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Research

Priority effects within coinfected hosts can drive unexpected population-scale patterns of parasite prevalence

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Organisms are frequently coinfected by multiple parasite strains and species, and interactions between parasites within hosts are known to influence parasite prevalence and diversity, as well as epidemic timing. Importantly, interactions between coinfecting parasites can be affected by the order in which they infect hosts (i.e. within-host priority effects). In this study, we use a single-host, two-pathogen, SI model with environmental transmission to explore how within-host priority effects scale up to alter host population-scale infection patterns. Specifically, we ask how parasite prevalence changes in the presence of different types of priority effects. We consider two scenarios without priority effects and four scenarios with priority effects where there is either an advantage or a disadvantage to being the first to infect in a coinfected host. Models without priority effects always predict negative relationships between the prevalences of both parasites. In contrast, models with priority effects can yield unimodal prevalence relationships where the prevalence of a focal parasite is minimized or maximized at intermediate prevalences of a coinfecting parasite. The mechanism behind this pattern is that as the prevalence of the coinfecting parasite increases, most infections of the focal parasite change from occurring as solo infections, to first arrival coinfections, to second arrival coinfections. The corresponding changes in parasite fitness as the focal parasite moves from one infection class to another then map to changes in focal parasite prevalence. Further, we found that even when parasites interact negatively within a host, they still can have positive prevalence relationships at the population scale. These results suggest that within-host priority effects can change host population-scale infection patterns in systematic (and initially counterintuitive) ways, and that taking them into account may improve disease forecasting in coinfected populations.

Keywords: coinfection, prevalence, priority effects, scaling, within-host interactions

Introduction

Understanding how within-host interactions between parasites scale up to determine parasite prevalence will help us to predict infection patterns and outbreaks (Handel and Rohani 2015). When two parasites infect a host, they can interact (e.g. via shared resources or the immune system, Graham 2008) and impact each other's fitness

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(transmission to new hosts). These within-host interactions influence host population-scale dynamics. As the prevalence (proportion of hosts infected) of one parasite increases, the prevalence of a coinfecting parasite can either increase or decrease, depending on whether parasites facilitate or repress one another within-hosts (Abu-Raddad et al. 2006, Vasco et al. 2007). However, a pair of parasites may not interact identically in all coinfected hosts. Rather, parasites across diverse taxa can experience priority effects, where the order in which they infect their host determines how they impact one another's fitness (Table 1). Within-host priority effects have been largely studied at the single host scale (though see Hall and Little 2013, Natsopoulou et al. 2015, Halliday et al. 2017, Wuerthner et al. 2017). Consequently, we still have a limited understanding of how priority effects may scale up to influence the prevalence of each parasite in a coinfected population.

Evidence from free-living communities provides a framework for understanding within-host priority effects. Priority effects may occur through niche preemption, where early arriving species deplete resources available to later-arriving species, thus limiting their population growth (Urban and De Meester 2009, Hernandez and Chalcraft 2012, Rasmussen et al. 2014, Fukami 2015). For niche preemption to occur within hosts, coinfecting parasites must compete for limiting resources such as nutrients (Wale et al. 2017) or space (Dobson and Barnes 1995). Priority effects may also occur via niche modification, where the first species to arrive in a patch alters available niches, thus increasing or decreasing the fitness of later arriving species (Scheffer et al. 2003, Petraitis et al. 2009, Fukami and Nakajima 2013). Niche modification may occur within hosts when parasites increase host susceptibility to secondary infections via immunosuppression, parasites trigger an immune response that prevents secondary infections, or when parasites alter host-resource allocation (Lawn 2004, Rajakumar et al. 2006, Cressler et al. 2014). The framework for priority effects in free living communities gives us tools to understand how within-host priority effects will alter parasite community assembly at the single-host scale. We must now take that framework and extend it to understand how within-host priority effects might alter parasite prevalence by altering community assembly within hosts.

Within-host priority effects can influence parasite prevalence by creating feedbacks between parasite fitness within individual hosts and parasite prevalence in the host population. In particular, higher parasite prevalence implies a higher force of infection, i.e. a higher rate at which susceptible individuals become infected. Higher rates of infection mean susceptible individuals will become infected sooner. Hence, the higher the force of infection, the earlier in its life a host will become infected (Egger et al. 2008). All else being equal, this means a host is more likely to be infected first by the parasite that has the highest prevalence in a population. Because within-host priority effects can influence within-host parasite fitness (e.g. transmission to vectors; Supplementary material Appendix 1), earlier infection in a host may yield

Table 1. Review of studies on the impact of infection order on parasite fitness. Commas separate categorizations for parasite A and parasite B; a single categorization is listed if the fitness of parasite B was not reported. Slashes indicate results for different strains of parasite A. The 'Order advantage' column indicates whether priority effects were absent (none) or a parasite had higher fitness in coinfected hosts in which it arrived first or second. The 'Facilitated and repressed' column indicates whether arrival order determined type of parasite interaction. 'Yes' means that whether coinfections facilitated or repressed coinfection depended on order of arrival, while 'No' means that coinfection always facilitated or always repressed a parasite. The 'Unimodal possible' column indicates whether a parasite's within-host priority effects meet the requirements for causing unimodal prevalence relationships. Details about how each study was categorized and the criteria for inclusion are given the Supplementary material Appendix 1.

Reference	Host	Parasite A	Parasite B	Order advantage	Facilitated and repressed	Unimodal possible
Adame-Álvarez et al. 2014	wild lima bean	*Pseudomonas syringae*	endophytic fungi	1st	yes	yes
Adame-Álvarez et al. 2014	wild lima bean	*Enterobacter* sp.	endophytic fungi	1st	no	yes
Al-Naimi et al. 2005	wheat	*Pyrenophora triticirepentis*	*Puccinia triticina*	1st, none	yes, no	yes, no
Balogun 2008	tomato	Potato virus X	tomato mosaic virus	1st, 1st	no, no	yes, no
Clay et al. 2019	*Daphnia dentifera*	*Metschnikowia bicuspidata*	*Pasteuria ramosa*	2nd, none	yes, no	yes, no
de Roode et al. 2005	mouse	*Plasmodium chabaudi*		1st	no	no
Doublet et al. 2015	honeybee	deformed wing virus	*Nosema ceranae*	1st, none	no, no	no, no
Goodman and Ross 1974	tobacco	potato virus X/-GM	potato virus Y	2nd/1st	no	yes
Hall and Little 2013	wheat	*Luteoviridae (PAV)*	*Luteoviridae (PAS)*	None, 1st	no, no	no, no
Hoverman et al. 2013	Pacific chorus frog	*Ribeiroia ondatrae*	*Echinostoma trivolvis*	1st, none	no, no	no, no
Jackson et al. 2006	clawed toad	*Protopolystoma xenopodis*	*Protopolystoma* sp.	2nd	no	yes
Levin 2007	mouse	*Anaplamsa phagocytophilum*	*Borrelia burgdorferia*	1st, 1st	no, no	no, no
Lohr et al. 2010	*Daphnia galeata*	*Metschnikowia bicuspidata*	*Caullerya mesnili*	2nd, 1st	no, no	yes, no
Marchetto and Power 2017	barley	barley yellow dwarf virus	barley stripe mosaic virus	None, none	no, no	no, no
Natsopoulou et al. 2015	European honeybee	*Nosema ceranae*	*Nosema apis*	1st, 1st	no, no	no, no
Rynkiewicz et al. 2017	white-footed mouse	*Borrelia burgdorferi (BL206)*	*Borrelia burgdorferi (LC734)*	1st, none	no, no	no, no
Sandoval-Aguilar et al. 2015	diamondback moth	*Zoophthora radicans*	*Pandora blunckii*	2nd, 2nd	no, no	yes, yes

higher or lower within-host fitness for a coinfecting parasite. This means that, in systems where parasites experience priority effects, parasite fitness indirectly depends on the relative prevalences of coinfecting parasites. Specifically, if a parasite's fitness is highest when it is the first parasite to infect a host, then its fitness will increase when its prevalence increases relative to the coinfecting parasite, as it becomes more likely to infect the host first. On the other hand, if a parasite's fitness is highest in secondary infections, then its fitness will increase when its prevalence decreases relative to the coinfecting parasite. Thus, within-host priority effects create a feedback where within-host parasite fitness depends on the prevalences of coinfecting parasites, which in turn depend on within-host parasite fitness. The specific nature of the feedback depends on the structure of the within-host priority effects.

Together, feedbacks between within-host priority effects, parasite fitness, and parasite prevalence mean that within-host priority effects can have unexpected impacts on patterns of parasite prevalence. Failing to account for these feedbacks in systems with within-host priority effects might lead to inaccurate predictions of parasite dynamics. For instance, we typically expect that if the prevalence of a parasite increases, the prevalence of coinfecting parasites will either decrease if those parasites compete within hosts or increase if the parasites facilitate one another (Abu-Raddad et al. 2006, Keeling and Rohani 2008). However, population prevalences can influence infection order, and priority effects imply fitness is context dependent. Consequently, priority effects may change the relationship between the prevalence of coinfecting parasites, changing host population-scale infection patterns. If within-host priority effects do change host population-scale infection patterns, then we may need to adjust how we infer within-host interactions from prevalence data in coinfected systems (as in Behnke et al. 2005, Shrestha et al. 2013), and how we predict prevalence dynamics in coinfected systems from within-host interactions (as in Abu-Raddad et al. 2006, Ezenwa and Jolles 2015).

In this study we ask: how do within-host priority effects alter the relative prevalences of coinfecting parasites at the host population-scale? More specifically, how does an increase in the prevalence of one parasite change the prevalence of a coinfecting parasite when priority effects are present or not? Our review of the literature on within-host priority effects (Table 1) shows that coinfecting parasites may or may not experience priority effects ('Order advantage' column); that parasites may have higher fitness when arriving first or second ('Order advantage' column); and that the order of parasite arrival may or may not determine whether parasites are facilitated or repressed by coinfection ('Facilitated and repressed' column). Thus, we created a model with six scenarios that capture all possible combinations of these observed outcomes (Fig. 1). The first scenario did not include any priority effects and coinfection did not influence the fitness of either parasite (scenario I). The next two scenarios included priority effects, with either the first arriver having a fitness advantage (scenario II) or the second arriver having the fitness advantage (scenario III) compared to single infections. In both of these scenarios, there was no net effect of coinfection on fitness, as the gain in fitness from arriving first (or second) was exactly offset by the loss in fitness from arriving second (or first). In the remaining scenarios, parasite fitness was reduced in coinfections as compared to single infections (Fig. 1). In these scenarios, the reduction can be independent of arrival order (scenario IV), the first arriver can experience less of a fitness reduction (scenario V), or the second arriver can experience less of a fitness reduction (scenario VI). All of these scenarios have been observed in empirical systems. Parallel examples of these types of priority effects may be found in free living systems or non-pathogenic symbionts – for instance, scenario V priority effects most likely correspond to niche preemption found in free living systems, where organisms that arrive early within a patch deplete resources necessary for the growth of later arriving organisms.

We found that, while negative prevalence relationships always arise in the absence of priority effects, priority effects often lead to unimodal prevalence relationships between coinfecting parasites. As a result, when priority effects occur, parasites that compete within hosts can show positive prevalence relationships at the host population-scale. Ultimately, our results indicate that disease forecast models might make qualitatively incorrect predictions about the relationships between parasites at the host population-scale if they fail to consider the priority effects that may occur in coinfected hosts.

Methods

Here, we use a general SI model with environmental transmission to simulate a host population infected by two parasites with environmental propagule densities A and B. We also analyzed models with density-dependent and frequency-dependent direct transmission, but our results were not sensitive to transmission mode (Supplementary material Appendix 1 Fig. A1, A2). Hosts are susceptible (S), singly infected by either parasite (I_A, I_B), or coinfected (C_{AB}, C_{BA}) (Fig. 2). In order to keep track of within-host priority effects, coinfected hosts are divided into two groups: those where parasite A arrived first (C_{AB}), and those where parasite B arrived first (C_{BA}); Table 2 for values and definitions of all parameters and variables. We initially included a class of hosts which were simultaneously coinfected, but for all parameter combinations explored, the proportion of coinfected hosts which were simultaneously coinfected was always less than 0.01, so we ignore simultaneous coinfections for the sake of simplicity. However, in systems where coinfecting pathogens are transmitted by the same vector species, simultaneous coinfections may be common (as explored by Marchetto and Power 2017). We model chronic infections with no recovery, as recovery is not a factor in most empirical studies on priority effects (Table 1).

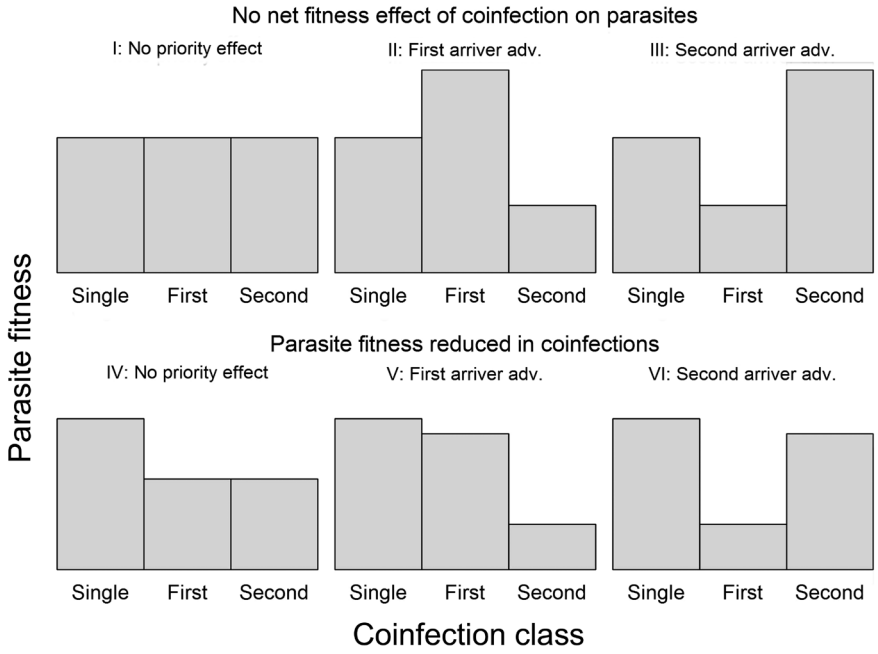

Figure 1. Six coinfection scenarios considered in this study. In our model, we alter parasite fitness via propagule production rates. All propagule production rates are relative to the propagule production rate from singly infected hosts, which is set to one in all scenarios. In all cases, priority effects are symmetric (e.g. if one parasite experiences a scenario II effect, so does the second parasite). Scenarios I, II and III- no net impact of coinfection on parasite fitness. Scenario IV, V and VI- parasite fitness reduced in coinfections. Scenario I and IV- no priority effects. Scenario II and V- first arriver advantage. Scenario III, VI- second arriver advantage. In the text, when we refer back to the scenarios, we use the following shorthand: scenario I: no priority effect, no fitness effect of coinfection; scenario II: first arriver advantage, no net fitness effect of coinfection; scenario III: second arriver advantage, no net fitness effect of coinfection; scenario IV: no priority effect, fitness reduced in coinfections; scenario V: first arriver advantage, fitness reduced in coinfections; scenario VI: second arriver advantage, fitness reduced in coinfections.

In our model, we implement priority effects via changes in propagule production. For within-host priority effects to arise, some component of parasite fitness (host mortality, parasite clearance, or transmission rate) must depend on infection order. Most empirical studies on within-host priority effects measure parasite transmission (Levin 2007, Lohr et al. 2010, Hall and Little 2013, Marchetto and Power 2017, Rynkiewicz et al. 2017), though some measure effects on host mortality (Lohr et al. 2010, Marchetto and Power 2017) or parasite clearance (Sandoval-Aguilar et al. 2015). Because it was the most common focus of the empirical studies, we chose to implement within-host priority effects by making parasite transmission, specifically the production of infectious propagules, depend on parasite arrival order. We keep host susceptibility and contact rate constant, making propagule production rate a direct proxy for transmission rate. We found that our results did not qualitatively change if within-host priority effects acted through host mortality or parasite clearance, so long as the impact of priority effects on total parasite transmission over the course of infection was the same (Supplementary material Appendix 1 Fig. A3, A4).

Propagule production is represented in our model by the parameter $\beta_{i(j)}$, which represents the production rate of propagule i from infection class j. Thus, if coinfection of parasites A and B affects the propagule production of parasite B, then the propagule production rates of parasite B in coinfected hosts ($\beta_{B(AB)}$ and $\beta_{B(BA)}$) will differ from the production rates of parasite B in singly infected hosts ($\beta_{B(B)}$). Further, if parasite B benefits from first infection in coinfected hosts, then $\beta_{B(BA)}$ will be higher than $\beta_{B(AB)}$, whereas if parasite B benefits from second infection in coinfected hosts, then $\beta_{B(BA)}$ will be less than $\beta_{B(AB)}$.

We choose to set priority effects directly rather than allowing them to emerge from mechanistic within-host interactions, as most empirical examples of within-host priority effects do not document how parasites mechanistically interact within hosts. Additionally, we know that there are numerous within-host interaction mechanisms that could produce priority effects, such as resource competition, immune suppression and escape, cross-immunity, and changes to host lifespan (Rolff and Siva-Jothy 2003, de Roode et al. 2005, Lohr et al. 2010). By specifying the observed fitness outcomes of within-host interactions rather than within-host interactions themselves, our results are more likely to apply broadly to systems with different underlying mechanisms. We set the mortality rate of coinfected hosts to be the same as in singly infected hosts because whether coinfections decrease, increase, or do not change host mortality is system specific (Alizon et al. 2013). Further, parasite fitness in our model is a function of

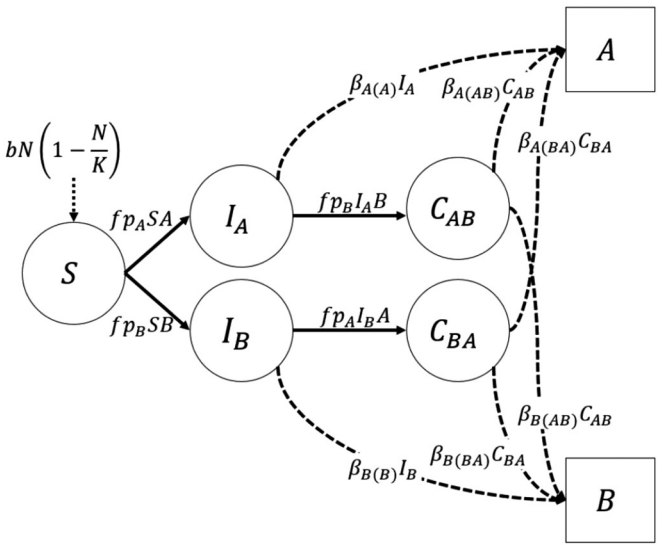

Figure 2. Flow diagram of model dynamics. Circles represent host classes, and squares represent environmental parasite pools. The black dotted line represents host birth, the black solid lines represent host infection, and the black dashed lines show propagule release from infected hosts to the environment. Host mortality rates and propagule degradation and uptake rates are not shown. In our model, hosts contact environmentally transmitted parasites, and then become singly infected. These singly infected hosts can become coinfected with parasite A arriving first or parasite B arriving first. Host mortality rates, propagule degradation rates, and the removal of propagules by host feeding are also included in model dynamics.

propagule production rate ($\beta_{i(j)}$) and parasite induced mortality (m). Thus, to control parasite fitness across infection classes, we keep parasite induced mortality constant across infection classes. Modeling parasite virulence via decreases in host fecundity does not qualitatively change our results (Supplementary material Appendix 1 Fig. A5).

The dynamics of the susceptible host class are given by

$$\frac{dS}{dt} = \overbrace{bN\left(1-\frac{N}{K}\right)}^{Births} - \overbrace{\left(fp_AA + fp_BB\right)S}^{Infection} - \overbrace{dS}^{Deaths} \quad (1)$$

where f is the propagule uptake rate of hosts, p_i is the infectivity of propagule i, K is the carrying capacity, N is total population size, b is the population birth rate, and d is the intrinsic death rate of the population. Susceptible hosts are born into the population via all host classes (no vertical transmission), become singly infected by consuming propagules from the environment ($(fp_AA+fp_BB)S$), and die at rate (d). Singly infected hosts can become coinfected by consuming propagules of the parasite they are not infected by (fp_BI_AB or fp_AI_BA), and all infected hosts die as a function of background mortality and parasite induced mortality ($d+m$), given by equations

$$\frac{dI_A}{dt} = \overbrace{fp_ASA}^{Infection} - \overbrace{fp_BI_AB}^{Coinfection} - \overbrace{\left(d+m\right)I_A}^{Deaths} \quad (2)$$

$$\frac{dI_B}{dt} = \overbrace{fp_BSB}^{Infection} - \overbrace{fp_AI_BA}^{Coinfection} - \overbrace{\left(d+m\right)I_B}^{Deaths} \quad (3)$$

$$\frac{dC_{AB}}{dt} = \overbrace{fp_BI_AB}^{Coinfection} - \overbrace{\left(d+m\right)C_{AB}}^{Deaths} \quad (4)$$

$$\frac{dC_{BA}}{dt} = \overbrace{fp_AI_BA}^{Coinfection} - \overbrace{\left(d+m\right)C_{BA}}^{Deaths} \quad (5)$$

Table 2. Model variables and parameters. $\beta_{i(i)}$ is set to 1 from singly infected hosts in all cases, and relative values of $\beta_{i(i)}$ from coinfected hosts are shown in Fig. 1. Values of p_A are varied as an independent variable.

Variable/parameter	Units	Value	Description
S	indiv./area	state variable	susceptible hosts
I_A	indiv./area	state variable	hosts infected by A
I_B	indiv./area	state variable	hosts infected by B
C_{AB}	indiv./area	state variable	coinfected hosts, A first
C_{BA}	indiv./area	state variable	coinfected hosts, B first
A	propagules/area	state variable	density of A propagules
B	propagules/area	state variable	density of B propagules
N	indiv./area	state variable	population density
b	1/time	0.2	birth rate
d	1/time	0.03	intrinsic death rate
K	indiv./area	500	carrying capacity
p_A	1/propagule/time	0–0.82	infectivity of A propagules
p_B	1/propagule/time	0.42	infectivity of B propagules
m	1/time	0.02	infected host mortality
$\beta_{i(i)}$	propagules/indiv./time	variable	propagule production rate
α	1/time	0.1	propagule degradation rate
f	1/indiv./time	0.0006	propagule removal by hosts

Infected hosts release propagules into the environment. The dynamics of environmental propagule densities are

$$\frac{dA}{dt} = \overbrace{\beta_{A(A)} I_A + \beta_{A(AB)} C_{AB} + \beta_{A(BA)} C_{BA}}^{\text{Propagule Release}} - \overbrace{\alpha A}^{\text{Degradation}} - \overbrace{fNA}^{\text{Uptake}} \quad (6)$$

$$\frac{dB}{dt} = \overbrace{\beta_{B(B)} I_B + \beta_{B(AB)} C_{AB} + \beta_{B(BA)} C_{BA}}^{\text{Propagule Release}} - \overbrace{\alpha B}^{\text{Degradation}} - \overbrace{fNB}^{\text{Uptake}} \quad (7)$$

where $\beta_{i(j)}$ is the propagule production rate of parasite i from host class j, and α is the propagule degradation rate. Thus, all hosts which are infected by parasite A add propagules of parasite A to the environment. Propagules degrade at rate (α) and hosts ingest them from the environment at rate (f).

Types of within-host priority effects

We surveyed sequential infection studies to find empirical patterns of within-host priority effects (Table 1). We included studies in our review that compared parasite fitness in singly infected hosts, coinfected hosts where the parasite was the first to arrive, and coinfected hosts where the parasite was the second to arrive. Given that within-host priority effects apply to mutualist symbionts, we also included one experiment on sequential inoculations of parasite/non-parasite combinations (Adame-Álvarez et al. 2014). Sequential infection studies did not meet all necessary criteria (Supplementary material Appendix 1) and were consequently excluded from our review. We found that the response of parasites to sequential infection can be described along three binary axes, and are categorized in Table 1. We explain in detail how we categorized each study in the Supplementary material Appendix 1.

First, parasites either do or do not experience priority effects. Coinfections do not create within-host priority effects when coinfections do not impact parasite fitness (Doublet et al. 2015, Marchetto and Power 2017, Rynkiewicz et al. 2017), or when coinfections uniformly reduce parasite fitness, regardless of infection order (Al-Naimi et al. 2005, Clay et al. 2019).

Second, if parasites experience within-host priority effects, they may have a higher fitness in coinfected hosts in which they arrive first, or coinfected hosts in which they arrive second (1st arrival advantage and 2nd arrival advantage). 1st arrival advantage may occur if first arriving parasites prevent resource utilization by later arriving parasites (de Roode et al. 2005), or trigger an immune response which specifically targets later arriving parasites (Brown and Grenfell 2001). 2nd arrival advantage may occur if the host immune system cannot fully target sequential infections, perhaps due to TH1/TH2 tradeoffs (Fenton et al. 2008), or if the 2nd parasite to arrive in a host can take advantage of resources made accessible by the 1st parasite (Harrison et al. 2006).

Thirdly, if parasites experience within-host priority effects, arrival order may or may not determine whether coinfection facilitates or represses parasites. This may occur if parasites have both positive and negative interaction pathways, and the relative importance of these pathways depend on parasite arrival order (Adame-Álvarez et al. 2014). For instance, two parasites may compete for resources, and the host immune system may only attack the first parasite to infect a host. In this case, coinfection may be detrimental to a parasite if it arrives first in coinfected hosts as it has to face resource competition, but may facilitate a parasite if it arrives second in coinfected hosts, if the benefit from escaping the immune system outweighs the cost of resource competition.

We model six sequential infection scenarios based on combinations of these three factors (Fig. 1). Each of these scenarios has been found in empirical systems. Scenario I is a baseline case without within-host priority effects where coinfecting parasites do not interact – rather parasite fitness is equal in all singly and coinfected hosts, as in Marchetto and Power (2017, ignoring vertical transmission).

In scenarios II and III, arrival order determines whether coinfection facilitates or represses parasite fitness. In scenario II, parasites are facilitated by coinfection if they arrive first, and repressed by coinfection if they arrive second. For example, the ability of *Anaplasma phagocytophilum* to transmit from mice to ticks is increased by coinfection with *Borrelia burgdorferia* if *A. phagocytophilum* arrives first, and decreased if it arrives second (Levin 2007). In scenario III, parasites are repressed by coinfection if they arrive first and facilitated by coinfection if they arrive second. In *Daphnia dentifera* hosts, for example, *Metschnikowia bicuspidata* infectious spore yield is decreased by coinfection with *Pasteuria ramosa* if *M. bicuspidata* arrives first, but increased by coinfection if *M. bicuspidata* arrives second (Clay et al. 2019).

Scenario IV represents the case where parasite fitness is uniformly reduced by coinfection, regardless of arrival order. This occurs in coinfections between *Puccinia triticina* and *Pyrenophora triticirepentis* in wheat, where coinfection uniformly reduces *P. triticina* load (Al-Naimi et al. 2005).

In scenarios V and VI, within-host competition always reduces parasite fitness, but the magnitude of reduction depends on the order of infection. In scenario V, coinfection reduces the fitness of all parasites, but fitness is most dramatically reduced in the second arriving parasite. For example, coinfection by *Plasmodium chabaudi* strains in a mouse host reduces the propagule production of both strains, but the strain that arrives 2nd has the most dramatic reduction in propagule production (de Roode et al. 2005). In scenario VI, coinfection reduces the fitness of all parasites, but fitness is most dramatically reduced in the first arriving parasite. For instance, in the clawed toad, production of *Protopolystoma xenopodis* is delayed by coinfection with *Protopolystoma sp.* if *P. xenopodis* arrives second, but completely halted if *P. xenopodis* arrives first (Jackson et al. 2006).

Our non-priority effects scenarios (I and IV) have propagule production rates in both coinfected classes that

are equal to the average propagule production rate across coinfection classes in corresponding priority effects scenarios (scenario I averages rates from scenario II and III, scenario IV averages rates from scenario V and VI). Thus, we can directly compare priority effects and non-priority effects scenarios. We do not address systems where parasites always facilitate one another in coinfected hosts because those cases are rare in the within-host priority effect literature (though see Goodman and Ross 1974).

To examine how priority effects alter infection patterns at the host population-scale, we focus on the relationship between the prevalence of coinfecting parasites. Specifically, we measure how the prevalence of parasite *B* responds to changes in the prevalence of parasite *A*. We cannot change the prevalence of *A*, a state variable, directly, because we examine equilibrium conditions. Rather, following Abrams and Cortez (2015) we increase the prevalence of *A* by increasing its fitness. Specifically, we increase the per propagule infectivity of parasite *A*(p_A) which always increases the prevalence and environmental propagule density of parasite *A*. We then measure changes in parasite *B* prevalence (combined prevalence of hosts singly and coinfected with *B*) in response to changes in p_A. Changes in the per propagule infectivity often alter parasite fitness in natural systems, particularly for environmentally transmitted parasites. The infectivity of propagules can be sensitive to environmental conditions such as temperature, humidity, and UV, and a decrease in propagule infectivity often indicates that a higher propagule dose is needed to infect a susceptible host (Steinkraus and Slaymaker 1994, Williamson et al. 2017, Shocket et al. 2018). All other parameters are held constant (values given in Table 2). We found that our model results were not sensitive to parameter values as long as both singly infected and coinfected individuals were present at some point along the p_A continuum (Supplementary material Appendix 1 Table A1). We repeat this procedure for all four priority effects scenarios in Fig. 1 and their associated scenarios without priority effects.

Data deposition

Data available from the Dryad Digital Repository: <http://dx.doi.org/10.5061/dryad.003k4g0> (Clay et al. 2018).

Results

Monotonic prevalence relationships without priority effects

In the absence of priority effects, increasing the fitness of parasite *A* always decreases the prevalence of parasite *B* (scenario I and IV, Fig. 3). The infectivity of parasite *A* is positively correlated with its prevalence, creating a negative correlation between the prevalences of parasites *A* and *B* (scenario I and IV, Fig. 4). Thus, as the per propagule infectivity of parasite *A* increases, the proportion of hosts that are coinfected increases (Fig. 5). In scenario I (no fitness effect of coinfection), where parasites have equal propagule release rates from all hosts, parasite *A* only negatively impacts parasite *B* by reducing the host population density. In scenario IV (no priority effect, fitness reduced in coinfections), parasite *A* has a much greater negative effect on parasite *B* than in scenario I (no priority effect, no fitness effect of coinfection), as parasite *A* both reduces host population size and reduces the propagule release rate of parasite *B* from coinfected hosts in scenario IV.

Priority effects can cause unimodal prevalence relationships

When priority effects are present, increasing the fitness, and thus prevalence, of parasite *A* has a unimodal effect on the

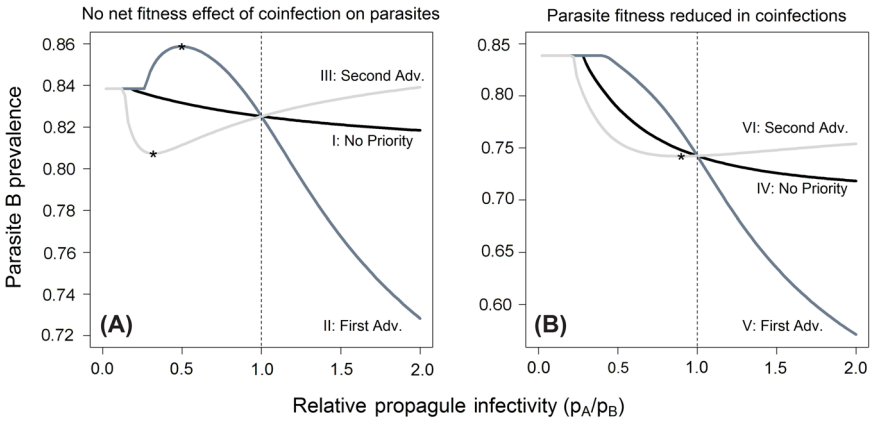

Figure 3. Prevalence of parasite *B* at equilibrium conditions versus infectivity of parasite *A* relative to the infectivity of parasite *B*. Dashed vertical lines mark where parasite *A* infectivity is equal to parasite *B* infectivity. As we increase parasite *A* infectivity, the prevalence of parasite *A* increases. Thus, relationships shown here approximate correlations between host prevalences. Asterisks indicate maximum or minimum values. Each curve refers to a different propagule production parameterization (Fig. 1). Scenario I: no priority effect, no fitness effect of coinfection; scenario II: first arriver advantage, no net fitness effect of coinfection; scenario III: second arriver advantage, no net fitness effect of coinfection; scenario IV: no priority effect, fitness reduced in coinfections; scenario V: first arriver advantage, fitness reduced in coinfections; scenario VI: second arriver advantage, fitness reduced in coinfections.

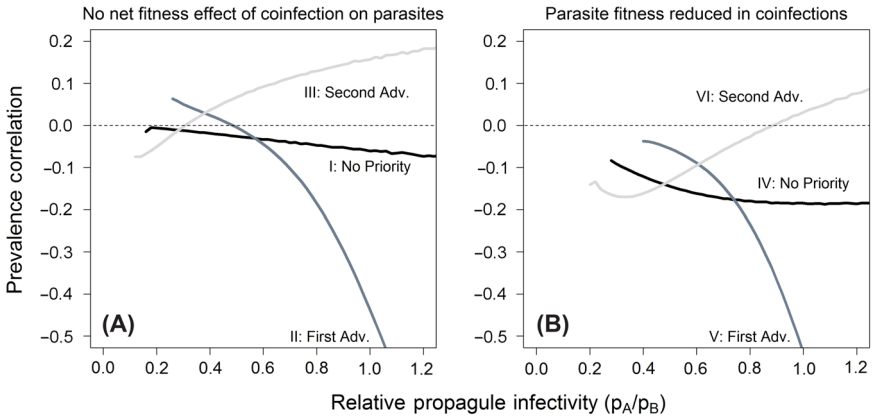

Figure 4. The correlation between the prevalence of parasite *A* and the prevalence of parasite *B*, as propagule infectivity increases. Prevalence correlations were calculated as the derivative of the relationships in Fig. 3. Scenario II (first arriver advantage, no net fitness effect of coinfection), III (second arriver advantage, no net fitness effect of coinfection), and VI (second arriver advantage, fitness reduced in coinfections) models all switch from positive to negative prevalence correlations, or vice versa, as parasite *A* propagule infectivity increases. Scenarios without priority effects (scenario I and IV) and scenario V (first arriver advantage, fitness reduced in coinfections) always show negative prevalence correlations.

prevalence of parasite *B* in three out of four scenarios. For example, in both scenarios where late arriving parasites have a higher propagule production rate than early arriving parasites (scenario III and VI), increasing parasite *A* fitness first decreases parasite *B* prevalence, then increases parasite *B* prevalence (Fig. 3). As a consequence, parasite *B* prevalence is minimized at intermediate parasite *A* prevalence for scenario III and VI. Parasite *B* prevalence is maximized at intermediate prevalence of parasite *A* for scenario II (first arriver advantage, no net fitness effect; represented by asterisks in Fig. 3). Scenario V (where fitness is reduced in coinfections and the first arriver has an advantage) is the only scenario where priority effects yield a continuously negative relationship between parasite A prevalence and parasite B prevalence (Fig. 4).

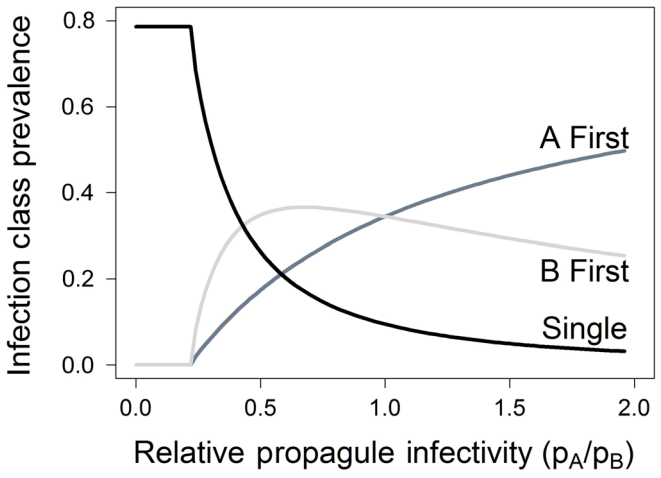

Figure 5. The prevalence of parasite *B* as parasite *A* propagule infectivity increases relative to parasite *B* infectivity, separated into infection classes. The black line represents prevalence of hosts singly infected by parasite *B*, the dark gray line represents prevalence of coinfected hosts in which parasite *A* arrives first, the light gray line represents prevalence of coinfected hosts in which parasite B arrives first. Data in this figure comes from the scenario I, where pathogen fitness is the same in all infection classes (no priority effect, no fitness effect of coinfections). However, this qualitative pattern is the same in all scenarios.

For three of the four priority effect scenarios, including priority effects switched the relationship between the prevalence of parasites *A* and *B* from negative to positive over part of the parameter space (Fig. 3, 4). In contrast, these relationships were always negative in the absence of priority effects (scenario I and IV). Our qualitative model results (unimodal prevalence relationships in scenariosII, III and VI, Fig. 3) were not sensitive to other model parameters, as long as changing model parameters did not prevent the existence of either coinfected or singly infected individuals (Supplementary material Appendix 1 Table A1).

Mechanisms driving unimodal prevalence relationships

We can explain the unimodal prevalence relationships in our model by examining how the average fitness of parasite *B* changes in response to increases in parasite *A* prevalence. For instance, in scenario II, a parasite is facilitated in coinfections if it arrives first ($\beta_{B(B)} < \beta_{B(BA)}$) and repressed if it arrives second ($\beta_{B(B)} > \beta_{B(AB)}$). In this scenario, parasite *B* first increases as the per propagule infectivity of parasite *A* increases, then begins to decrease once parasite *A* infectivity is approximately half of parasite *B* infectivity (dark gray curve in left panel of Fig. 3). This unimodal relationship is created by changes in the frequencies of host classes infected by parasite *B* as parasite *A* infectivity increases. When parasite *A* is at low infectivity, parasite *B* mostly occurs in single infections (far left side of Fig. 5), where its propagule production is intermediate (Fig. 1 scenario II). As parasite *A* infectivity increases (middle-left of Fig. 5), coinfections where parasite *B* is the

first to arrive in the host become more common than single infections. Parasite *B* produces more propagules from coinfected hosts with first arrival than from singly infected hosts. Consequently, parasite *B* prevalence increases. However, as parasite *A* infectivity increases further (right side of Fig. 5), coinfections where parasite *B* is the second to infect become more frequent than coinfections where parasite *B* is the first to arrive. Parasite B produces fewer propagules from coinfected hosts when it is the second to arrive. This causes parasite *B* prevalence to decrease. Overall, this yields a unimodal relationship between parasite *A* infectivity and parasite *B* prevalence, where parasite *B* prevalence initially increases and then decreases (dark gray curve in Fig. 3a).

The explanation above shows that the changes in parasite *B* fitness as it moves from single infections, to first arrival in coinfections, to second arrival in coinfections, directly map to the prevalence relationship between parasite *A* and parasite *B*. In general, if a parasite has its highest or lowest fitness when it arrives first in a coinfected host compared to all other infection classes, then we expect the parasite prevalence relationship to be unimodal. This explains why unimodal relationships arise for scenario II, III and VI. One unexpected effect of these mechanisms is that since $\beta_{B(BA)} < \beta_{B(AB)}$ in scenario VI (second arriver advantage, fitness reduced in coinfections), we see a partially positive prevalence relationship between parasites *A* and *B*, even though they reduce one another's propagule production in all coinfected hosts (Fig. 1, 4). These mechanisms also explain why we see a continuously negative prevalence relationship in scenario V (first arriver advantage, fitness reduced in coinfections). In that scenario, $\beta_{B(B)} > \beta_{B(BA)} > \beta_{B(AB)}$, so as parasite *A* infectivity increases, parasite *B* moves from highest fitness to intermediate fitness to lowest fitness.

Further, as long as a parasite has its highest or lowest fitness when it arrives first in a coinfected host compared to all other infection classes, it can experience unimodal prevalence relationships even if it does not fall into one of the priority effect scenarios in our model. It is difficult to assign empirical studies of within-host priority effects to scenario I–VI due to interactions between host and parasite genotypes, the intrinsic impact of host age at infection on parasite fitness, and the fact that our models do not capture every possible combination of relative parasite fitness across infection classes. However, even without assigning empirical examples of within-host priority effects to individual model scenarios, we can identify the parasites which meet the criteria for unimodal prevalence relationships (Goodman and Ross 1974, Al-Naimi et al. 2005, Jackson et al. 2006, Balogun 2008, Lohr et al. 2010, Adame-Álvarez et al. 2014, Sandoval-Aguilar et al. 2015, Clay et al. 2019).

We model all priority effects to be symmetric (e.g. both parasites experience scenario II priority effects), though our results hold even if priority effects are asymmetric. Changes to the arrival order, and thus propagule production rate, of parasite A as we increase parasite *A* infectivity are small compared to changes in parasite *A* transmission due to the direct effects of infectivity. Consequently, as we increase parasite *A* infectivity, the relationship between parasite *A* prevalence and parasite *B* prevalence depends only on what priority effects parasite *B* experiences.

Discussion

Given that coinfection is common (Petney and Andrews 1998, Brogden et al. 2005, Balmer and Tanner 2011, Cox 2011), it would be valuable to understand the relationship between within-host interactions and infection patterns in coinfected populations (Handel and Rohani 2015). When modeling infection dynamics in coinfected populations, many studies assume that the impact parasites have on each other in coinfected hosts is homogenous across coinfected individuals. In reality, however, parasite fitness can depend on the order of infection, i.e. priority effects (Table 1). Our study shows that with priority effects, shifts in parasite prevalence change the prevalence of coinfecting parasites by altering the order of arrival in coinfected hosts (Fig. 5). This shift in arrival order can drive a unimodal relationship between parasites at the host population-scale, maximizing or minimizing the prevalence of one parasite at an intermediate prevalence of the other parasite (Fig. 3). Furthermore, parasites that always have negative interactions within hosts can still have a positive prevalence relationship at the host population-scale if parasites gain a fitness advantage from secondary arrival in coinfected hosts (Fig. 4, scenario VI: second arriver advantage, parasite fitness reduced in coinfections). This demonstrates that within-host interactions can drive initially unexpected patterns at the host population-scale. Importantly, the patterns hold true regardless of the specific model formulation or type of transmission mode, indicating that our results are applicable to most systems in which priority effects are found and there is a significant level of coinfection at the individual host scale.

The prevalence of parasites often shifts due to changes in climate or season (Altizer et al. 2006, Grassly and Fraser 2006), and predicting how the rest of the parasite community will change in response is necessary for disease forecasting in coinfected populations. Mechanistic models often predict relationships between parasites at the host population-scale using models in which parasites have the same interactions in all coinfected hosts (Bentwich et al. 1995, Abu-Raddad et al. 2006, 2008, Ezenwa and Jolles 2015). Our results indicate that if models ignore existing priority effects, they may incorrectly predict the direction of parasite interactions at the host population-scale. For instance, in the absence of priority effects (scenario I and IV), interference between two parasites within hosts is predicted to lead to a negative prevalence relationship at the host population-scale, after controlling for other factors. With priority effects, however, parasites that always decrease each other's fitness within hosts may still have a partially positive relationship at the host population-scale if parasites gain a fitness advantage

from secondary arrival in coinfected hosts (scenario VI), a scenario observed in coinfected frogs, *Daphnia*, and moths (Jackson et al. 2006, Lohr et al. 2010, Hoverman et al. 2013, Sandoval-Aguilar et al. 2015). Ultimately, our results suggest that coinfection models may benefit from incorporating priority effect data.

If we link specific parasite interactions to priority effect scenarios, then we may be able to predict prevalence relationships from within-host studies. The more similar two organisms are, the more likely that priority effects will be generated by niche preemption (Fukami 2015). Niche preemption should create 1st arrival advantage, and does not involve any within-host facilitation, thus leading to scenario V, which does not create unimodal prevalence relationships. Thus, intra-strain coinfections, where coinfecting organisms are very similar, may not show unimodal prevalence relationships (as we see in de Roode et al. 2005 and Rynkiewicz et al. 2017). Priority effects between parasite species, on the other hand, may be more likely to have priority effects scenarios leading to unimodal prevalence relationships. This is important, as inter-specific co-infection alters disease patterns in highly virulent pathogens such as malaria, HIV and tuberculosis (Abu-Raddad et al. 2006, Borkow et al. 2007, Ezenwa et al. 2010). The types of priority effects that cause unimodal prevalence relationships may be caused by variation in the relative importance of positive and negative within-host interactions. For instance, infections of the wild lima bean by the bacterial pathogen *Pseudomonas syringae* may be facilitated within-hosts by an endophytic fungus if *P. syringae* arrives first due to a high host cost of resisting both symbionts, but may be repressed by coinfection if *P. syringae* arrives second due to competition for space (scenario II, Adame-Álvarez et al. 2014). Similarly, infections of *Daphnia dentifera* by *Metschnikowia bicuspidata* may be facilitated by the bacterium *Pasteuria ramosa* if *P. ramosa* arrives first, because *P. ramosa* castrates the host (Cressler et al. 2014), redirecting energy towards *M. bicuspidata*. On the other hand if *M. bicuspidata* arrives first, it may prevent castration, thus limiting within-host interaction to competition for resources, creating scenario VI priority effects (Clay et al. 2019). Thus, by looking for coinfections that have both positive and negative within-host interactions, we may find systems which exhibit unimodal prevalence relationships.

Our study adds to a growing body of evidence that it is difficult to infer within-host interactions from population-level observations of parasite prevalence (Fenton et al. 2010). Past studies have used correlations between parasite prevalence data across time or space to infer within-host parasite interactions (Behnke et al. 2005, Keeling and Rohani 2008, Shrestha et al. 2013). For instance, relationships between the prevalence of the influenza virus and *Streptococcus pneumoniae* over time have been used to infer the within-host interactions between these two pathogens (Shrestha et al. 2013). When paired with mechanistic models, these studies can give valuable insights into the likelihood that pathogens are facilitating or repressing one another. Mechanistic models which contain a single coinfection class (and do not allow for priority effects) infer within-host facilitation from positive prevalence relationships, and within-host interference from negative prevalence relationships, when controlling for environmental factors that which influence both parasites (Keeling and Rohani 2008). With within-host priority effects, however, partially positive prevalence relationships can exist even in circumstances when parasites always interfere with one another within hosts (Fig. 4). Thus, attempts to infer within-host parasite interactions from relationships between the prevalence of coinfecting parasites across time (as in Shrestha et al. 2013) or space (as in Behnke et al. 2005) may give unreliable and contradictory results if within-host priority effects exist and are unaccounted for.

However, observational approaches may still be used to indicate whether within-host priority effects need to be taken into account. We can use these approaches because our model predicts that within-host priority effects will create specific prevalence relationship patterns. Thus, all else being equal, if data show that the prevalence of one parasite is maximized or minimized at intermediate prevalence of a coinfecting parasite, then there may be priority effects occurring in individual hosts. This prediction can be tested using controlled experiments that test for priority effects in individual hosts and controlled experiments that measure the response of the prevalence of one parasite to changes in the prevalence of a coinfecting parasite. However, it is important to note that in natural systems, many factors can drive prevalence relationships, such as parasites having different reactions to a seasonal forcing or sharing a transmission route (Altizer et al. 2006, Grassly and Fraser 2006), and these mechanisms might create larger swings in parasite prevalence than do within-host priority effects. Thus, unimodal prevalence relationships should not be attributed to within-host priority effects until these factors have been accounted for. Fortunately, in natural systems, within-host priority effects may be detected by measuring longitudinal changes in parasite intensity in individual hosts (Fenton et al. 2014, Halliday et al. 2017). Thus, within-host interactions may best be inferred from combinations of observational approaches.

To best make use of our results, we first need to understand the systems in which within-host priority effects are most likely to create unimodal prevalence relationships. First, the lifetime fitness of a parasite must be highest or lowest when it is the first parasite to infect a host (as compared to when it is in single infections and when it is the second parasite to infect a host). These types of priority effects were documented in eight out of 16 of the studies we found on intra-specific within-host interactions which compared the fitness of parasites in single infections, coinfections with first arrival, and coinfections with second arrival (Table 1); however, it is important to note that we do not know how representative these 16 studies are of all systems. Unimodal prevalence relationships will also be most likely when coinfection is common, as occurs in plant-pathogen communities or gut macroparasite communities in mammals (Petney and Andrews 1998, Fitt et al. 2006).

Finally, unimodal prevalence relationships are not limited by transmission mode, as our results hold for various transmission modes, including environmentally transmitted parasites (as in Lohr et al. 2010, Hoverman et al. 2013, Fig. 3), density-dependent directly transmitted parasites (as in Adame-Álvarez et al. 2014, Natsopoulou et al. 2015, Supplementary material Appendix 1 Fig. A1), and frequency-dependent directly transmitted parasites (de Roode et al. 2005, Levin 2007, Hall and Little 2013, Marchetto and Power 2017, Rynkiewicz et al. 2017, Supplementary material Appendix 1 Fig. A2), as well for various types of within-host priority effects, including within-host priority effects which alter parasite transmission (Fig. 3), parasite induced mortality (Supplementary material Appendix 1 Fig. A3), and parasite clearance (Supplementary material Appendix 1 Fig. A4).

The condition that must be met to create unimodal prevalence relationships (highest or lowest parasite fitness in coinfected hosts with first arrival) is simple in theory, but several factors complicate it in practice. First, specific host or parasite genotypes may interact with arrival order to determine parasite fitness. For example, coinfection only facilitates the parasite *Pyrenophora* when it arrives first in coinfected hosts in two out of three host genotypes tested in Al-Naimi et al. (2005). Second, host age at infection can intrinsically alter parasite fitness (Hoverman et al. 2013, Halliday et al. 2017). As the prevalence of a parasite increases, the average host age at infection will decrease, and the chances of the parasite being the first to infect a host will increase. Unimodal prevalence relationships may then be disrupted if infecting younger hosts has an opposite effect on parasite fitness than arriving first in coinfected hosts. Thus, while we have shown that priority effects may create unimodal prevalence relationships, the specific biology of coinfected systems must be considered before our theory is applied.

We should also understand the conditions that will prevent unimodal prevalence relationships. In systems where hosts are most likely to clear their infections or die before they become coinfected, prevalence relationships will be largely driven by environmental co-variates or how both parasites alter the pool of susceptible hosts (Rohani et al. 2003). Another factor to consider is that coinfections can synergistically increase or decrease host mortality (Alizon et al. 2013). As coinfected host mortality increases, the total transmission from coinfected hosts will most likely decrease, making differences between transmission rates of coinfected classes less important.

Our results were based on an analysis of equilibrium conditions, but within-host priority effects may have an even larger impact on non-equilibrium dynamics, when different epidemic phenologies might bias the order of infection in coinfected hosts. Shifting host and parasite phenologies alter infection prevalence in multi-parasite epidemics by interacting with within-host priority effects (Halliday et al. 2017). Thus, we must create a theoretical framework to predict how phenology will alter feedbacks between within-host and between host processes during non-equilibrium conditions. This is especially true as it is often difficult to apply theory based on equilibrium conditions to non-equilibrium settings, as changes in the prevalence of one parasite will rarely be the only effect on the prevalence of other parasites in the system, and will be confounded by changes in host population density, proportion of resistance hosts, and environmental changes.

Ultimately, within-host priority effects are a potentially common trait of parasite communities that our results indicate may have important impacts on infection patterns at the host population-scale. Given that research on priority effects has been an important development in understanding community assembly and function in free-living communities (Fukami 2015, Fukami et al. 2016), more research should be devoted to understanding the extent to which within-host priority effects alter patterns of infection in natural communities.

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Supplementary material (available online as Appendix oik-05937 at <www.oikosjournal.org/appendix/oik-05937>). Appendix 1.