns and decrease per-propagule infectivity. We thus reran our analysis replacing the k in Eqs. 1A–1C with

$$k = \max(k0 - fP \times k1,\ 0) \quad (2)$$

such that k decreased with dose (fP), though never becomes negative. Using Bayesian inference, we then estimate values of β, $k0$, $k1$, and f for each experiment. This formulation has the benefit that if $k1$ is high enough, our model creates a humped relationship between dose (fP) and the infection rate ($\beta(fP)^{\max(k0-fP\times k1,0)}S$), a pattern observed in some dose–infectivity experiments (Strauss et al. 2019). We considered a sigmoidal dose–infectivity relationship to best fit an experiment if the model DIC was lower than that for our constant k model, and if the 95% confidence interval of k fell above 1 for low dose and fell below 1 for higher experimental dose.

In addition to infection prevalence, studies in our meta-analysis sometimes reported changes in mortality or propagule excretion from infected hosts with propagule dose. However, studies were inconsistent in the metrics they used to measure mortality and parasite load (e.g., mortality could be measured as proportion of dead individuals, time until death, or visible damage to individuals). We noted general trends but did not analyze the dose relationships of these metrics, as the metrics used were too variable.

Meta-analysis Results

Wte found that the majority of published dose–infectivity relationships are decelerating ($k < 1$), where increasing propagule dose lowers per-propagule infectivity (Fig. 2). The 95% confidence intervals of k values fell below 1 for 79 of 98 host–parasite combinations (decelerating), overlapped 1 for 12 of 98 host–parasite combinations (linear), and fell above 1 for 7 of 98 host–parasite combinations (accelerating). We found no support for sigmoidal dose–infectivity relationships. While ΔDIC values gave strong support for our non-constant k compared to our constant k model in 12 out of 98 studies (ΔDIC > 10) and weak support in 3 out of 98 studies (10 > ΔDIC > 5), in 0 studies out of 98 did the 95% confidence interval of k fall above 1 for low propagule densities and fall below 1 for higher experimental propagule densities.

Model Exploration of Dose Relationships: Methods

To understand how dose–response relationships alter the impact of heterospecific host density on infection prevalence, we first built a two-host, one-parasite model with either linear, accelerating, or decelerating dose–infectivity relationships. Our model contains two host species, N_1 and N_2, made up of susceptible classes S_1 and S_2, and infected classes I_1 and I_2. Growth of the susceptible classes is parameterized by their intrinsic growth rates, r_i, intraspecific competition coefficients, α_{ii}, and interspecific competition coefficients, α_{ij}. Individuals move from S_i to I_i as a function of parasite propagules in the environment at density P, contact rate f_i, and per-propagule infectivity, β_i. Propagule dose is calculated as f_iP, and is raised to the dose shape parameter, k_i. We treat k_i as a constant based on the results of our meta-analysis. Infected individuals then die at a rate m_i. All infected individuals excrete parasite propagules into the environment at a rate x_i. Propagules then leave the environment as a function of their degradation rate, μ, and via contact with hosts. The full model (Fig. 3) is thus

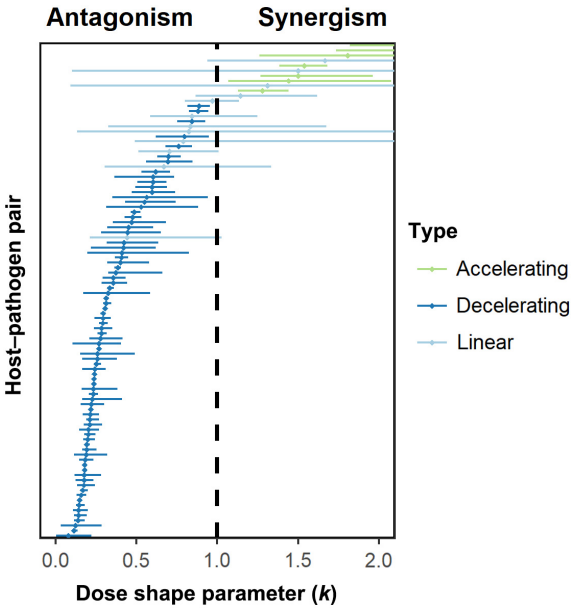

FIG. 2. Most empirical dose–infectivity relationships are decelerating. Values on the x-axis show Bayesian estimates of the dose shape parameter (k) values from published dose–infectivity relationships, with bars showing 95% confidence intervals of the posterior distribution. If an interval overlaps the 1 line, then we do not reject the null hypothesis that infection rate increases linearly with dose, which implies that dose does not alter per-propagule infectivity. If intervals lie below one, then per-propagule infectivity decreases with dose, and dose–infectivity relationships have a decelerating increase. If the interval lies above the 1 line, then per-propagule infectivity increases with dose, and dose–infectivity relationships have an accelerating increase.

$$\frac{dS_1}{dt} = \overbrace{N_1[r_1 - \alpha_{11}N_1 - \alpha_{12}N_2]}^{\text{growth and competition}} - \overbrace{\beta_1(f_1P)^{k_1}S_1}^{\text{infection}} \quad (3)$$

$$\frac{dI_1}{dt} = \overbrace{\beta_1(f_1P)^{k_1}S_1}^{\text{infection}} - \overbrace{m_1I_1}^{\text{mortality}} \quad (4)$$

$$\frac{dS_2}{dt} = \overbrace{N_2[r_2 - \alpha_{22}N_2 - \alpha_{21}N_1]}^{\text{growth and competition}} - \overbrace{\beta_2(f_2P)^{k_2}S_2}^{\text{infection}} \quad (5)$$

$$\frac{dI_2}{dt} = \overbrace{\beta_2(f_2P)^{k_2}S_2}^{\text{infection}} - \overbrace{m_2I_2}^{\text{mortality}} \quad (6)$$

$$\frac{dP}{dt} = \overbrace{x_1I_1 + x_2I_2}^{\text{Propagule release}} - \overbrace{\mu P}^{\text{degradation}} - \overbrace{f_1(N_1)P - f_2(N_2)P}^{\text{Host Contact}} \quad (7)$$

For all the analyses we present in the main text, we assume the focal host species and competing host species

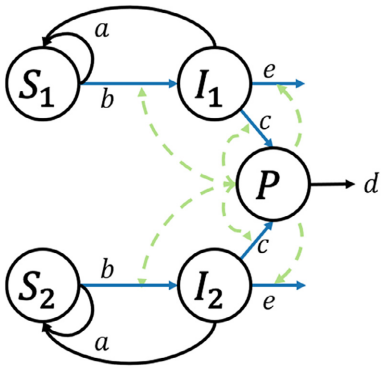

FIG. 3. Schematic of Eqs. 3–9. Black lines represent dose-independent processes and blue lines represent dose-dependent processes. Dashed green lines connect environmental propagule density to dose-dependent processes to visualize feedback loops. S_1 and I_1 represent susceptible and infected individuals of species 1, S_2 and I_2 represent susceptible and infected individuals of species 2, and P represents environmentally transmitted parasite propagules. (a) All hosts give birth as a function of intraspecific and interspecific density and competition (Eqs. 3, 5). (b) Susceptible individuals become infected at a rate determined by parasite dose (Eqs. 4, 6). (c) Infected individuals excrete parasite propagules into the environment as a function of dose (Eqs. 7, 8). (d) Propagules degrade over time (Eq. 7). (e) Finally, infected individuals die as a function of parasite dose (Eqs. 4, 6, 9).

have identical parameter values except for their population growth rates $s(r_i)$ and propagule excretion rates (x_i) (see Appendix S2 for all parameters). However, we repeated the analyses for scenarios where the two host species have unequal competitive abilities ($\alpha_{12} \neq \alpha_{21}$), susceptibility to infection ($\beta_1 \neq \beta_2$), and shape parameters ($k_1 \neq k_2$). Our results are qualitatively the same in all scenarios; see Appendix S3 for details.

Testing the impact of heterospecific host density on infection prevalence

We use our model to test whether increasing the density of a "competitor" host species, N_2, will increase or decrease (1) the infection prevalence in our "focal" host species, (I_1/N_1), (2) the parasite propagule density in the environment, P, and (3) the density of the focal host species, N_1. Biological reasons for considering these three variables are the following. Responses in the propagule density in the environment allow us to measure the effect of competitor density on likelihood of infection in the focal host as well as get a general sense for how competitor density will alter spillover risk for other unmodeled hosts. The likelihood of spillover will likely scale positively, though not linearly, with propagule dose, and is relevant for spillover of infection from multi-host communities into human or agricultural systems. Responses in infection prevalence will allow us to relate our model to disease indexes observed by field ecologists; we say a competitor host species dilutes or amplifies disease in the focal host when infection prevalence in the focal host is lower or higher, respectively, in the presence of the competitor host species. Responses in the focal host density (N_1) allow us to measure the total effect of competitor density on focal host viability. To increase the density of the competitor, we increase its intrinsic growth rate, r_2, from 0 to $2r_1$.

Dose–infectivity relationships

For all analyses, we measure the impact of competing host density on model dynamics under three dose–infectivity relationships: when $k_1 = 0.5$ (decelerating dose–infectivity relationship), when $k_1 = 1.0$ (linear dose–infectivity relationship), and when $k_1 = 1.5$ (accelerating dose–infectivity relationship, Fig. 1A). For our main results, we assume that $k_1 = k_2$, but we explore asymmetric dose–infectivity relationships in Appendix S3.

In our model, k alters both the shape of dose–infectivity relationships, and the magnitude of parasite transmission. As k increases, the infection rate, $\beta_i(f_i P)^{k_i} S_i$, increases in an exponential manner, thus increasing infection likelihood. Thus, to solely examine how the shape of dose–response relationships alters infection likelihood, we vary β as we vary k such that disease prevalence in the focal host in the absence of the competing host is always 0.5 at equilibrium. If we vary k in our model without altering β, then increasing k always increases parasite transmission. The full relationship between k and β is

$$\beta_i = \frac{m_i}{\left(f_i \frac{x^{\frac{2r_i - m_i}{4\alpha_{ii}}}}{\mu + f_i^{\frac{2r_i - m_i}{2\alpha_{ii}}}} \right)^{k_i}} \tag{8}$$

(See Appendix S2 for full derivation.) This ensures that varying the dose shape parameter k does not affect the equilibrium level of disease in the focal host when the second host is absent. Whether a competitor increases disease in a focal host often depends on the ability of the competitor to become infected and excrete parasite propagules (i.e., host competency). Thus, we ran our model while varying competitor excretion rates. We additionally ran a scenario where the focal host cannot maintain parasite transmission, and the infection prevalence in the absence of the competing host is 0 (Appendix S3).

Dose–excretion and dose–mortality relationships

In our meta-analysis, we found four additional effects of propagule dose across multiple host–parasite combinations. As propagule dose increased (1) propagule excretion could decrease, (2) propagule excretion could increase, (3) infected host mortality rate could increase, and (4) propagule excretion and host mortality could

concurrently increase. (In some cases, we interpreted higher parasite load within-hosts as higher propagule excretion.) Thus, we ran our model under these four scenarios concurrently with decelerating, linear, and accelerating dose–infectivity relationships.

To model changes in the excretion rate with increasing dose, we replace propagule excretion rate, x_i, with dose-dependent propagule excretion rate, $x_{i,\text{dose}}$, given by

$$x_{i,\text{dose}} = x_i\left(\frac{1}{2}+\frac{f_iP}{2f_iP_1}\right)^{\gamma} \quad (9)$$

where f_iP_1 is the propagule dose at equilibrium when $N_2 = 0$ using Eqs. 3–7. We use this parameterization because it guarantees that the excretion rate of host i is equal to x_i when at equilibrium in the absence of the competing host. This simplifies our analysis because it means the dose–excretion relationship only affects prevalence in host i when the competing host is present. Models without dose–excretion relationships are equal to models with dose–excretion relationships if $\gamma = 0$. In addition to models without dose–excretion relationships, we explore dose–excretion models where $\gamma = -3$ (exponential decrease in excretion with dose) and $\gamma = 0.5$ (decelerating increase in excretion with dose, Fig. 1B).

To increase infected host mortality with dose, we replaced infected host mortality, m_i, with a dose-dependent mortality, $m_{i,\text{dose}}$, given as

$$m_{i,\text{dose}} = m_{\min} + (m_i - m_{\min})\left(\frac{f_iP}{f_iP_1}\right)^{\rho} \quad (10)$$

where f_iP_1 is once again the propagule dose at equilibrium when $N_2 = 0$ using Eqs. 3–7, and $m_{\min}$ is the minimum mortality of infected individuals. Thus, the mortality rate of host i is equal to m_i when at equilibrium in the absence of the competing host, and so dose–mortality relationships do not alter infection prevalence in the absence of the competing host. In our model, host mortality is independent of dose for $\rho = 0$, increasing at a decelerating rate with dose for $\rho = 0.5$, increasing linearly with dose for $\rho = 1$, and increasing at an accelerating rate with dose for $\rho = 1.5$ (Fig. 1C).

Model Exploration of Dose Relationships: Results

Confirming previous models (Cáceres et al. 2014), infection prevalence in the focal host is influenced by both the density of the competing host and the rate at which it releases parasite propagules when infected (Fig. 4B). Analytical solutions to our model show that increases in competitor density increase focal host infection prevalence and propagule density (i.e., amplify disease) when the competitor is a larger source of parasite propagules, and lower focal host infection prevalence and propagule density (i.e., dilute disease) when the competitor is a smaller source of parasite propagules than the focal host (Appendix S4: Section S1). A host is a large "source" of propagules if it has a high propagule excretion rate, and/or if it removes few propagules from the environment. Our numerical simulations match this result: increases in competitor density decrease disease prevalence in the focal host when competitor propagule excretion is lower than the focal host (competitor excretion < 100, light blue lines in Fig. 4B), and increase disease prevalence in the focal host when competitor propagule excretion is higher than the focal host (competitor excretion > 100, light blue lines in Fig. 4B). Thus, our model confirms pre-existing multi-host theory in the absence of dose relationships.

Dose–infectivity relationships

Accelerating dose–infectivity relationships increase the strength of dilution/amplification, while decelerating dose–infectivity relationships decrease the strength of dilution/amplification. Analytical solutions to our model show that the absolute value of the relationship between competitor density and infection prevalence increases as k increases. This means that, for accelerating dose–infectivity relationships (high k), as competitor density increases, there is a large change in infection prevalence; for decelerating dose–infectivity relationships (low k), there is a smaller change in infection prevalence (Appendix S4: Section S1). These analytical results are matched by our numerical results, which also show that decelerating dose–infectivity relationships lead to a smaller change in infection prevalence due to competitor density than accelerating dose–infectivity relationships (Fig. 4B). We find that, qualitatively, changes in prevalence match changes in environmental propagule density (Fig. 4E).

Accelerating and decelerating dose–infectivity relationships alter the impact of competitor density on infection prevalence and propagule density by creating feedback loops between propagule dose and per-propagule infectivity. Decelerating dose–infectivity relationships create negative feedback loops. If a competing host releases fewer parasite propagules than the focal host, this lowers propagule density in the environment, which lowers propagule dose. Lowering propagule dose increases per-propagule infectivity, thus buffering the impact of competing host density on infection prevalence, and in turn propagule density/dose. On the other hand, accelerating dose–infectivity relationships create positive feedback loops. If a competing host releases fewer parasite propagules than the focal host, this lowers propagule density in the environment, which lowers propagule dose. Lowering propagule dose decreases per-propagule infectivity, thus accelerating the impact of competing host density on infection prevalence, and in turn propagule density/dose. (The converse can also happen if competing hosts increase parasite dose.) Thus, infection prevalence is generally more sensitive to changes in competitor density under accelerating dose–

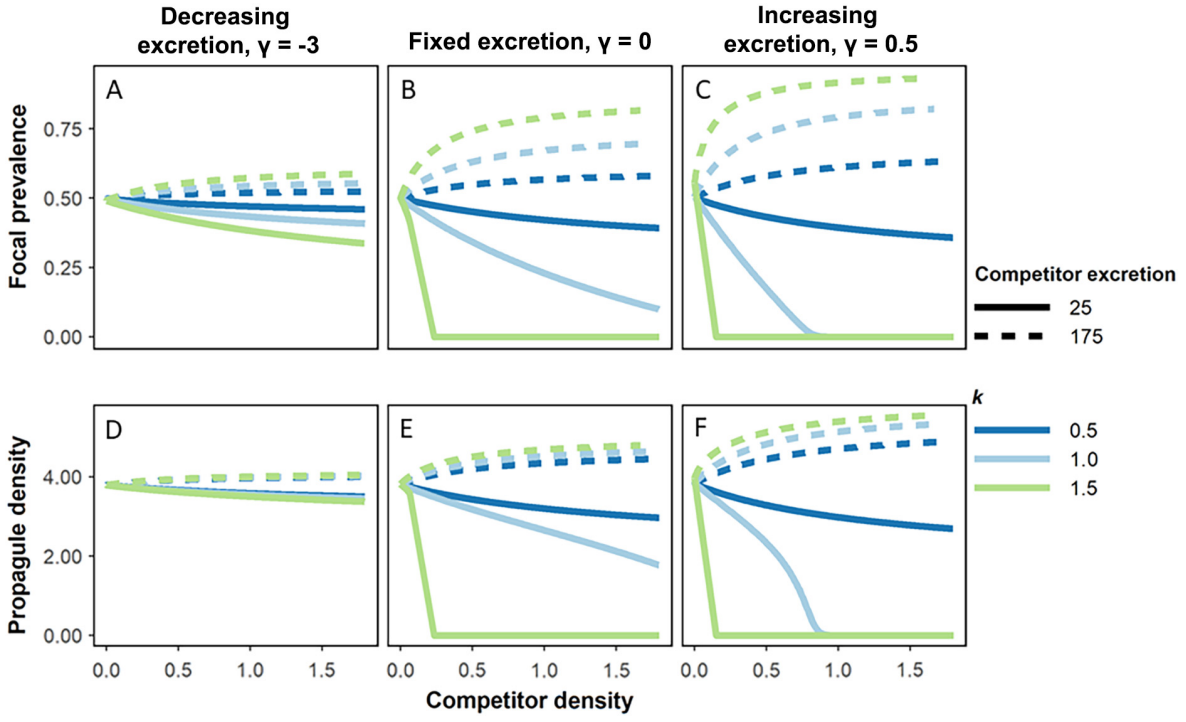

FIG. 4. Negative dose–excretion relationships or decelerating dose–infectivity relationships decrease (and positive dose–excretion relationships or accelerating dose–infectivity relationships increase) the magnitude of the relationship between infection prevalence and competitor density and between propagule density and competitor density. Changes in infection prevalence of the focal host (A–C *y*-axis) and log propagule density (D–F *y*-axis) as competitor density increases (*x*-axis). Panels represent models with (A, D) negative dose–excretion relationships, (B, E) no dose–excretion relationship, or (C, F) positive dose–excretion relationships. Solid lines represent competitors with lower propagule excretion than the focal host species, while dashed lines represent competitors with higher propagule excretion than the focal host species. Dark blue lines show decelerating dose–infectivity relationships, light blue lines show linear dose–infectivity relationships, and green lines show accelerating dose–infectivity relationships.

infectivity relationships than under decelerating dose–infectivity relationships.

Dose–excretion relationships

Our literature survey showed that propagule excretion from infected hosts can increase or decrease with propagule dose (Data S1). Increasing dose may decrease propagule excretion if parasites face within-host competition, where initial crowding may limit the production of parasite propagules. On the other hand, increasing propagule dose may increase propagule excretion if high doses overwhelm the host's immune system.

Under decreasing dose–excretion relationships, increases in competing host density have less of an impact on focal host infection prevalence (Fig. 4A vs. 4B); this occurs because of negative feedback loops. Under these negative feedback loops, increasing propagule dose decreases propagule excretion, which in turn decreases propagule dose. Similarly, decreasing propagule dose increases propagule excretion, which in turn increases propagule dose. This creates smaller changes in prevalence as competing host density increases, compared to a scenario with fixed excretion.

Conversely, under increasing dose–excretion relationships, this creates positive feedback loops: increasing propagule dose increases propagule excretion, which in turn increases propagule dose. Similarly, decreasing propagule dose decreases propagule excretion, which in turn decreases propagule dose. This positive feedback loop increases the impact of competitor density on infection prevalence (Fig. 4C vs. 4B). Because positive feedback loops destabilize systems, adding both a positive dose–excretion relationship and a positive dose–infectivity relationship to our system causes the system to shift from 0% infection prevalence to 100% infection prevalence with small changes to system parameters (Fig. 4C). Our analytical solutions support these results (see Appendix S4: Section S2). We again find that, qualitatively, changes in prevalence match changes to environmental propagule density (Fig. 4).

Dose–mortality relationships

In some host–parasite combinations, increasing propagule dose increases infected host mortality (dose–mortality relationship). This could occur if parasites damage the host upon contact. Alternatively, if hosts die

when parasites reach a certain density within the host, increasing propagule dose could decrease the amount of time it takes for parasites to reach that density, thus decreasing time until host death.

Dose–mortality relationships represent negative feedback loops. As dose increases, the infectious period of infected hosts shrinks due to increased mortality, lowering transmission and thus dose. As dose decreases, the infectious period of infected hosts increases due to reduced mortality, lowering transmission and thus dose. As with negative feedback loops created by decelerating dose–infectivity and negative dose–excretion relationships, the negative feedback loops created by dose–mortality relationships decrease the ability of competitor hosts to influence infection likelihood. We see this reflected in environmental propagule density; low-competence competitor hosts lower environmental propagule density less under dose–mortality relationships, and competent competitor hosts raise propagule density less (Fig. 5D–F vs. 4E).

However, dose–mortality relationships can reverse the impact that competitors have on infection prevalence. This is because increasing propagule dose both increases infection prevalence by increasing the rate at which susceptible individuals become infected ($\beta_i(f_iP)^{k_i}$), and additionally decreases infection prevalence by increasing the mortality rate of infected hosts ($m_i(f_iP/f_iP_1)^{\rho}$). The combined effects of dose-dependent mortality and infection rate depend on the values of the shape parameters k_i and ρ. If infection rate changes with parasite dose faster than mortality ($\rho < k_i$), increasing competitor density will increase infection prevalence when the competitor is a large source of propagules, as expected, and vice versa (Fig. 5A–C). In contrast, if mortality changes with parasite dose faster than infection rate changes with parasite dose ($\rho > k_i$), then we see a reverse in whether competitor density increases or decreases infection prevalence—increasing the density of competitors that are large sources of parasite propagules decreases infection prevalence and increasing the density of competitors that are small sources of propagules increases infection prevalence (Fig. 5A–C). This pattern occurs because, if $\rho > k$, mortality increases with dose faster than infectivity. When $\rho \cong k$, changes in mortality and infectivity approximately cancel each other out as dose changes, so competitor density will have little effect on infection prevalence (Fig. 5A–C, see Appendix S4: Section S3 for full analysis). Combining positive dose–excretion relationships with dose–mortality relationships does not qualitatively change the impact of either dose relationship on prevalence and propagule patterns (Appendix S3).

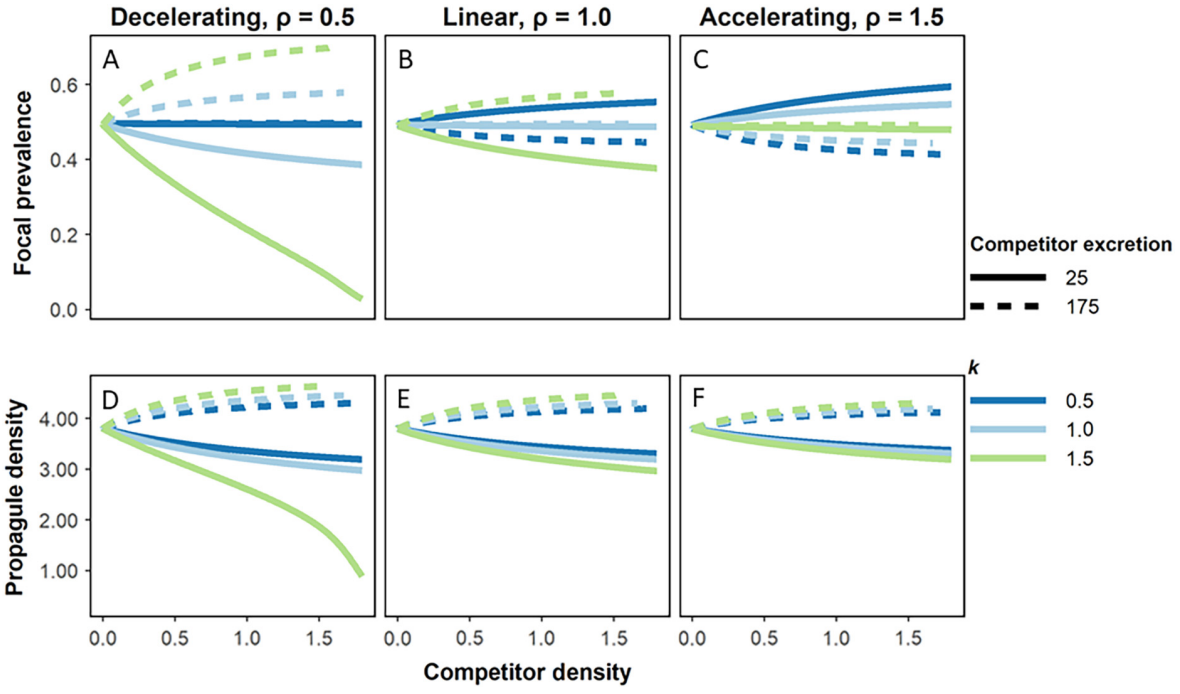

FIG. 5. Decelerating dose–mortality relationships decrease (and accelerating dose–mortality relationships increase) the magnitude of the relationship between infection prevalence and competitor density and between propagule density and competitor density. Changes in infection prevalence of the focal host (A–C *y*-axis) and log propagule density (D–F *y*-axis) as competitor density increases (*x*-axis). Panels represent models with (A, D) decelerating dose–mortality relationships, (B, E) linear dose–mortality relationships, or (C, F) accelerating dose–mortality relationships. Solid lines represent competitors with lower propagule excretion than the focal host species, while dashed lines represent competitors with higher propagule excretion than the focal host species. Dark blue lines show decelerating dose–infectivity relationships, light blue lines show linear dose–infectivity relationships, and green lines show accelerating dose–infectivity relationships.

Friendly competition

Confirming previous theory, in the absence of dose relationships competitors with weak inter-specific competition and low competence increase the density of the focal host (i.e., friendly competition), while competitors with strong inter-specific competition and high competence decrease the density of the focal host (Fig. 6B). Note that in our model, if the effect of interspecific competition on the focal host is greater than zero, increasing competitor density will always eventually drive the focal host to extinction. Thus, "friendly competition" in our model does not represent a monotonic positive effect of competing host density on focal host density, but rather a humped relationship. In these circumstances, increasing competitor density initially increases focal host density by decreasing the infection rate. However, as competitor density increases, the negative effect of direct competition on focal host density eventually outweighs the positive effects of the removal of infectious propagules.

Positive feedback loops facilitate friendly competition. Our model shows that dose relationships that create positive feedback loops (accelerating dose–infectivity relationships, positive dose–excretion relationships) increase the parameter space where competing hosts can increase focal host density (Fig. 6, green vs. light blue in all panels, and B,E,H,K vs. C,F,I,L). Alternatively, dose relationships that create negative feedback loops (decelerating dose–infectivity relationships, all dose–mortality relationships, negative dose–excretion relationships) decrease the parameter space where competing hosts can increase focal host density (Fig. 6, dark blue vs. light blue in all panels, A–C vs. D–L, and B,E,H,K vs. A,D,G,J). This is because friendly competition occurs when competing hosts strongly dilute disease. As we see

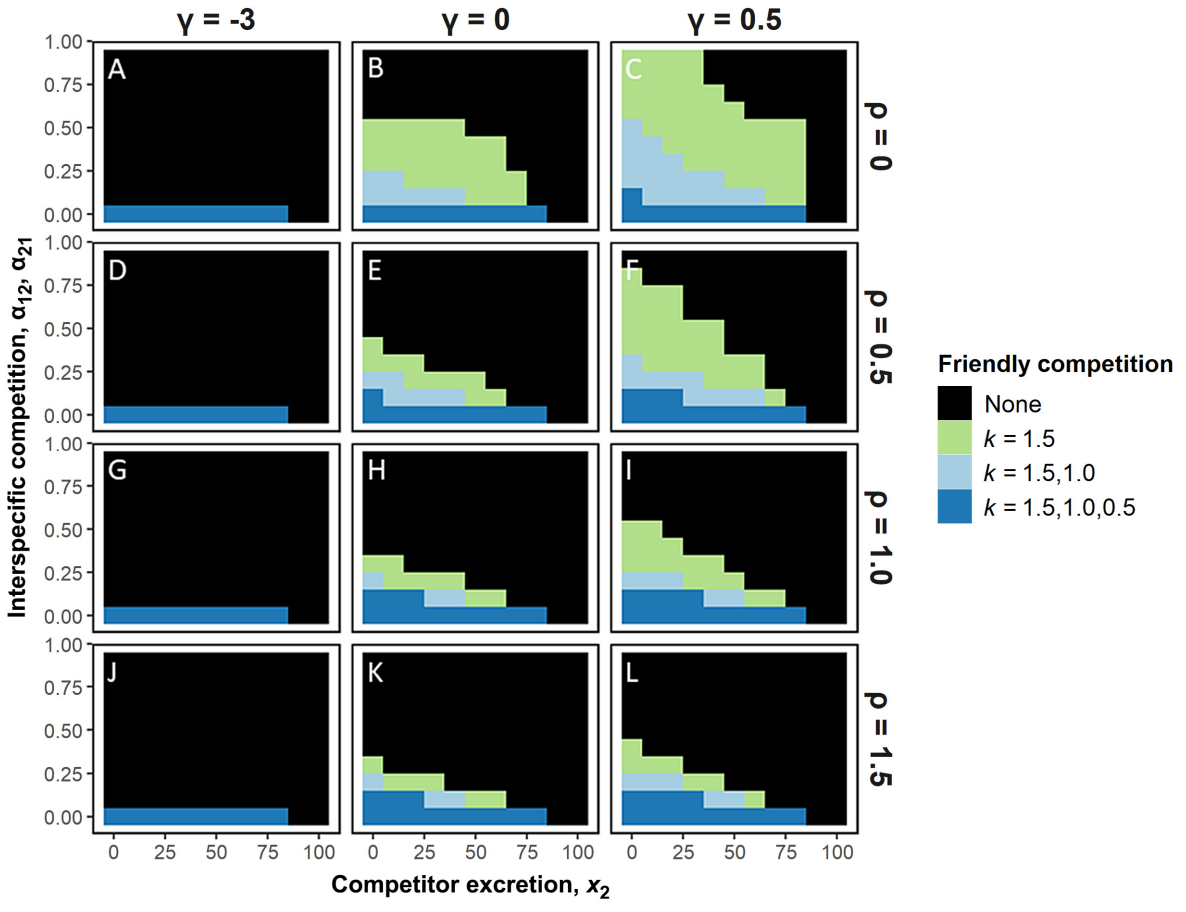

FIG. 6. Positive dose-mediated feedbacks loops facilitate friendly competition. Regions of parameter space show whether focal host density can increase with density of competing hosts (friendly competition), with competitor propagule excretion rate (x_2) on the x-axis and interspecific competition (α_{12} and α_{21}) on the y-axis. Dark blue indicates friendly competition for all dose–infectivity relationships, light blue indicates friendly competition if per-propagule infectivity increases linearly or accelerates with dose, green indicates friendly competition only if per-propagule infectivity accelerates with dose, and black indicates no friendly competition. Panels indicate different dose–mortality relationships ($\rho = 0$ for none, $\rho = 0.5$ for decelerating, $\rho = 1.0$ for linear, $\rho = 1.5$ for accelerating) and different dose–excretion relationships ($\gamma = -3$ for negative, $\gamma = 0$ for none, $\gamma = 0.5$ for positive).

in Fig. 4, dose relationships that create positive feedback loops increase the strength of dilution.

Discussion

Parasite dose underlies every aspect of infectious disease transmission, and can transform interactions between hosts who share parasites. Our study shows that the effect of parasite dose on per-propagule infectivity, host mortality, and propagule excretion can strengthen, weaken, or even reverse the impact of heterospecific host density on disease in a focal host. Our meta-analysis indicates that most dose–infectivity relationships are decelerating (Fig. 2), and thus may decrease the impact of heterospecific host density on infection prevalence and infectious propagule density via negative feedback loops (Fig. 4). Dose–excretion relationships can create positive or negative feedback loops, increasing or decreasing the impact of heterospecific hosts on infection prevalence and propagule density (Fig. 4). Further, dose–mortality relationships can make the impact of heterospecific hosts on infection prevalence negatively correlated with the effects on propagule density (Fig. 5). Finally, our results show that positive feedback loops created by accelerating dose–infectivity relationships and positive dose–infectivity relationships can facilitate friendly competition, even in the face of high interspecific competition. Together, these results suggest that dose relationships could fundamentally alter how interspecific host interactions influence disease dynamics, and that models that ignore dose relationships may mislead us in our efforts to understand and predict how changes in host communities will alter disease patterns.

Dose-response feedback loops

Dose-response relationships create feedback loops that can increase or decrease the extent that competing hosts alter disease prevalence, parasite propagule density, and density of focal hosts (Table 2). The transmission of a parasite within an ecosystem increases with (1) parasite dose, (2) the probability that each parasite in that dose will infect a host, (3) the rate of propagule excretion from hosts once they are infected, and (4) the life span of those infected hosts. If increasing dose increases any of these factors, then propagule dose and parasite transmission enter a positive feedback loop. If increasing dose decreases any of these factors, then propagule dose and parasite transmission enter a negative feedback loop (feedback loops in Fig. 3). Ultimately, through these feedback loops, dose-response relationships can strengthen, weaken, or reverse predictions for whether a host will amplify or dilute disease based purely on their competence.

Dose–infectivity relationships

Most dose–infectivity relationships in our meta-analysis decelerate (Fig. 2). Previously, the vast majority of dose-response experiments showed that infection probability increases in a sigmoidal pattern with log(dose) (Smith et al. 1997, Regoes et al. 2003). However, this pattern can be created by accelerating, linear, or decelerating dose–infectivity relationships (Fig. 1B). In fact, the null assumption for most studies has been that parasite propagules behave independently of one another, creating a linear dose–infectivity relationship (Zwart et al. 2009). Our analysis suggests decelerating

Table 2. Summary of model outcomes, compared to the model with no linear dose–infectivity, static dose–excretion, and static dose–mortality relationships.

Scenario	Infection prevalence	Propagule density	Friendly competition	Mechanism
Decelerating dose–infectivity relationship	Decrease	Decrease	Prevent	Negative feedbacks between dose and per-propagule infectivity
Accelerating dose–infectivity relationship	Increase	Increase	Facilitate	Positive feedbacks between dose and per-propagule infectivity
Negative dose–excretion relationship	Decrease	Decrease	Prevent	Negative feedbacks between dose and propagule excretion rate
Positive dose–excretion relationship	Increase	Increase	Facilitate	Positive feedbacks between dose and propagule excretion rate
Positive dose–mortality relationship ($\rho \leq k$)	Decrease	Decrease	Prevent	Negative feedbacks between dose and infected host life span; infected host mortality changes with dose slower than infection rate
Positive dose–mortality relationship ($\rho > k$)	Reverse	Decrease	Prevent	Negative feedbacks between dose and infected host life span; infected host mortality changes with dose faster than infection rate

Notes: Dose relationships can increase or decrease the magnitude of the impact of heterospecific host density on infection prevalence in the focal host or propagule density or can reverse the trend entirely. Dose relationships can also facilitate or prevent friendly competition. There are no qualitative synergies between dose relationships, when dose has an impact on multiple aspects of transmission, so we only describe outcomes for individual dose relationships.

dose–infectivity relationships are what we expect to see in most systems.

As dose increases, the per-propagule probability of infection decreases under decelerating dose–infectivity relationships. This creates a negative feedback loop between dose and the infection rate that should weaken the ability of competing hosts to increase or decrease disease, and should weaken the ability of hosts to increase one another's density via dilution in the face of interspecific competition (Figs. 4–6). This information can help us interpret experiments. For example, in our meta-analysis we found decelerating dose–infectivity relationships for *Daphnia dentifera* infected by *Metschnikowia bicuspidata* (Dallas and Drake 2014), a model system for the dilution/amplification effect in two-host experiments (Hall et al. 2009, Strauss et al. 2015, Searle et al. 2016). Mechanistic models of this system have thus far assumed mass-action infection processes and would most likely be improved by implementing decelerating dose–infectivity relationships. Further, if dose–infectivity relationships are usually decelerating, then changes to parasite dose due to competing hosts will have the largest impact on infection rate, and thus infection prevalence, at low doses (Fig. 1A). Knowing this will help us identify natural systems where host community composition will likely alter infection prevalence.

While our meta-analysis found that most experimental dose–infectivity relationships are decelerating (Fig. 2), many dose–infectivity relationships exhibit a minimal infective dose (Ward and Akin 1984), a feature not possible under a purely decelerating dose–infectivity relationships. A decelerating dose–infectivity relationship that nevertheless has a minimal infective dose could fit a piecemeal function that is 0 below the minimal infective dose and decelerates above the minimal infective dose, or a sigmoidal function where per-propagule infectivity increases at low doses and decreases at higher doses. Mechanistically, a dose–infectivity relationship that both accelerates or decelerates depending on propagule dose could be possible because infection is determined by interactions between parasites and many host defenses, and defenses such as the immune system may respond nonlinearly to propagule dose (Stewart Merrill et al. 2019, Van Leeuwen et al. 2019). We tested for this latter possibility, but found no evidence for sigmoidal dose–infectivity relationships in our meta-analysis. Nonetheless, our results explain how a sigmoidal dose–infectivity relationship would affect the relationship between focal infection prevalence and competitor density or between parasite density and competitor density: at low doses, changes in dose will create positive feedback loops, while at high doses, changes in dose will create negative feedback loops.

Dose–excretion relationships

While dose–infectivity and dose–mortality relationships mostly cause negative feedback loops, dose–excretion relationships can cause both positive and negative feedback loops, either increasing or decreasing disease amplification and dilution. To cause a negative feedback loop, parasite propagule excretion must decrease with dose. This could potentially occur if increasing dose lowers the within host growth rate of the parasite (Regoes et al. 2002). Or in cases where hosts only excrete parasites at host death, dose may decrease excretion rates if it simultaneously decreases host life span, limiting the amount of time that parasites have to grow (Ebert et al. 2000). To cause a positive feedback loop, parasite propagule excretion must increase with dose. This is most likely for macroparasites that do not reproduce in certain hosts, and thus excretion is limited by parasite dose (Johnson et al. 2012). Ultimately, dose–excretion relationships might be the most important dose-response relationship to measure in future experiments, as we do not have strong prior assumptions about whether these relationships should be positive or negative.

Dose–mortality relationships

Increasing dose generally decreases infected host life span (Data S1). This creates a negative feedback loop between dose and the infection rate, which should weaken the ability of competing hosts to dilute or amplify disease, and should prevent friendly competition (Figs. 5, 6). Further, we found that while infection prevalence is generally positively related with propagule density, dose–mortality relationships can reverse this relationship (Fig. 5). Traditionally, we assume that competing hosts are more likely to decrease infection prevalence if they remove many propagules from the environment, if they have a low transmission rate or susceptibility, and if they are strong competitors (Cáceres et al. 2014, Strauss et al. 2015). Competing hosts with these traits reduce disease because they lower environmental propagule density, lowering dose and infection rate, and ultimately lowering infection prevalence. However, dose–mortality relationships can make infection rate and infection prevalence negatively correlated, and thus challenge our assumptions of which hosts should reduce infection prevalence in a community. If host mortality increases at a faster rate with propagule dose than infection rate does, then infection rate will be negatively correlated with prevalence, thus the low competence, strongly competing hosts that might otherwise be expected to decrease disease will actually increase disease prevalence over some range of densities. This scenario is potentially common, as many systems display positive dose–mortality relationships (i.e., Ashworth et al. 1996, Agnew and Koella 1997, Blair and Webster 2007, De Roode et al. 2007). Further, it is when decelerating dose–infectivity relationships, which our meta-analysis shows to be common (Fig. 2), are combined with dose–mortality relationships that we see expected low-competence hosts increase disease, and vice versa

(Fig. 5). Indeed, highly competent hosts with positive dose–mortality relationships and decelerating dose–infectivity relationships have been shown to dilute disease (Ebert et al. 2000, Dallas and Drake 2014, Searle et al. 2016). Arguably, infection prevalence is only indirectly important, and what matters is that competent hosts increase infection rates, and low-competence hosts decrease infection rates, regardless of infection prevalence. However, infection prevalence is important in that we can readily measure it, and thus use it as a proxy for infectious disease severity in ecosystems. Thus, infectious disease ecologists should factor in dose–mortality relationships when trying to infer infection processes from infection prevalence.

Future directions

Pairing multi-host empirical studies with mechanistic dose models will allow us to uncover the mechanisms driving disease patterns in multi-host communities. Mechanistic models paired with empirical data have generated valuable insights into the processes driving disease in multi-host communities, such as when inter-host interactions are simultaneously amplifying and diluting disease (Luis et al. 2018), or the relative contributions of competition and host competency to disease dilution (Strauss et al. 2015). Pairing mechanistic dose models with empirical data will allow us to answer many open questions about the real-world importance of dose relationships, such as (1) do dose relationships often alter biodiversity–disease relationships in natural populations? (2) Are decelerating dose–infectivity relationships truly common in natural populations? And (3) do dose effects alter infection prevalence most strongly via infectivity, host mortality, or propagule excretion? Overall, an improved understanding of dose response relationships will enable us to better understand the impact of host species interactions on disease risk, and thus make more informed conservation and public health decisions.

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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.3422/suppinfo

Open Research

Code (Clay et al. 2021) for simulations, meta-analysis, and meta-analysis data are available from Dryad: https://doi.org/10.5061/dryad.3tx95x6fz