The impact of coinfection dynamics on host competition and coexistence

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Full equations: Specific model equations (generalized forms presented in main text).

Table S1. Full model state variable and parameter descriptions, values, and ranges

Figure S1: Parasite-free competitive dynamics of the two hosts

Figure S2: Host density outcomes given variation in mortality and recovery among host species to the focal parasite in single infection and when parasites interact only indirectly

Figure S3: Parasite prevalence outcomes given variation in mortality and recovery among host species to the focal parasite when parasites interact only indirectly

Figure S4: The impact of mortality-modulating direct interactions among coinfecting parasites on parasite prevalence

Figure S5: Sensitivity analysis of coinfecting parasite prevalence and overall coinfection prevalence to model parameters and transmission mode of the focal infection

Manuscript_Model_2020_10_08.R: R code for obtaining model results

Sensitivity_Analysis_Manuscript_2020_10_08.R: R code for recreating the sensitivity analyses

P3_sensitivity_2020_10_08.R: R code for the sensitivity of outcomes relative to transmission mode

Abstract

Parasites can mediate competition among host species in an ecological community by differentially affecting key parameters that normally give one species a competitive edge. In nature, however, coinfecting parasites that antagonize or facilitate each other, for example by altering cross-protective host immune responses, can modulate host infection outcomes and parasite transmission relative to a single infection. Under what conditions is coinfection likely to interfere with parasite-mediated apparent competition among hosts? To address this question, we created a model of two coinfected host species. Parasites could interact indirectly by affecting host reproduction, or directly by modulating recovery and disease-induced mortality of each host species to a focal infection. We grounded our model with parameters from a classic apparent competition system but allowed for multiple parasite transmission modes and interaction scenarios. Our results suggest that infection-induced mortality has an outsized effect on competition outcomes relative to recovery, but that coinfection-mediated modulation of mortality can produce a range of coexistence or competitive exclusion outcomes. Moreover, while infection prevalence is sensitive to variation in parasite transmission mode, host competitive outcomes are not. Our generalizable model highlights the influence of immunological variation and parasite ecology on community ecology.

Introduction

Parasitism is a common life strategy, with conservative estimates suggesting that parasites comprise almost one-third of named species (de Meeûs and Renaud 2002). Given the ubiquity of parasites, it is not surprising that coinfection, or the infection of a host with more than one parasite, also occurs frequently (de Meeûs and Renaud 2002; Petney and Andrews 1998). Just as free-living animal species can compete with and facilitate each other at the community level, coinfecting parasites can interact directly or indirectly within their hosts, with cascading effects on within-host population dynamics, parasite community structure, and host phenotypes (Seabloom et al. 2015). As a result, parasite competition and facilitation within hosts may scale up to shape competition between hosts. To the extent that interactions within the host parallel and influence interactions between hosts, coinfection provides a lens with which to study the integration of fundamental ecological processes across multiple levels of organization.

Parasites are capable of regulating host populations through their influence on host reproduction, mortality, and other demographic parameters (Hudson et al. 1998), but coinfections often drastically change the outcome of infection for both parasite and host (Petney & Andrews 1998). Mechanisms by which coinfecting parasites can facilitate or antagonize each other within the host include suppressing the immune system or competing for space or energetic resources (Ezenwa and Jolles 2011), among other interaction modes highlighted in Table 1. Understanding how parasite facilitation and competition modify host recovery and survival relative to a single infection – whether through changes in host tolerance and resistance or parasite growth and virulence (see Table 1) – may be crucial to understand if and how within-host interactions influence host ecology at higher levels of biological organization.

Interactions among coinfecting parasites and their influence on host population dynamics can have complex effects on parasite transmission, leading to sometimes counterintuitive patterns of disease spread in host populations. If coinfection inhibits transmission of a virulent microbe, for example, interventions aimed at reducing one infection can promote epidemics of another, as illustrated by coinfection in African buffalo. Helminth infection suppresses the Th1-mediated response to intracellular microbes within the buffalo, thereby increasing mortality associated with bovine tuberculosis (BTB) in coinfected hosts (Ezenwa and Jolles 2015). By killing helminths, anthelminthic treatments decrease mortality at the individual level. However, for buffalo coinfected with BTB, this decrease in mortality increases the transmission potential of BTB at the population level and promotes the possibility of a deadly epidemic (Ezenwa and Jolles 2015; Gorsich et al. 2018). Despite the ubiquity of coinfection in natural systems, its impact on host population dynamics may not be predictable from studies of single host-parasite systems (Jolles et al. 2008), requiring better integration of multiple infections into estimates of disease dynamics across different levels of biological organization.

Just as parasite infections within a host do not occur in isolation, host species are integrated into a larger multi-host, multi-parasite community. Interactions among host species can be direct, as when they compete for the same resource, but they can also appear to regulate each other by affecting the dynamics of a shared parasite or predator, known as apparent competition (Aliabadi and Juliano 2002; Hatcher et al. 2006; Holt and Bonsall 2017). Parasites, for example, can exert strong effects on competitive outcomes among intra-guild host species within a community, as illustrated by the role of a malaria parasite in promoting coexistence of two *Anolis* lizards (*A. wattsi* and *A. gingivinus*) when *A. gingivinus* otherwise competitively excludes *A. wattsi* (Schall 1992). Conversely, the host immune system can mediate apparent

competition among parasites that do not otherwise directly compete if, for example (e.g. Table 1), an immune response mounted against one parasite provides cross-protection against another (Fenton and Perkins 2010).

Competitive dynamics among flour beetles (*Tribolium* spp.) provide an archetypal example of the importance of host-parasite interaction mechanisms for predicting host species coexistence and exclusion (Park 1948; Leslie et al. 1968). In parasite-free cultures, the red flour beetle *T. castaneum* dominates the confused flour beetle *T. confusum* due to its superior intrinsic rate of growth, resulting in competitive exclusion. However, introduction of the sporozoan parasite *Adelina tribolii* reverses the outcome of competition and allows *T. confusum* to dominate (Park 1948). In contrast, tapeworm infection reinforces the competitive dominance of *T. castaneum* by promoting its voracious appetite for *T. confusum* eggs (Yan and Stevens 1995; Yan et al. 1998). A previous model of parasite-mediated apparent competition among generic host species suggests that an intermediate infection recovery rate maximizes the probability that a host species will dominate or coexist with another; if it is too low, the host is too susceptible, but if it is too high, they cannot transmit the parasite efficiently enough to deter their competitor (Wodarz and Sasaki 2004). Variation among host species in their immunological and behavioral responses to infection is therefore likely to play a key role in modulating the influence of infection and coinfection on apparent competition.

A potentially important issue when considering the impact of multiple infections on host and parasite community dynamics is that the different parasites can exhibit different transmission modes. In mammalian systems, many of the best-characterized infections are horizontally transmitted, such that premature host mortality reduces the window of time available for parasite transmission (Anderson and May 1979). Obligate killer parasitism, on the other hand, is a

common strategy among the parasites of invertebrate hosts, including the protozoan parasite from Park's experiments, and requires host death to release spores and achieve transmission (Park 1948; Berenos et al. 2009; Redman et al. 2016). Obligate killer viruses, bacteria, and microsporidia feature prominently as regulators of natural insect population cycles (Anderson and May 1980) and in pest biocontrol strategies (Lacey et al. 2015). In a similar vein, plants can play host to both biotrophic and necrotrophic pathogens that respectively suffer or benefit, with regard to transmission, from the death of host tissue (Suzuki and Sasaki 2019). Depending on whether coinfecting parasites have similar or divergent transmission strategies (Jones et al. 2010; Kamiya et al. 2018), the same within-host competition and facilitation mechanisms could lead to divergent epidemiological and host community dynamics. For example, if coinfecting parasites hasten host death through immunosuppression, obligate killers would reap a benefit at the expense of parasites that require a live host. If competition for resources among the host and its myriad parasites exacerbates host mortality, on the other hand, transmission stage spore production for an obligate killer could suffer and the second parasite may fail to transmit at all.

To understand how coinfection could modify parasite-mediated apparent competition among host species, we created a model consisting of two host species that share a focal parasite capable of mediating their competitive dynamics. Each host species is also uniquely susceptible to a second environmentally transmitted parasite that induces minimal host morbidity but some reduction in fecundity, similar to a gut worm or the eugregarine protozoa that are ubiquitous among *Tribolium* spp. and other insect taxa (Clopton 2009; Locklin and Vodopich 2010; Logan et al. 2012) and that can influence the fitness of secondary parasites (Randall et al. 2013). We parameterized our model using the *T. castaneum* and *T. confusum* flour beetles used in Park's original experiments, for which we have evidence of naturally occurring coinfections (Tate and

Graham 2015) and an abundance of demographic data, including reproductive parameters, natural death rates, and carrying capacity for each species (Park 1948; Park 1954; Sokoloff 1974).

To examine the impact of coinfection on competitive outcomes among the two host species, we: 1) manipulated the disease-induced mortality and recovery rates of each host species to the single focal infection to identify conditions that favored particular competitive outcomes, including coexistence or competitive exclusion of each host species, 2) introduced the coinfecting parasites into the host community to explore if *indirect* interactions among parasites through host demography (but not infection parameters) impact the competitive dynamics modulated by the focal infection, and 3) introduced the coinfecting parasites into the host communities to explore if *direct* interactions among parasites that promote shifts in mortality and recovery rates could impact the competitive dynamics modulated by a focal infection, given variation in its transmission mode.

While previous theoretical and empirical studies have confirmed that coinfection can alter disease dynamics within host populations (Fenton 2008; Seabloom et al. 2015; Gao et al. 2016; Clay et al. 2018), our work predicts that coinfection is likely to affect host competition outcomes and underscores the importance of host defense mechanisms in parasite-mediated apparent competition. While we ground this framework with the example of flour beetles, it could easily be extended to shed new light on host biodiversity, biological invasions, disease spillover, and biocontrol efforts.

Methods

We developed a model to simulate the dynamics of two competing host species (Fig. 1). The model consists of eleven coupled ordinary differential equations (ODEs) describing the changes in each susceptible, infected, and coinfected host compartment (generalized in Eq. 1-4 respectively) and transmission stage reservoirs of each parasite (E_k), as generalized in Eq. 5. For the full set of expanded equations, see the Online Supplemental Material.

Each infection follows an SIS (Susceptible-Infected-Susceptible) trajectory, where hosts who recover from infection return to the susceptible class (Fig. 1). This framework is likely to be broadly representative of invertebrate communities (Anderson and May 1980). For each host species (indexed by i = 1 or 2) there are individuals susceptible to both parasites (S_i, Eq. 1), individuals infected ($I_{i,k}$) with a single host-specific ($k = i = 1, 2$) or shared ($k = 3$) parasite (Eq. 2 and 3), or coinfected with both parasites ($I_{i,*}$, Eq. 4). Each of these infection stages is represented by a box in Fig. 1. The parasite spreads when a host susceptible to parasite k encounters previously shed environmental infectious stages (E_k; Eq. 5). We will refer hereafter to the shared parasite as the **focal parasite** or infection, and the species-specific parasite as the **coinfecting parasite**. While we initially allow the focal parasite to adopt an obligate killer transmission strategy, we subsequently relax these assumptions in our sensitivity analyses (see below).

$$\frac{dS_i}{dt} = \boldsymbol{R}\big(S_i, I_{i,k}, I_{i,*}\big) - S_i \sum_{k\,\epsilon\,\{i,3\}} (\beta_k E_k) + \sum_{k\,\epsilon\,\{i,3\}} \big(\gamma_{i,k} I_{i,k}\big) - \delta_i S_i \qquad \text{(Eq. 1)}$$

$$\frac{dI_{i,(k=i)}}{dt} = S_i \beta_k E_k - \big(\alpha_{i,k} + \gamma_{i,k} + \delta_i\big) I_{i,k} - \beta_{(k=3)*} E_{(k=3)} I_{i,k} + \gamma_{i,(k=3)*} I_{i,*} \qquad \text{(Eq. 2)}$$

$$\frac{dI_{i,(k=3)}}{dt} = S_i \beta_k E_k - \big(\alpha_{i,k} + \gamma_{i,k} + \delta_i\big) I_{i,k} - \beta_{(k=i)*} E_{(k=i)} I_{i,k} + \gamma_{i,(k=i)*} I_{i,*} \qquad \text{(Eq. 3)}$$

$$\frac{dI_{i,*}}{dt} = \beta_{(k=i)}E_{(k=i)}I_{i,(k=3)} + \beta_{(k=3)}E_{(k=3)}I_{i,(k=i)}$$

$$-\left(\sum_{k\,\in\,\{i,3\}}(\alpha_{i,k*}) + \sum_{k\,\in\,\{i,3\}}(\gamma_{i,k*}) + \delta_i\right)I_{i,*}$$ (Eq. 4)

$$\frac{dE_k}{dt} = \sum_{i\,\in\,\left\{\begin{smallmatrix}\{k\},k<3\\\{1,2\},k=3\end{smallmatrix}\right.} \boldsymbol{T}(\lambda_k, p_k, I_{i,k}, I_{i,*}) - \left((\mu_k + \nu_k)\left(\sum_{i=1}^{2}(N_i)\right)\right)E_k$$ (Eq. 5)

$$\boldsymbol{R}(S_i, I_{i,k}, I_{i,*}) = b_i e^{\left(-(c_i N_i + c_{ij}N_j)\right)}\left(S_i + \sum_{k\,\in\,\{i,3\}}\left(I_{i,k}(1 - \phi_{i,k})\right) + I_{i,*}(1 - \phi_{i,*})\right)$$ (Eq. 6)

$$\boldsymbol{T}(\lambda_k, p_k, I_{i,k}, I_{i,*}) = \lambda_k p_k(I_{i,k} + I_{i,*}) + \lambda_k(1 - p_k)(\alpha_{i,k}I_{i,k} + \alpha_{i,k*}I_{i,*})$$ (Eq. 7)

The change in the number of hosts susceptible to both parasites is determined by the influx of new individuals from reproduction (represented by the function $\boldsymbol{R}$ in Eq. 6), the loss of susceptible individuals to infection with either parasite species $\left(S_i \sum_{k\,\in\,\{i,3\}}(\beta_k E_k)\right)$, the gain of individuals newly recovered from single parasite infections $\left(\sum_{k\,\in\,\{i,3\}}(\gamma_{i,k}I_{i,k})\right)$, and the loss of hosts from the natural background death rate $(\delta_i S_i)$. $\boldsymbol{R}$ depends on the number of hosts (N_i) of all infection statuses for species i. The parameter b_i represents the birth rate of host species i. Intra- and inter-specific competition among host species are represented coefficients c_i and c_{ij}, respectively, which impose density-dependent reductions in birth rate through a mechanism such as egg cannibalism (Edmunds et al. 2003; Tate and Rudolf 2012). $\phi_{i,k}$ represents the proportional reduction in reproductive rate of host species i from parasite k (i.e. if $\phi = 1$, parasite infection reduces host reproduction to zero).

The parameter β_k represents the transmission rate for parasite species k, $\alpha_{i,k}$ indicates infection-induced mortality of host species i by parasite k, and $\gamma_{i,k}$ the recovery of host species i

from parasite k. δ_i represents the natural death rate of host species i. All parameters with a subscripted asterisk (*) indicate the parameter under coinfection. For example, $\alpha_{i,k*}$ indicates the parasite-induced death rate in a coinfected individual of host species i from parasite k.

The parameters λ_k and μ_k represent, respectively, the shedding and natural death rate of infectious stages in the environment of parasite k. Whether parasite infectious stages are released while the infected host is alive or after it dies from the infection is determined by p_k, which is the proportion of infectious stages shed while alive. For the focal parasite, $p_k = 0$, indicating that it must kill its host to be transmitted. For the coinfecting parasites, which require host survival for transmission, $p_k = 1$ (Tate 2017). The number of external infectious stages of each parasite k increases with $\mathbf{T}$ (Eq. 7), a function describing shedding by each single- and co-infected host compartment, and decreases as stages die or are ingested by the population (v_k, Eq. 5).

<u>Model assumptions and evaluation</u>

Natural host communities collectively contain a mixture of generalist and specialist parasites (Vázquez et al. 2005; Ellis et al. 2020), such that some parasites will be unique to each host species (including the gregarines of *Tribolium* beetles (Detwiler and Janovy 2008)), while some can be shared among them. To reflect this, our model assumes that one parasite (the focal infection) is a shared generalist, while the coinfecting parasites are specialists but otherwise share similar life history characteristics. Further, as a majority of ecologically and agriculturally important invertebrate parasites and pathogens contain an environmental stage in their transmission cycle (including most entomopathogenic bacteria and baculoviruses, gregarines, and other protozoa (Anderson and May 1981)), we include an environmental stage for all of the parasites in this model. We assume that the absorption (ingestion) rate of external parasite stages

is equivalent to the transmission rate ($v_k = \beta_k$) (Anderson and May 1980), even though not all ingested parasites may ultimately contribute to infection in nature (Civitello et al. 2013).

Additionally, hosts first pass through single infections before becoming coinfected – i.e. parasites are acquired sequentially, reflecting the low probability in nature that hosts become simultaneously infected. Parasite infections are also lost sequentially, as recovery from one parasite occurs before recovery from the other. However, there are no priority effects; the order in which hosts acquire infection does not change parasite infection parameters, a simplifying assumption (Clay et al. 2018; Clay et al. 2019) that may or may not hold for various systems that we will discuss later on. Infection parameters are independent of parasite load, and there is no vertical transmission of any infection. Infection with the coinfecting parasite is species-specific and therefore stages are only shed by one host species and not transmittable to the other host. Coinfecting parasites are assumed to affect hosts equivalently and therefore parasite-specific parameter values (β, λ, & v) are the same for the two (e.g. $\beta_1 = \beta_2$). The focal infection is assumed to act by increasing host mortality ($\alpha_{i,3}$) but does not affect host fecundity ($\phi_{i,3} = 0$). As we are mainly interested in how coinfection changes infection parameters for the focal parasite, we assume that coinfection parameters for the second parasite remain constant (e.g. $\alpha_{i,k*} = \alpha_{i,k}$).

We approximated competition outcomes among host species by first confirming via simulations over time that the system reached a stable equilibrium within the relevant parameter space, and then by calculating the proportion of host species 1 in the community ($N_1 /(N_1 + N_2) =$ the community proportion of *T. confusum*), where at least one host species had an $N > 0$. We first examined the system under disease-free conditions to reflect the baseline competitive relationship between the two species. We then added single or coinfecting parasites into the

population, and allowed the parasites to influence host demographic or infection-related parameters, as described below.

Estimating competitive outcomes when coinfecting parasites interact indirectly through host demography or directly through within-host facilitation or antagonism

A coinfecting parasite could indirectly influence host competitive dynamics instigated by a focal parasite through host demographic variables like birth rate or cannibalism, altering the influx of new susceptibles to the system, for example, rather than directly influencing recovery or disease-induced mortality. To explore the contribution of these indirect effects on parasite-mediated apparent competition among host species, we treated infection parameters similarly to the single infection scenario but allowed coinfection to influence birth rate and interspecific cannibalism coefficients.

On the other hand, a coinfecting parasite could modify host mortality and recovery rates associated with the original parasite, possibly through immune-mediated interactions or competition for resources. To understand how these direct interactions could change the outcome of competition among host species, we first allowed host recovery from the focal infection to improve or worsen in the presence of the coinfecting parasite. We varied the recovery of host species i in coinfected individuals while the recovery of individuals infected solely with the focal parasite was kept constant (default value, Table 2). In a similar fashion, we manipulated the survival of coinfected individuals relative to individuals infected with only the focal infection for both host species. As our interest was in the focal infection that most substantively impacts the population dynamics of each species, we did not examine the effect of the focal infection on mortality and recovery rates associated with the coinfecting parasites (i.e. coinfection parameters equal single infection parameters for the coinfecting parasite).

Model Parameterization

Parameters for the model (Table 2, Table S1) were inspired by *Tribolium* beetles and the diversity of their parasites. The focal infection reflects spore-forming obligate killers like the parasite from Park's original experiment (*A.tribolii*) and *Bacillus thuringiensis* (Bt), a bacterium commonly used as a biocontrol agent (Gassmann et al. 2009; Raymond et al. 2010). *T. confusum* is more likely than *T. castaneum* to survive infection with either of these parasites (Jent et al. 2019). The coinfecting parasite is inspired by eugregarines, gut-dwelling and relatively benign protozoa that coinfect *Tribolium* spp. and potentially modify their susceptibility to bacterial coinfection (Tate and Graham 2015; Critchlow et al. 2019). We acquired host demographic parameters, including birth, death, and cannibalism, from extensive empirical estimates available for host species (Sokoloff 1974; Hastings and Costantino 1987; Dennis et al. 2001). Infection parameters were chosen to provide plausible but still generalizable temporal dynamics reflecting a relatively virulent focal infection like Bt (high mortality, low to intermediate equilibrium prevalence) and a relatively asymptomatic but highly transmissible second parasite (low mortality, high prevalence) like gregarines. Subsequent sensitivity analyses (see below) allowed us to evaluate the sensitivity of the results to deviations from these values. Because $0 < \alpha_i < 1$, we represent host survival as $(1 - \alpha_i)$ in the results. It is worth noting that previous models of *Tribolium* population dynamics have highlighted the importance of life stage-specific cannibalism and mortality parameters for population stability (Costantino et al. 1997) and disease transmission (Tate and Rudolf 2012). However, given the complexity of the multi-host multi-parasite framework here, we make the simplifying assumption of homogenous populations. In all simulations, parameter values were constrained within biologically plausible ranges when exact estimates were not available.

As the above analyses are restricted to varying two parameters at a time while holding others steady, we may miss important aspects of the system. To capture how the model reacts as all parameters are changed, we conducted a sensitivity analysis with respect to the competitive outcomes of the hosts. We used Latin hypercube sampling to create random parameter value sets and then estimated which parameters had the greatest impact on the system by computing the correlation of parameter changes with changes to model outcome (Legrand et al. 2007; Carnell 2019).

All simulations were run using R version 3.5.2 (R Core Team, 2018). To solve the ODEs, we used the 'deSolve' R package (Soetaert et al. 2010), for constructing the contour plots 'plotly' (Sievert 2020), and for running the sensitivity analysis the packages 'lhs' and 'sensitivity' (Iooss et al. 2018; Carnell 2019). All code used to perform the simulations is available in the Supplementary Material.

Results

Parasite-free dynamics

We first performed simulations under parasite-free conditions to understand the competitive relationship between the two host species at the disease-free equilibrium (the DFE, Fig. S1). In agreement with previous models of apparent competition in *Tribolium* (Sokoloff 1974; Costantino et al. 1997; Yan et al. 1998) and other systems (Searle et al. 2016; Auld et al. 2017), we found that the competitive outcome is dependent (Fig. S1) on both the interspecific density-dependent coefficients (c_{21} relative to c_{12}) and fecundity (b_2 relative to b_1). A species' proportional representation in the community increases as it gains a reproductive advantage or its

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interspecific density-dependent impact increases regardless of base values for competition and fecundity. As estimated from empirically-derived demographic parameter values (Table 2), the second host species, *T. castaneum*, holds the competitive advantage due to its higher reproductive rate and relatively equal interspecific competitive ability relative to host species 1, *T. confusum* (Fig. S1, white dot). From here on, *T. castaneum* (species 2) will be referred to as the DFE superior competitor, because in the absence of parasites it dominates the community.

Mortality and recovery rates affect host competition mediated by a focal infection

Next, we introduced the focal infection, an obligate killer parasite. To recapture previous findings that show that parasite-mediated competition can flip competitive outcomes as well as to understand whether these outcomes are robust to changes in the recovery and mortality of each species, we changed the equivalent parameter values, γ and α, of the inferior competitor relative to the superior competitor. We found that changing recovery rates had a minimal impact on competitive outcomes (Fig. 2A, Fig. S2) and only a modest effect on infection prevalence (Fig. 2B). At high survival ($1-\alpha$), however, the inferior competitor can now dominate to the exclusion of the formerly superior one (Fig. 2A). Interestingly, at their highest survival levels, the inferior competitor's proportion in the community decreases again (Fig. 2A), potentially because the parasite prevalence is low enough to reduce pressure on the superior competitor (Fig. 2B), as indicated by the modest increase in its density (Fig. S2B). This decrease in parasite prevalence likely stems from the parasites' dependence on host death for transmission -- insufficient mortality of the DFE inferior competitor prevents parasite propagation, re-releasing the DFE superior competitor from parasite pressure.

Indirect consequences of a coinfecting parasite

A coinfecting parasite could impose its own mortality or fecundity costs to a host, as it would in single infection, even if the parasite does not directly interfere with mechanisms that alter survival and recovery rates associated with the focal parasite. Our model predicts that introducing coinfecting parasites that slightly decrease the fecundity ($\phi = 0.1$) and slightly increase the mortality of their respective host species ($\alpha = .008$) does not qualitatively change host competitive outcomes (Fig. 2C) and focal infection prevalence (Fig. S3A) relative to the single infection scenario (Fig. 2A-B), although it slightly depresses host population densities (Fig. S2C-D). The cumulative prevalence of the two coinfecting parasites is highest when species 1 (the DFE inferior competitor) dominates (Fig. S3B). The prevalence of coinfected hosts is highest where species 2 (the DFE superior competitor) dominates and a small region where species 1 dominates and has low relative resistance (Fig. 2D). This indicates that recovery from the focal infection does not affect the coinfecting parasites' prevalence since the parasites do not directly interact, but slightly affects coinfected host prevalence. Finally, a coinfecting parasite that alters interspecific density-dependent coefficients, such as through increased cannibalism of the competitor, produces nearly identical results as when the coinfecting parasite reduces host fecundity (e.g. Fig. 2C and D).

Direct consequences of coinfecting parasites that alter rates of mortality and recovery associated with the focal infection

It is possible that the parasites interact within the host, for example by competing for resources or altering the immune system, and that the coinfecting parasites could therefore increase or decrease host resistance to the focal infection relative to the single infection scenario.

We examined this by changing the recovery rate of coinfected hosts relative to single-infected hosts for each species ($\gamma_{i,3*}/\gamma_{i,3}$) at two regions in Fig. 2A (as indicated by white dots)—

where single-infection mortality rates are equal ($\alpha_{1,3} = \alpha_{2,3} = .2$), and where the inferior

competitor's relative mortality is low enough to flip competition ($\alpha_{1,3} = .08$, $\alpha_{2,3} = .2$). Once

again, changing relative host recovery in these scenarios had a negligible impact on competitive

outcomes or any infection prevalence. When coinfection changes host survival of the focal

infection, however, our results predict that it expands the parameter space over which the DFE

inferior competitor can exclude or coexist with the DFE superior competitor (Fig. 3), even if the

inferior competitor's survival of the focal infection was not high enough to prevent its exclusion

in the single infection scenario (Fig. 3A). When baseline host mortality rates were asymmetrical

to begin with (Fig. 3B), a coinfecting parasite promotes host species coexistence if it decreases

the survival of both to the focal parasite. As observed in the single infection scenario, the region

where the inferior competitor most strongly dominates is not at the highest survival levels.

Our results predict that the focal infection will reach its highest prevalence where neither

species fully dominates (Fig. S4A-B). Meanwhile, the prevalence of the coinfecting parasites is

higher when coinfection induces greater survival in either host species, while the proportion of

the community that is coinfected is lowest at these values (Fig. S4C-F).

Sensitivity Analysis

We conducted a sensitivity analysis to understand which parameters had the greatest

impact on the system when all other parameters were also allowed to vary. These results agreed

with the more focused simulations, such that all parameters that represent tolerance to the focal

infection as well as some reproduction, transmission, and competition parameters greatly affect

the system while only one resistance parameter does, with respect to competitive outcome (Fig.

4A). Focal infection prevalence (Fig. 4B), coinfecting parasite prevalence (Fig. S5A,C), and

coinfection prevalence (Fig. S5B,D) are also sensitive to a similar set of parameters, with

mortality consistently affecting the system and recovery parameters contributing more modestly. We also found that when we relaxed the assumption that $p_3 = 0$ (i.e. that the focal parasite is an obligate killer), the relative impact of survival and recovery on competition outcomes remains consistent (Fig. 4C) even though focal infection prevalence decreases with increasing mortality rates as p_3 increases (Fig. 4D). In other words, increased mortality has a positive effect on focal parasite prevalence when the parasite is an obligate killer, but as a larger proportion of infection stages come from living rather than dead hosts, increasing mortality now hinders transmission and decreases parasite prevalence. This indicates that our model results are robust and may be broadly applicable to a variety of parasite transmission modes.

Discussion

A single shared parasite or predator can alter the dynamics of competition among host species in a community (Park 1948; Chantrey et al. 2014), and analogously the host immune system can modulate apparent competition among different parasite taxa within a single host (Holt and Bonsall 2017). In this study, we united these two concepts to understand how within-host interactions among parasites are likely to alter host competition after accounting for the role of epidemiological feedbacks. Our results predict that mortality plays an outsized role in allowing a previously inferior competitor to competitively exclude a previously dominant host species in the presence of a shared obligate killer parasite. Furthermore, our model predicts that coinfection can reinforce parasite-mediated competition by a single parasite, reverse it, or even promote host coexistence if it alters the mortality rate of either host to the focal parasite.

Our findings provide insight into previous studies of parasite-mediated competition results and generate new hypotheses for the role of immunological variation in community

ecology. For example, in Park's 1948 experiments, *T. confusum* dominated *T. castaneum* when the obligate killer parasite *Adelina tribolii* was present but was outcompeted in its absence (Park 1948). Our model predicts that this is due to a lower disease-induced mortality rate in *T. confusum* relative to *T. castaneum,* with recovery providing little additional benefit. In our model and the *Tribolium* system, increased survival may aid in competition because, unlike recovery, it does not remove hosts from the infected class. Rather, it allows the host additional time to reproduce while still ultimately contributing to disease transmission, as long as mortality is not so low that it depresses disease prevalence (Fig. 2) and releases the DFE superior competitor from the pressure of the focal infection. These epidemiological feedbacks might help explain a more puzzling example of apparent competition among *Tribolium* species, where exposure to the rat tapeworm parasite *Hymenolepis diminuta* reinforced the competitive dominance of *T. castaneum* even though *T. confusum* suffered lower susceptibility and disease-induced mortality (Yan et al. 1998). In this example, there was no inter-species transmission because the final host (the rat) was not present to sustain the transmission cycle. Moreover, tapeworm infection increases the cannibalistic tendencies of *T. castaneum* more than its competitor, and *T. castaneum* can preferentially cannibalize heterospecific eggs (Yan and Stevens 1995; Yan et al. 1998). In this case, parasite-mediated indirect effects on host demography may override immunological differences or epidemiological feedbacks to promote competitive outcomes.

In our model, recovery may not confer a competitive advantage, or at least not one stronger than survival, because of the shared nature of the focal parasite and because infected individuals were still allowed to reproduce (in contrast to (Wodarz and Sasaki 2004)). The external stage of the parasite ensures that even if hosts recover from infection, they will continue to become infected due to parasite shedding by the other host species (Auld et al. 2017). If

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recovered individuals gained partial or complete immunity, then recovery could convey a greater competitive advantage assuming (probably incorrectly (Khan et al. 2019)) that it did not come at the cost of fecundity or susceptibility to interspecific competition. In insects, a recovered and resistant status would likely be mediated by immune priming, where primary exposure facilitates a more protective innate immune response upon subsequent infection (reviewed in (Milutinović et al. 2016)). Priming has been demonstrated in *Tribolium* beetles (Roth et al. 2009; Tate and Graham 2015), but unlike the robust resistance provided by vertebrate adaptive immunity, priming only provides partial protection from disease-induced mortality (Tate et al. 2017). Evidence from this and other priming systems suggests that multiple infections could inhibit priming or even facilitate subsequent infection (Tate and Graham 2015; Ferro et al. 2019; Ben-Ami et al. 2020), further underscoring the need to understand the immune-mediated interactions of coinfecting parasites in a given system.

Our results suggest that when studying or attempting to predict parasite-mediated competition, it is important to ascertain the presence of coinfections and quantify their direct and indirect effects on host phenotypes and the transmission of each parasite. Otherwise, coinfection could mask or artificially exacerbate parasite-mediated competition. For example, if coinfecting parasites exist in only a subset of the hosts' ranges but the focal infection is prevalent throughout, then it would appear in some regions that the focal infection mediated competition but in other areas did not. This could be relevant to systems like *Anolis* lizards infected with the malarial parasite *Plasmodium azurophilum* in the Caribbean (Hatcher et al. 2006). The parasite maintains host biodiversity by infecting the superior competitor, *A. gingivinus*, and allowing *A. wattsi* to coexist in a subset of each species' range where the parasite is present. If another

parasite were to invade these communities, would it promote or obliterate the fragile coexistence dynamics of these two host species?

When the invasive grey squirrel, *Sciurus carolinensis*, was introduced to Great Britain, it spread a lethal parapox virus to native red squirrels (*S. vulgaris*). The virus causes chronic infection but low mortality in the more tolerant gray squirrels (Chantrey et al. 2019), allowing them to successfully invade infected red squirrel territory (Tompkins et al. 2002; Hatcher et al. 2006). Interestingly, in gray squirrels, coinfection with an adenovirus facilitates higher parapox viral loads during the acute phase of infection but delayed viral shedding from the forearms during the chronic phase (Chantrey et al. 2014; Chantrey et al. 2019), suggesting that immune-mediated apparent facilitation among parasites within coinfected gray squirrels could actually reduce or alter the timing of transmission to red squirrels. This system presents an opportunity to quantify how within-host interactions between parasites may modify host recovery, survival, and pathogen transmission dynamics, potentially changing the competitive outcome between the two squirrel species.

Recent studies integrating models and experiments in a *Daphnia* coinfection system have emphasized that priority effects, or the order in which parasites infect their hosts, can result in positive correlations between parasites at the population level even when they antagonize each other within the host (Clay et al. 2018; Clay et al. 2019). While our current study does not account for priority effects, uncovering interactions between the within-host drivers of priority effects and host community dynamics represents an important future direction.

These considerations might be particularly important for implementing biocontrol strategies and mitigating disease spillover or transmission in multi-host systems. For example, more tolerant or competent hosts, like the white-footed mouse in the case of Lyme disease

(Wood and Lafferty 2013), serve as infection reservoirs in multi-host communities. However, wild mice host many different parasite taxa (Fenton et al. 2014; Clerc et al. 2018) and coinfection could modify their competence for a focal infection in unforeseen ways (Streicker et al. 2013; Wood and Lafferty 2013). In a similar fashion, coinfection could complicate biocontrol efforts. Both *T. castaneum* and *T. confusum* are important agricultural pests worldwide and are commonly infected with protozoan parasites (Detwiler and Janovy 2008). Bt is often introduced to populations of agricultural pests and disease vectors in an attempt to control them (Hagstrum et al. 1999). If competitors differentially respond to biocontrol agents based on their coinfection status or priority effects, then competitive outcomes could be unpredictable and even favoring a more destructive community member, undermining the efficacy of the pest control strategy.

While this model advances an ecological understanding of competitive outcomes, it also hints at possible evolutionary pressures on both hosts and parasites. Faster coinfected host recovery is likely to be intimately tied to direct or apparent (immune-mediated) competition among parasites, as it is hard to imagine a scenario where parasite facilitation promotes host recovery (Table 1). On the other hand, both parasite competition and facilitation can modify host mortality in either direction through their impact on resistance, tolerance, and parasite virulence traits (Table 1). A reduction in mortality rate mediated by host tolerance is predicted to drive up parasite prevalence (unless the parasite is an obligate killer) and thereby select for both higher host tolerance (Roy and Kirchner 2000; Best et al. 2008) and parasite virulence (Fleming-Davies et al. 2018). Host strategies that reduce transmission but impose a cost to host fitness, such as immunological resistance or avoidance behaviors (Cumnock et al. 2018), are not expected to reach fixation and may stably coexist with alternate strategies in a population (Boots and Bowers 1999; Miller et al. 2007; Best et al. 2008) or drive evolutionary arms races between host and

parasites (Rabajante et al. 2015; Koskella 2018). Parasites that suppress host immune responses to achieve transmission can facilitate a second infection that drives up mortality rates, reducing transmission and leading to complex interactions between epidemiological feedbacks and optimal virulence for the focal parasite (Kamiya et al. 2018).Thus, disambiguation of the within-host contributors to mortality rate and transmission could refine our understanding of the maintenance of natural immunological variation among populations and species.

In conclusion, our model provides a flexible and generalizable framework to connect apparent competition and facilitation among parasites within a host to apparent competition in host communities. The predictions generated by this model should inspire comparative analyses of within-host interaction mechanisms in multi-host, multi-parasite systems, and spur further evaluation of the importance of parasite transmission mode in the evolution of host immunity and parasite life-history strategies.

Statement of Authorship

A.T.T. conceptualized the project and provided funding. F.H.R. and A.T.T. developed the model, and F.H.R. coded and performed model analysis. F.H.R. and A.T.T. wrote the manuscript.

Data and Code Accessibility

All code to recreate the results can be found in the online supplementary material.

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Table 1. Examples of the impact of parasite competition and facilitation on host recovery and survival outcomes

Host	Outcome	Parasite	Mechanism	System	Description	Reference(s)
Mortality	↓	Competition	Cross-immunity (apparent competition)	*Trypanosoma brucei* strains in mice	Co-infection with less virulent parasite strains boosts host immunity, thereby supressing the growth of the virulent strain	Balmer et al. 2009
Mortality	↓	Competition	Resource competition	Agrobacterial (crown gall disease) strains in plants	Avirulent strains of agrobacteria break down a nitrogen resource (opine), prohibiting more virulent strains from scavenging it; reduces overall virulence for plant host	Platt et al. 2012
Mortality	↓	Competition	Trade-offs between competition and virulence	*Bacillus thuringiensis* or *Xenorhabdus nematophila* strains in caterpillars	Production of bacteriocins to aid inter-strain competition comes at the cost of reduced virulence protein production and lower host mortality	Garbutt et al. 2011; Bhattacharya et al. 2019
Mortality	↓	Facilitation	Immunomodulation reduces immunopathology (increased host tolerance)	*Schistosoma* & *Plasmodium* in mice	*Schistosoma*-driven Th2 immune responses reduce the risk of immunopathology and cerebral malaria	Waknine-Grinberg et al. 2010; Ezenwa and Jolles 2011
Mortality	↓	Facilitation	Modified host energetics/metabolism (increased host tolerance)	*Wolbachia* & *Plasmodium* in mosquitoes *(Culex pipiens)*	*Wolbachia* bolster energy storage by host, mitigating relative energetic cost of *Plasmodium* infection	Zélé et al. 2012; Zélé et al. 2014; Zélé et al. 2018
Mortality	↑	Competition	Resource competition	Nucleopolyhedrovirus and entomopoxvirus in the tea tortix *Adoxophyes honmai*	Resource competition between the viruses and the host drains energy, damages tissue, and exacerbates host mortality	Ishii et al. 2002; Pedersen et al. 2007; Cressler et al. 2014
Mortality	↑	Competition	Increased virulence	*Flavobacterium columnare* strains in salmon	Competition between strains increases symptom severity leading to higher mortality	Pulkkinen et al. 2010
Mortality	↑	Facilitation	Supplied product or cross-feeding	*Staphylococcus aureus* & *Enterococcus faecalis* in *Caenorhabditis elegans*	Public good iron-scavenging siderophores maintain virulence	Ford et al. 2016; Zélé et al. 2018
Mortality	↑	Facilitation	Immunosuppression	Parasitic mites *(Varroa destructor)* and Deformed wing virus (DWV) in honeybees *(Apis mellifera)*	Parasitic mite infection leads to immunosuppression, leading to rapid replication of DWV and increased bee mortality	Nazzi et al 2012; Zélé et al. 2018
Mortality	↑	Facilitation	Immune polarization trade-offs	Helminths and *Mycobacterium bovis* in African buffalo	Helminths alter T cell polarization state (Th2), leading to reduction in protective responses (Th1-mediated) against intracellular bacteria and increased host mortality	Ezenwa et al 2010; Ezenwa and Jolles 2015
Mortality	↑	Facilitation	Tissue damage	*Legionella pneumophila* & influenza virus in mice	Influenza virus damages lungs and decreases infection tolerance, leading to increased *Legionella*-induced mortality	Jamieson et al. 2013
Mortality	↑	Facilitation	Resource Partitioning	*Plasmodium spp.* in mice	*Plasmodium chabaudi* and *P. yoelii* infect red blood cells of different ages; *P. chaubadi* stimulates increased production of reticulocytes by host, to the benefit of *P. yoelii*	Ramiro et al. 2016
Recovery	↑	Competition	Space/Resource Competition	Helminth & *Giardia* in humans	Direct competition for space in the small intestine enhances clearance from host	Blackwell et al. 2013; Pedersen et al. 2007
Recovery	↑	Competition	Cross-immunity (apparent competition)	Helminth & *Giardia* in humans	Cross-immunity via Th2-mediated immune responses leads to enhanced clearance	Blackwell et al. 2013; Pedersen and Fenton 2007; many examples in Holt and Bonsall 2017
Recovery	↑	Facilitation	Immunological suppression	No known examples	Possibly, with two self-limiting infections (e.g. helminths), coinfection may reduce the time from colonization to transmission (parasite pace of life), decreasing length of infection	*None*
Recovery	↓	Competition	Shift from acute to chronic infection	*Ribeiroia* and *Echinostoma* parasites in frogs	Competition among parasites (either immune or resource-mediated) leads to lower numbers of each species but prolongs the length of the infected larval period	Johnson and Buller 2011
Recovery	↓	Facilitation	Inappropriate immune polarization	*Pseudomonas aeruginosa* & lysogenic bacteriophage in mice	Phage RNA biases immune response toward type I interferon production and suppresses phagocytosis of bacteria, leading to host failure to resolve wounds	Sweere et al. 2019
Recovery	↓	Facilitation	Tissue conditioning	Influenza A virus, *Streptococcus pneumoniae* & *Staphylococcus aureus* in mice	Tissue damage by influenza virus facilitates bacterial colonization	Mina et al. 2014; Zélé et al. 2018

Notes: Upward arrow indicates that the host trait is increased in the example (e.g. higher mortality or faster recovery), while downward arrow indicates decreased rates of that parameter

Table 2. Focal parameter symbols, definitions, values, and relevant figures for key results

Symbol	Definition	Default Value	Value Range	Figure(s)
b_1	Reproductive rate of host species 1	1.2	NA	Fig. S1
b_2	Reproductive rate of host species 2	1.92	0 to 2.4	Fig. S1
$\gamma_{1,3}$	Recovery rate of host species 1 from the focal parasite	0.1	0 to 0.2	Fig. 2
$\gamma_{1,3*}$	Recovery rate of coinfected host species 1 from the focal parasite	0.1	0 to 0.2	NA
$\gamma_{2,3}$	Recovery rate of host species 2 from the focal parasite	0.1	NA	Fig. 2
$\gamma_{2,3*}$	Recovery rate of coinfected host species 2 from the focal parasite	0.1	0 to 0.2	NA
$\alpha_{1,3}$	Parasite-induced mortality rate of host species 1 from the focal parasite	0.08, 0.2	0 to 0.4	Figs. 2,3
$\alpha_{1,3*}$	Parasite-induced mortality rate of coinfected host species 1 from the focal parasite	0.08, 0.2	0 to 0.4	Fig.3
$\alpha_{2,3}$	Parasite-induced mortality rate of host species 2 from the focal infection	0.2	NA	Figs. 2,3
$\alpha_{2,3*}$	Parasite-induced mortality rate of coinfected host species 2 from the focal infection	0.2	0 to 0.4	Fig.3
$\phi_{1,1}$ and $\phi_{1,*}$	Fecundity reduction in host species 1 from the coinfecting parasite	0.1	NA	Fig. 2
$\phi_{2,2}$ and $\phi_{2,*}$	Fecundity reduction in host species 2 from the coinfecting parasite	0.1	NA	Fig. 2

Notes: For full set of state variables and parameters as well as references, see Table S1

Figures

Figure 1. Conceptual diagram of the model. Host compartments are square while parasite external infectious stages (E_k) are represented with circles. Solid lines entering compartments represent entry of individuals from birth and solid lines exiting compartments are death of individuals. The dotted line represents the competition between the two hosts exerted on each other's' reproductive capacity (e.g. by egg cannibalism). Short dashed lines represent the flow of individuals of species i between infection classes: moving down the arrows represents infection and movement upwards recovery. The long dashed lines show shedding of parasite k external stages from infected hosts. Host species 1 is represent by the four squares on the left and host species 2 on the right. The top-most box of each species are susceptible (S_i) individuals, middle two boxes single infections ($I_{i,k}$), and the bottom-most box represents coinfected ($I_{i,*}$) individuals.
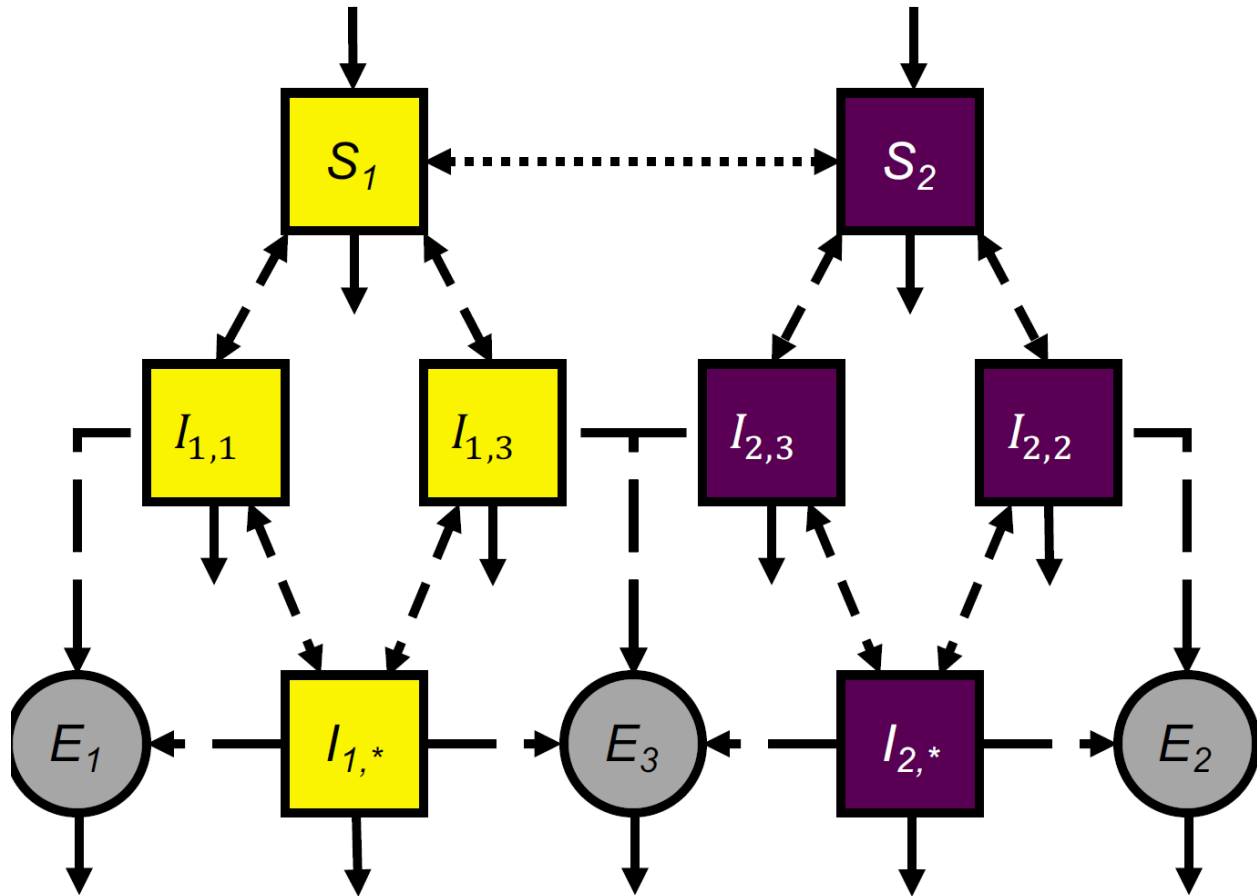
Figure 2. Competitive outcome and parasite prevalence over different relative recovery and mortality rates among host species when hosts are infected only with the focal parasite ($k=3$) or coinfected with indirectly (host birth rate-mediated) interacting parasites. The x-axes represent the focal parasite recovery rate (γ) of species 1 relative to species 2 (γ_1/γ_2). The y-axes represent the focal infection survival (1- the mortality rate α) of species 1 relative to species 2 ($(1-\alpha_1)/(1-\alpha_2)$). In the presence of the focal parasite only, relative survival modifies the relative abundance of each host species (A.; blue = species 2 dominates, yellow = species 1 dominates), while having a modest effect on focal infection prevalence (B., yellow = high, blue = low). White dots in (A) indicate parameter values used in subsequent analyses. When hosts can be coinfected but parasites interact only indirectly (through coinfecting parasite-mediated modification of host reproductive rate (ϕ = 0.1), results are similar for host competition outcomes (C), and both recovery and survival ratios have modest impacts on overall coinfection prevalence (D). Parameter ranges: $\gamma_{1,3}$ = 0 to 0.2, $\alpha_{1,3}$ = 0 to 0.4; $\gamma_{2,3}$ = 0.1, $\alpha_{2,3}$ = 0.2 (see Table S1 for other values).
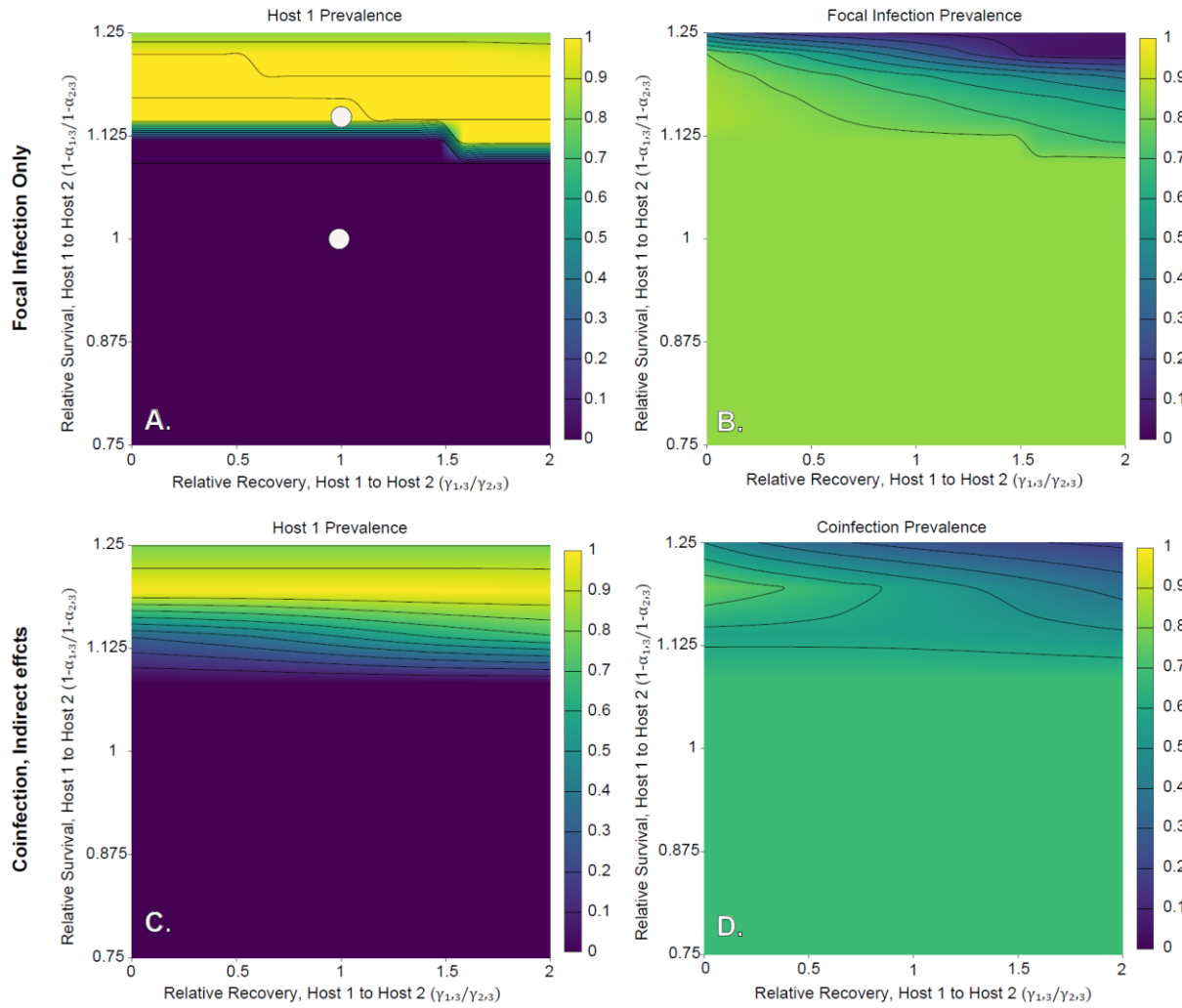
Figure 3. The impact of mortality-modulating direct interactions among coinfecting parasites on host community composition. The x- and y-axes represent the survival of species 1 and species 2, respectively, to the focal infection in the presence of the coinfecting parasite relative to its absence $((1-\alpha_{i,3*})/(1-\alpha_{i,3}))$. For both panels, the shading indicates proportion of species 1 in the community (yellow = dominant). When mortality rates to the focal parasite are equal among host species in single-infection scenarios (A.; $\alpha_1 = \alpha_2 = 0.2$), species 1 can dominate or coexist with species 2 only if the coinfecting parasite renders species 1 much more likely to survive the focal parasite. However, when species 1 is more likely to survive the single focal infection (B.; $\alpha_1 = 0.08$, $\alpha_2 = 0.2$) species 1 can coexist with species 2 even in the coinfecting parasite reduces its survival.
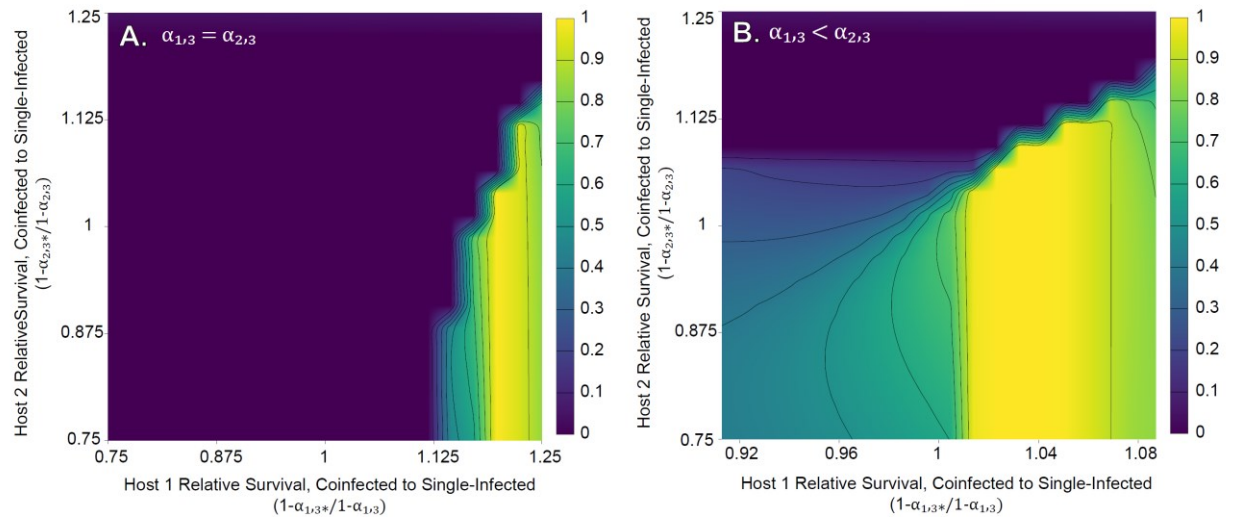
Figure 4. Sensitivity analysis of competitive outcomes and focal infection prevalence to model parameters and transmission mode of the focal infection. The greater the absolute value of the coefficient, the greater the influence of small positive changes to a parameter value (Table S1) on system outcomes. For column 1, parameters with coefficient values below zero have a significant negative effect (purple), i.e. decrease host species 1 (A) or focal parasite prevalence (B), while values above zero have a significant positive effect (green). In column 2, to test the effect of obligate killer vs horizontal transmission mode on competition and focal infection prevalence, sensitivity coefficients for mortality (solid lines) and recovery rates (dashed lines) of single and co-infected individuals for host competitive outcome (C) and focal infection prevalence (D) were derived for different values of p_3 (0 = obligate killer, 1 = transmission only from live individuals). Parameters associated with host species 1 are in yellow/green and host species 2 in purple/blue. Circles represent the coefficient value estimates and the vertical bars the 95% confidence intervals for all panels.