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LETTER

Parasite consumption and host interference can inhibit disease spread in dense populations

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Abstract

Disease dynamics hinge on parasite transmission among hosts. However, canonical models for transmission often fit data poorly, limiting predictive ability. One solution involves building mechanistic yet general links between host behaviour and disease spread. To illustrate, we focus on the exposure component of transmission for hosts that consume their parasites, combining experiments, models and field data. Models of transmission that incorporate parasite consumption and foraging interference among hosts vastly outperformed alternatives when fit to experimental data using a zooplankton host (*Daphnia dentifera*) that consumes spores of a fungus (*Metschnikowia bicuspidata*). Once plugged into a fully dynamic model, both mechanisms inhibited epidemics overall. Foraging interference further depressed parasite invasion and prevalence at high host density, creating unimodal (hump-shaped) relationships between host density and these indices. These novel results qualitatively matched a unimodal density–prevalence relationship in natural epidemics. Ultimately, a mechanistic approach to transmission can reveal new insights into disease outbreaks.

Keywords

Daphnia, foraging, host–parasite, interference, parasite consumption, transmission.

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INTRODUCTION

Epidemiologists focus a lot of attention on disease transmission because it fundamentally shapes interactions between hosts and their parasites and the dynamics of disease. Indeed, the particular mode of transmission can determine a parasite's ability to invade, spread throughout and harm host populations (Anderson & May 1986, 1992). To illustrate this point, consider two canonical functions for transmission, density and frequency dependence. Parasites transmitted with density dependence require a minimum (threshold) population density of susceptible hosts to start an epidemic. For these parasites, transmission and infection prevalence increase as host density rises (Anderson & May 1992; Keeling & Rohani 2008). In sharp contrast, parasites transmitted with frequency dependence do not require such a threshold population density of susceptible hosts to invade. Furthermore, their transmission rates do not depend on host density. Therefore, these parasites should not reach higher prevalence as populations become more dense (Anderson & May 1992; Keeling & Rohani 2008). Such stark differences between these classic examples illustrate how disease dynamics can hinge on transmission biology. Therefore, we must deeply understand transmission to explain and predict the emergence, spread and consequences of disease.

A major problem arises when trying to use these canonical transmission models, however. They often perform poorly in empirical tests of transmission across host and parasite gradients (Dwyer *et al.* 1997; Fenton *et al.* 2002; Ryder *et al.* 2005; Ben-Ami *et al.* 2008) or when fit to time series data (Smith *et al.* 2009). This shortcoming usually arises because transmission changes in nonlinear ways with host or parasite density. One solution to this problem involves replacing linear per capita transmission rates with generic but phenomenological, nonlinear ones (Hochberg 1991; McCallum *et al.* 2001; Fenton *et al.* 2002). These more complex phenomenological functions often provide a better fit to experimental and observational data. They also suggest unique consequences for the invasion, persistence and stability of host–parasite systems (Hochberg 1991; McCallum *et al.* 2001; Fenton *et al.* 2002; Ryder *et al.* 2007; Smith *et al.* 2009). However, they still lack potentially important biology – they cannot identify the mechanisms underlying transmission. Therefore, why not build models around key mechanisms of host ecology, behaviour or immunity that influence transmission? This approach would likely produce superior yet parsimonious predictions for disease transmission. Perhaps more importantly, it might better predict the emergence, spread and impact of parasites for host populations.

To illustrate the promise of such a mechanistic approach to modelling transmission, we focus on the exposure of hosts to their parasites. For a broad array of diseases, hosts contact their parasites while foraging (e.g. mammals – anthrax/worms [Arneberg *et al.* 1998], gypsy moths – viruses [Parker *et al.* 2010] and shellfish – trematodes [Thieltges *et al.* 2008]). Although these types of parasites can substantially impact livestock and wildlife populations, theory for transmission through consumption-based exposure remains surprisingly underdeveloped. However, the tight connection between foraging and exposure could reveal general mechanisms underlying the transmission process. For example, while foraging rate of hosts should determine exposure to these parasites, consumption by hosts depletes parasites from the environ-

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ment. Parasite depletion should reduce overall transmission and should occur most strongly in dense host populations. In addition, foraging hosts may interfere with each other through physical interactions, territorial defence, harassment or infochemicals, especially at high host densities (Skalski & Gilliam 2001; Vahl *et al.* 2005; Hargrave *et al.* 2011). If interference reduces foraging rates, it could reduce exposure – and therefore depress transmission. Thus, these components of foraging biology might inhibit disease spread at high host densities.

We evaluated the performance of foraging-based transmission functions and their population-level implications using models, experiments and field data. First, we constructed models of transmission that infuse parasite consumption and host interference. We then parameterised and competed these models with density-dependent and phenomenological alternatives. The data stemmed from an experiment using a zooplankton host (*Daphnia dentifera*) that inadvertently consumes infectious stages (spores) of its fungal parasite (*Metschnikowia bicuspidata*) while eating its algal resource. The mechanistic model constructed with parasite consumption and host interference provided the best fit to the data, vastly outperforming each alternative. Then, once plugged into a fully dynamic epidemiological model, these two foraging processes depressed epidemic size relative to that predicted under classic density-dependent transmission. Furthermore, strong foraging interference could depress or even prevent epidemics at *high* host densities, thereby causing parasite invasion (R_0) and equilibrial prevalence to become unimodal (hump-shaped) functions of host density. This surprising result contradicts standard ideas linking host density to epidemic size (reviewed above). Still, it forecasts the unimodal density–prevalence relationship seen in a field survey of fungal epidemics in *Daphnia*. Thus, by building a mechanistic yet general representation of transmission, we gleaned new insights into factors that drive variation in disease epidemics

METHODS AND RESULTS

Disease system

The host, *Daphnia dentifera,* is a widespread invertebrate grazer in small, thermally stratified freshwater lakes in the mid-western USA (Herbert 1995). Hosts become infected with the virulent fungus, *Metschnikowia bicuspidata*, after inadvertently consuming free-living spores (Ebert 2005; Hall *et al.* 2007). The fungus reproduces within the haemolymph of infected hosts, substantially reducing reproduction and survival (Hall *et al.* 2009b). New infectious spores are released into the environment only after the host dies (Ebert 2005). As dominant grazers (Tessier & Woodruff 2002; Hall *et al.* 2010b), *Daphnia* could substantially deplete free-living spores from the environment (Hall *et al.* 2009a). In addition, *Daphnia* exhibit strong interference competition. Per capita foraging rates of *Daphnia* decline at high densities, in part due to physical interactions. *Daphnia* also engage in potent chemical interference. Simply exposing *Daphnia* to water that was previously inhabited by conspecifics or congeners can substantially depress foraging rates (Matveev 1993; Hargrave *et al.* 2011). In contrast, *D. dentifera* foraging rates do not depend on the presence or density of parasites (see Appendix S1 in Supporting Information). Thus, physical and chemical interference among hosts could reduce transmission at high host densities.

Submodel parameterisation

Transmission models

We built submodels of disease transmission when hosts consume free-living parasites. The key epidemiological component is the per capita transmission rate, T_R, and its connection, or lack thereof, to per capita foraging rate of hosts, F_R. Each submodel focuses on foraging and the infection processes alone. Therefore, they ignore host births and deaths, which occur on timescales longer than the 1-day experimental exposure. We sought to select among these competing models for transmission. Then, we inserted three of the submodels into a fully dynamical epidemiological model, one that includes births, deaths, etc. With this full model, we could then characterise the implications of foraging-exposure connections for disease dynamics at the population level (see the *Dynamic epidemiological model* section below).

To build the competing transmission models, we can start with a general template (Eqn 1). In this general model, susceptible hosts, S, become infected, I, after consuming free-living parasites, Z. Parasite consumption is proportional to per capita foraging rate, F_R, of all hosts, (S+I). Infection then proceeds at the per capita transmission rate, T_R:

$$dS/dt = -T_R \times S \times Z \quad (1a)$$

$$dI/dt = T_R \times S \times Z \quad (1b)$$

$$dZ/dt = -F_R \times (S + I) \times Z \quad (1c)$$

We specify each function for rates of transmission, T_R, and foraging, F_R, in Table 1 (see Eqns 2–6).

First, we present two fairly standard transmission models with which we can compare the performance of our foraging-based models. We designated classical density-dependent transmission without parasite consumption as a null model (Fenton *et al.* 2002; Hall *et al.* 2007; Ben-Ami *et al.* 2008, 2010). For the *density-dependent model*, susceptible hosts become infected at a constant per capita transmission rate, β, but they do not deplete parasites (Eqn 2 a,b, Table 1a). Often, this model is competed against a flexible, nonlinear, but phenomenological transmission function (Eqn 3a,b; Hochberg 1991; Fenton *et al.* 2002). For the *phenomenological model*, the exponents p and q allow the per capita transmission rate to increase ($p > 0$, $q > 0$) or decrease ($p < 0$, $q < 0$) with host or parasite density respectively. This model reduces to the *density-dependent model* when $p = q = 0$. Following other applications of this model (Fenton *et al.* 2002), we assumed no parasite consumption, that is, $F_R = 0$.

Then, we built three foraging-based transmission functions. In each case, we specified the per capita foraging rate of hosts, F_R. Hosts become exposed to parasites at this rate, but they also remove these parasites from the environment (Eqn 1c). We specified the per capita transmission rate, T_R, as the product of the foraging rate and the susceptibility of hosts per parasite consumed, u (i.e. for each model $T_R = u \times F_R$). We first incorporated parasite consumption by foraging hosts at a constant (i.e. density-independent) rate, f, in the *constant foraging model*. (eqn 4 a,b). Next, we added

Table 1 (A) Construction of the competing models for disease transmission. (B) Results of the model selection analysis for all models fit to the infection data (*Competition 1*). (C) Results of the model selection analysis for the three foraging-explicit models fit to the infection and parasite consumption data (*Competition 2*)

(A). *Model building*: competing models for disease transmission

Model	Foraging rate (F_R)[1]	Equation	Transmission rate (T_R)[1]	Equation
Density dependent (null)	0	2a	β	2b
Phenomenological	0	3a	$\beta S^{q} Z^{q}$	3b
Constant foraging	f	4a	uf	4b
Linear interference	$f(1\text{-}c_f N)$	5a	$uf(1-c_f N)$	5b
Exponential interference	$f\exp(\text{-}c_f N)$	6a	$uf\exp(-c_f N)$	6b

(B). *Competition 1*: Model selection results using infection data only

Model	Parameters[2]	AIC	ΔAIC[3]	Akaike weight (w_j)[4]
Linear interference	4	541.5	0	0.98
Exponential interference	4	549.3	7.8	0.02
Constant foraging	3	557.1	15.6	4.0×10^{-4}
Phenomenological	4	564.3	22.8	1.1×10^{-5}
Density dependent (null)	2	615.4	73.9	8.8×10^{-17}

(C). *Competition 2*: Model selection results using infection and spore consumption data

Model	Parameters[2]	AIC	ΔAIC[3]	Akaike weight (w_j)[4]
Exponential interference	5	697.0	0	0.70
Linear interference	5	698.7	1.7	0.30
Constant foraging	4	727.1	30.1	2.0×10^{-7}

[1]Per capita rates.
[2]Number of estimated parameters. For *Competition 1*, we also estimated a common beta-binomial overdispersion parameter, θ. For *Competition 2*, we estimated θ and a common standard deviation for the parasite consumption data, s.
[3]The winning model has ΔAIC = 0. In general, ΔAIC > 10 indicates poor performance.
[4]Akaike Weights represent the probability that the model is the best among those under consideration.

interference among foraging hosts as a negative density dependence on foraging rate, so now $F_R = f(N)$, where N is total host density, $S + I$. We represented $f(N)$ in two different ways. Neither of these representations, however, use existing functional responses based only on physical interference (reviewed in Skalski & Gilliam 2001) – they are not appropriate for the chemical interference involved (Hargrave *et al.* 2011). Instead, we first considered a *linear interference model* (Eqn 5 a–b). In this model, foraging rate, and therefore exposure, declines at a linear rate (at strength c_f) with host density: $f(N) = f(1-c_f N)$. Then, to allow for a nonlinear decline in foraging rate due to interference, we built an *exponential inference model* (Eqn 6a, b). In this model, increases in host density cause a relative decrease (governed by c_f) in foraging/exposure rate: $f(N) = f\exp(\text{-}c_f N)$. In both cases, we assumed that both host classes (S and I) depress foraging equivalently.

Infection experiment

Each transmission model yields distinct predictions for disease transmission across density gradients of hosts and parasites. Therefore, we parameterised and competed these models with data from an infection experiment in which we manipulated the density of *Daphnia* hosts and fungal spores. We used a single clone of *D. dentifera* and a fungal isolate collected from Baker Lake, Michigan, USA. We raised hosts in filtered (1 μm) lake water, and cultured the parasite *in vivo*. We exposed 7-day-old *Daphnia* to fungal spores for 24 h in 50-mL filtered lake water in centrifuge tubes at favourable conditions (20 °C, 16 : 8 light : dark cycle, fed 1.0 mg dry weight L^{-1} of a nutritious green alga (*Scenedesmus acutus*)]. We manipulated the density of hosts [1 (n = 20 replicates per parasite density), 4 (n = 12), 8 (n = 8), 12 (n = 6), 16 (n = 4) hosts per tube) and parasites (10, 30, 60, 150, 250 spores mL^{-1})] factorially. These host density treatments generally correspond to densities potentially experienced by *Daphnia* during epidemics in our focal lakes (DJ Civitello *et al.*, unpublished data). In total, there were 1340 *Daphnia* in 250 tubes. After 24 h, we transferred all hosts to new water, free of spores and maintained them for 11 days until diagnosis. We visually diagnosed infections using a dissecting microscope (Ebert 2005). For treatments in which we exposed more than four hosts in a single tube, we transferred the hosts from a single replicate to multiple tubes, at a maximum density of four hosts per tube, to maximise survival until infections became visible.

We also estimated the density of parasites remaining (i.e. not consumed) after the 1-day exposure in 65 replicates from the two highest spore-density treatments. These parasite-density counts facilitated more direct estimates of the *Daphnia* foraging parameters (f and c_f, see *Competition 2* below). We estimated parasite density by staining, filtering and then counting spores in water samples (see Appendix S2 for more details; Civitello *et al.* 2012).

Parameterisation and submodel selection

We present full details for the parameterisation and model selection in Appendix S2. Therefore, we briefly outline our methodology here. In general, we followed standard maximum likelihood techniques to parameterise and compete models of transmission using the results of infection experiments (Burnham & Anderson 2002; Hall *et al.* 2007; Rachowicz & Briggs 2007; Ben-Ami *et al.* 2008). We fit the models using the mle2 function in the bbmle package in R (R Development Core Team 2008). First, in *Competition 1*, we fit and competed all models using only the infection data and assuming a beta-binomial distribution ("Infection data only," Table 1b, Fig. 1). Second, in *Competition 2*, we fit the foraging-explicit models (Eqns 4–6) simultaneously to the infection and parasite consumption data (assuming a log-normal distribution) using an integrated modelling approach (Besbeas *et al.* 2005; see Appendix S2 for details). We then ranked the performance of each model with statistics derived from Akaike information criterion (AIC; Burnham & Anderson 2002). We used ΔAIC to rank relative model performance, and calculated Akaike weights, w_j, for each model (see Table 1 and Appendix S2).

Results from transmission experiment and model selection

In the transmission experiment, infection prevalence generally increased with spore density, but decreased with host density (Fig. 1). When fit to the infection data only (*Competition 1*; Table 1b), the models varied greatly in their ability to match these observations. The *density-dependent model* fit the infection data very poorly because it predicted constant infection prevalence across the host density gradient (ΔAIC = 73.9, $w = 8.8 \times 10^{-17}$; Fig. 1a). The *phenomenological model* exhibited a decrease in prevalence from low to high host densi-

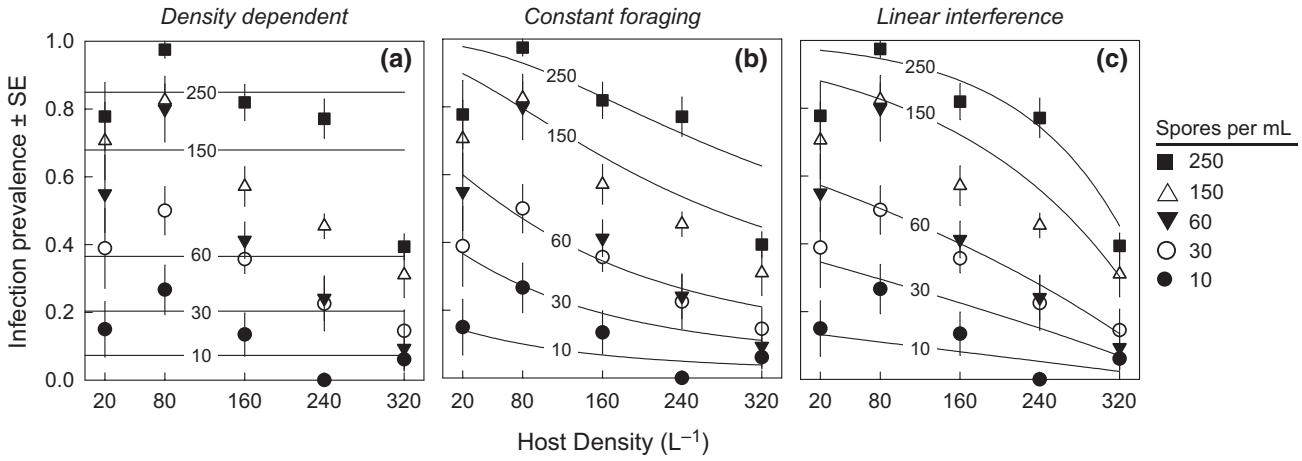

Figure 1 Results of *Competition 1* (infection data only). Best-fit predictions of three focal transmission models for the infection prevalence results (mean ± SE). (a) The *density-dependent* model readily anticipates increasing infection prevalence with spore density. However, it cannot match the decrease in prevalence with host density. In contrast, the models that included parasite consumption and interference performed much better. (b) The *constant foraging* model anticipated the decline in infection prevalence with increasing host density. However, (c) the *linear interference* model fit the data superiorly. It best captured the sharp decline in infection prevalence with host density. Best-fit predictions for the other two models shown in Table 1 are presented in Appendix S2.

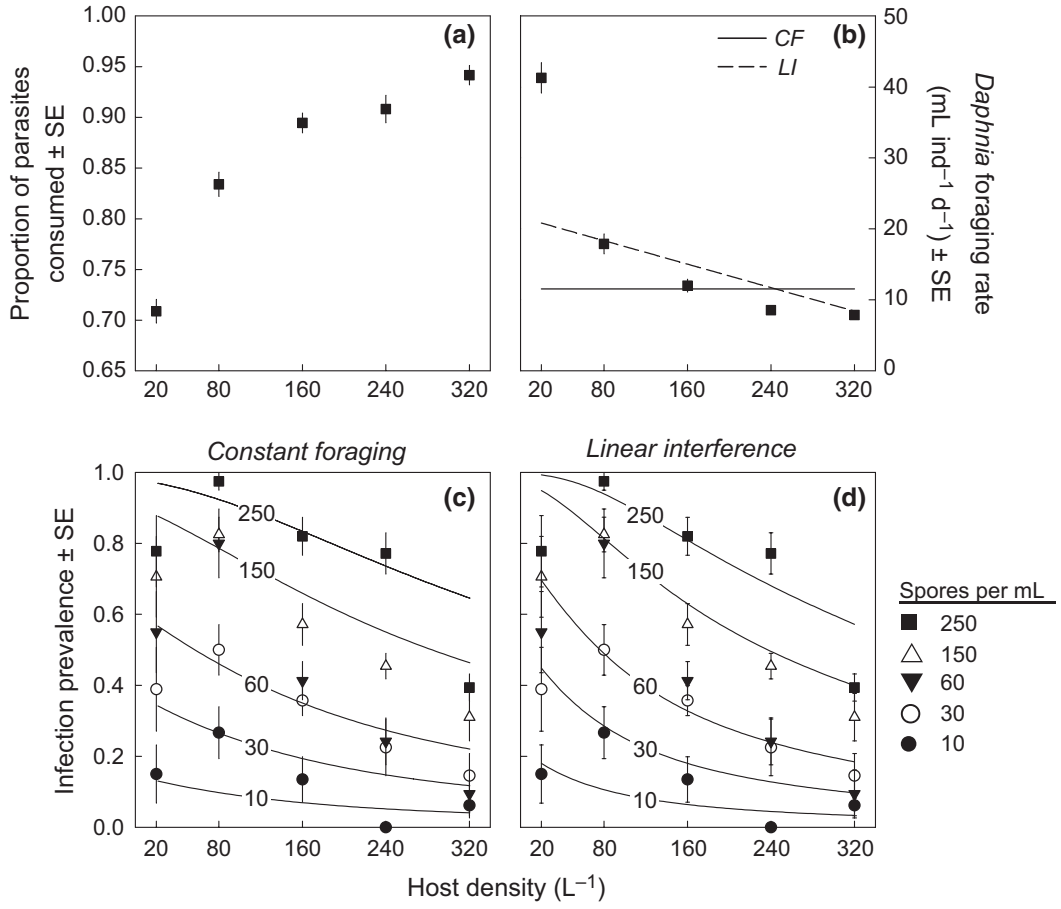

Figure 2 Results of *Competition 2*, using infection and parasite consumption data. (a) The proportion of parasites consumed by hosts during the 1-day exposure (mean ± SE) increased with host density. (b) However, the per capita foraging rate of hosts (mean ± SE) decreased with host density – indicating foraging interference. When fit simultaneously to the infection and parasite consumption data, the *constant foraging* (CF) model (c, solid line in b) performed extremely poorly. In contrast, the *linear interference* (LI) model (d, dashed line in b) and the *exponential interference* model (see Appendix S2) fit the data equally well (see Table 1c).

ties. However, it still performed quite poorly because it overestimated infection prevalence at the highest host density (ΔAIC = 22.8, $w = 1.1 \times 10^{-5}$; see Appendix S2). The *constant foraging model* performed much better than the density dependent and phenomenological models (ΔAIC = 15.6, $w = 4.0 \times 10^{-4}$; Fig. 1b). The *exponential interference model* improved further upon this fit (ΔAIC = 7.8, $w = 0.02$; see Appendix S2). However, the *linear interference model* provided a substantially better fit than all of the other models considered (ΔAIC = 0, $w = 0.98$: Fig. 1c).

In the second analysis (*Competition 2*; Table 1c, Figure 2), the foraging-explicit models simultaneously fit the infection and parasite consumption data sets. Hosts consumed a large majority of the free-living spores, especially as host density increased (Fig. 2a). However, per capita foraging rates declined with host density (Fig. 2b). Both the linear (ΔAIC = 1.7, $w = 0.30$) and exponential interference models (ΔAIC = 0, $w = 0.70$) simultaneously fit both data sets substantially better than the constant foraging model (ΔAIC = 30.1, $w = 2 \times 10^{-7}$; Table 1b, Fig. 2). In this case, the linear and exponential interference models fit the observations similarly well. The interference model fit the infection data better, but the exponential interference model fit the parasite consumption data better. (The overall performance of each model reflects this statistical compromise because the integrated modelling approach maximises the simultaneous fit to both data sets. See Appendix S2 for the fit of the *exponential interference* model). Overall, parasite consumption and host interference provided the best representation of transmission in the experiment.

Dynamic epidemiological model

Model formulation

We used a fully dynamic epidemiological model to investigate how these foraging mechanisms, evaluated in the submodel competitions, could influence parasite invasion (R_0), disease spread (equilibrial prevalence) and harm to the host population. We compared three transmission submodels: *density dependent (null)*, *constant foraging* and *linear interference*. We plugged each submodel into a general, fully dynamic epidemiological model for a free-living parasite. We then determined the parasite's basic reproductive ratio, R_0, the equilibrium prevalence of infection, and the equilibrium density of susceptible hosts after parasite introduction across a gradient of host density. The R_0 quantity is an indicator of disease spread, and the parasite can initiate an epidemic (invade) if $R_0 > 1$. The epidemiological model tracks changes in density of susceptible hosts (S), infected hosts (I) and fungal spores (Z) through time (t) following a set of differential equations:

$$dS/dt = b(S + \rho I)(1 - c_b(S + I)) - dS - TR \times SZ \quad (7a)$$

$$dI/dt = T_R \times SZ - (d + v)I \quad (7b)$$

$$dZ/dt = \sigma(d + v)I - mZ - F_R \times (S + I)Z \quad (7c)$$

Susceptible hosts increase with density-dependent births, governed by the maximal birth rate (b) for both host classes, but reduced by the strength of density dependence (c_b). Infected hosts may exhibit reduced fecundity ($0 \leq \rho \leq 1$). Hosts die at background death rate d (Eqn 7a). Susceptible hosts also decrease through infection at the per capita transmission rate T_R. We incorporated the transmission submodels by inserting the per capita foraging, F_R, and transmission, T_R, rates defined for each submodel (*density dependent*, *constant foraging* and *linear interference*). Infected hosts increase through infection, at rate T_R, and die at an elevated rate due to virulent effects of infection, $d + v$ (Eqn 7b). Free-living parasites increase through release from dead infected hosts, with per capita yield σ; they decrease at a constant rate, m; and they are consumed by hosts at the per capita foraging rate F_R (Eqn 7c). Notice that there is negative density dependence on the host birth rate in this family of models. Furthermore, there is negative density dependence on the host foraging rate (F_R) and therefore the transmission rate (T_R) in the linear interference model. Finally, in principle, other traits may also be affected by host foraging rate. However, we took an all-else-equal approach to isolate the effects of foraging-based transmission.

Parasite invasion, prevalence and regulation of hosts

We used both analytical and simulation-based approaches to study the dynamical model. We found analytical solutions for R_0 for each model (see Appendix S3). However, when both per capita birth and foraging rates decline with density, the models become analytically intractable. Therefore, we examined equilibrial prevalence and susceptible host density by numerically integrating the models with the lsoda function in R (R Development Core Team 2008). We varied equilibrium host density without disease by changing the strength of density dependence on host birth rate, c_b (where low values yield high densities). We only considered biologically feasible cases in which $c_b > c_f$ (this ensures that per capita feeding rates remain positive across all host densities). We then simulated each model with high and low estimates of per-parasite susceptibility for hosts, u, spanning a range estimated previously for the host (Table 2).

With classic *density-dependent* transmission R_0 is a linear function of host density without disease (Fig. 3a, b solid lines). Equilibrial prevalence increases monotonically with density (Fig. 3c, d). Susceptible hosts (S^*_{int}) are regulated at a level independent of the disease-free carrying capacity (Fig. 3e, f). With the *constant foraging* model, R_0 still increases linearly with host density (Fig. 3a, b dotted lines), albeit with a smaller slope compared with the density-dependent model. Equilibrial prevalence still increases monotonically with density, but it reaches a lower asymptote (Fig. 3c, d). Furthermore, equilibrial density of susceptible hosts during an epidemic now increases with the disease-free carrying capacity (Fig. 3e, f). Thus, parasite depletion reduces the parasite's ability to regulate the host population. The *linear interference* transmission model further alters disease dynamics; the R_0 equation becomes a unimodal (quadratic) function of host density (Fig. 3a, b, dashed line). This occurs because increasing density decreases the host – parasite contact rate (*Daphnia* foraging rate). High host densities can even suppress R_0 below 1, preventing parasite invasion. Equilibrial prevalence also becomes a unimodal function of host density (Fig. 3c, d). If the parasite persists, its negative effects on host density are weakened further by interference (i.e. S^*_{int} is higher, Fig. 3e, f). Thus, the linear interference model recaptures the classic lower density threshold required for parasite invasion, but it reveals another, higher threshold, above which the parasite cannot invade (see Appendix S3 for more details). In general, these disease-inhibiting effects increase as host

Table 2 State variables and parameters used in the epidemiological model (Eqn 7a–c)

Term	Units	Definition	Value	Source
State variables				
S	host L^{-1}	Density of susceptible hosts	–	
I	host L^{-1}	Density of infected hosts	–	
Z	spore L^{-1}	Density of free-living parasites	–	
Parameters:				
b	day^{-1}	Maximum birth rate of hosts	0.30	(Hall *et al.* 2010a)
ρ	–	Relative fecundity of infected hosts	1	Plausible value
c_b	L $host^{-1}$	Strength of density dependence on host birth rate	varied	
c_f	L $host^{-1}$	Strength of host foraging interference	1.9×10^{-3}	This study[1]
d	day^{-1}	Background death rate of hosts	0.05	(Duffy & Sivars-Becker 2007)
u	host $spore^{-1}$	Per-parasite susceptibility of hosts (low, high)	2.03×10^{-4}, 1.16×10^{-3}	This study[1], (Hall *et al.* 2010a)
f	L $host^{-1}$ day^{-1}	Maximum foraging rate of hosts	2.17×10^{-2}	This study[1]
v	day^{-1}	Parasite virulence on survival	0.05	(Duffy & Sivars-Becker 2007)
σ	spore $host^{-1}$	Parasite yield from infected hosts upon death	7.5×10^{3}	Hall *et al.* in review
m	day^{-1}	Loss rate of free-living parasites	0.9	Plausible value[2]

[1]Maximum likelihood estimates from *linear interference* model in *Competition 2*.
[2]Incorporates loss of free-living parasites due to UV/PAR damage (Overholt *et al.* 2012), consumption by other species (Hall *et al.* 2009a) and sinking.

density in systems without disease becomes higher (larger S^*_{bnd}, smaller c_b) and as host susceptibility decreases (lower u; Fig. 3).

Field survey

Field survey methods

We looked for the predicted unimodal relationship between density and prevalence using a field data set. We surveyed natural epidemics of *Metschnikowia* among *Daphnia* populations in 19 lakes in southern Indiana, USA, weekly from August to December 2009. At each visit, we collected zooplankton with vertical tows of a Wisconsin bucket net, then estimated *Daphnia* density and infection prevalence using a dissecting microscope (Hall *et al.* 2009b). Epidemics typically begin between August and September, and they can significantly reduce host density (Hall *et al.* 2011). Therefore, we estimated initial host density as the average density from 15 August to 15 September 2009. We tested for a unimodal relationship between initial host density (log transformed) and peak prevalence of infection using quadratic regression and the Mitchell-Olds Shaw test (MOS-test; Mitchell-Olds & Shaw 1987) implemented using the MOS test function from the vegan package in the R Statistical Computing Language (R Development Core Team 2008; Oksanen *et al.* 2012). The MOS-test relies on quadratic regression to test the null hypothesis of a monotonic (i.e., not unimodal) relationship (Mitchell-Olds & Shaw 1987; Leibold 1999).

Field survey results

There was a significant unimodal relationship between host density and maximum prevalence (Fig. 4, MOS-test, $P = 0.029$). There was a significant negative quadratic coefficient (quadratic regression: $Density^2$: $P = 0.009$). This indicates a maximum epidemic size at intermediate initial host density.

DISCUSSION

Transmission critically shapes host–parasite dynamics (Anderson & May 1992). However, the canonical, classic representations of transmission often do not adequately capture changes in transmission with host or parasite density (Hochberg 1991; McCallum *et al.* 2001; Fenton *et al.* 2002). Phenomenological approaches to modelling transmission may better match these changes in a statistical sense, but they ignore the key mechanisms driving transmission. Instead, models of transmission that infuse these mechanisms could provide deeper insights into the emergence and impacts of infectious disease on host populations. To illustrate this focal point, we quantified disease transmission across gradients of *Daphnia* hosts and fungal parasites. By emphasising how foraging biology – and thus parasite exposure – interacted with gradients of host density, we revealed key mechanisms influencing transmission in this system. More specifically, a model competition showed how two key components of foraging biology, parasite consumption and foraging interference, drove transmission. The *linear interference model* statistically crushed the standard and phenomenological alternatives. One component of this foraging-based representation of transmission (foraging interference) then produced a surprising unimodal relationship between host density and disease prevalence in a fully dynamic model.

Parasite consumption plays a central role in a suite of results in this study. Parasite consumption underpinned the outcome of the infection experiment because it reduced transmission at high host densities. At the population level, our results reiterated that parasite removal by hosts can inhibit parasite invasion, slow disease spread and diminish the negative effects of epidemics on host density relative to classic density-dependent transmission. (However, parasite depletion alone did not cause the unimodal relationship between disease and density.) These points may apply broadly: depletion of parasites by hosts themselves may affect disease spread for many host species that consume their free-living parasites. This depletion biology means that hosts that consume parasites quickly might become infected faster (all else equal), but rapid depletion of parasites through consumption also reduces infection risk for other hosts. Furthermore, other, non-host species, such as competitors or predators, may also consume parasites (Kagami *et al.* 2007; Hall *et al.* 2009a; Orlofske *et al.* 2012). If these resistant species rapidly consume parasites, they too could potently inhibit epidemics in

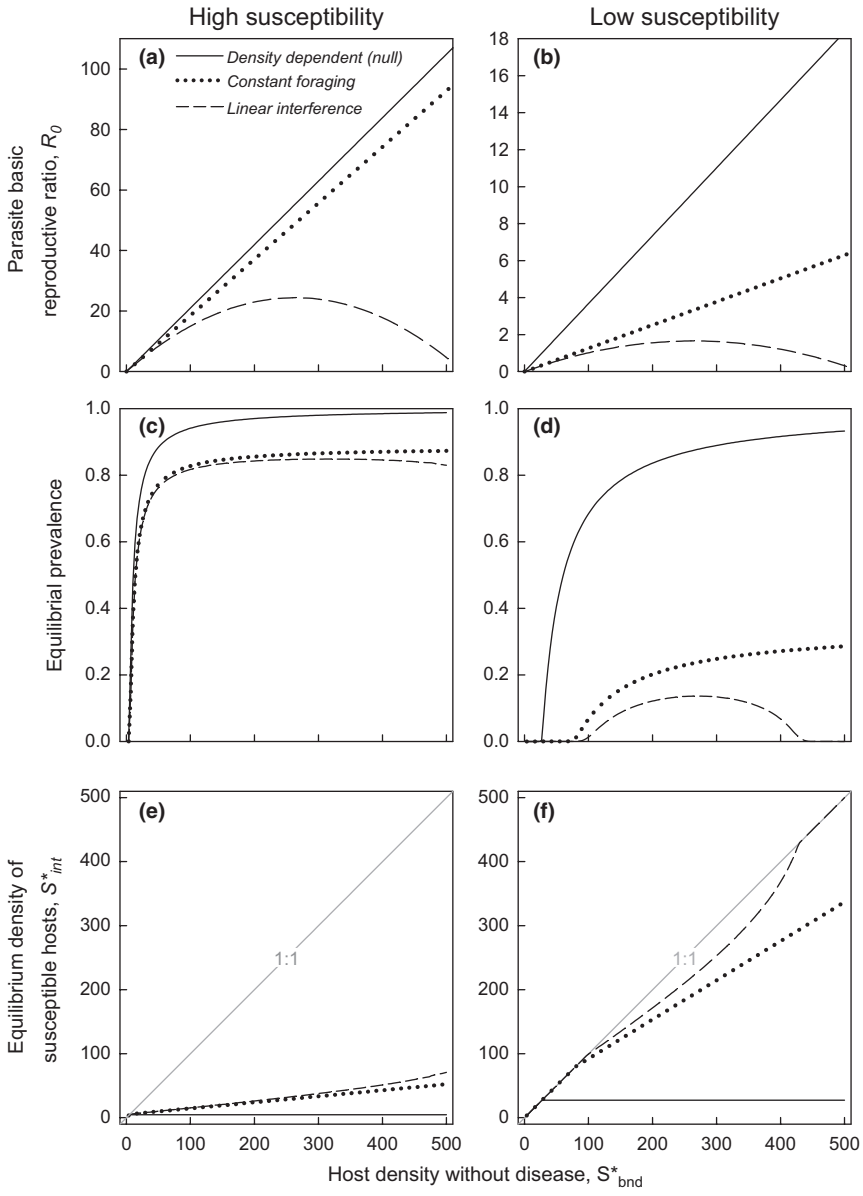

Figure 3 Dynamics from the epidemiological model with the three transmission submodels, simulated at high (panels a, c, e) and low (b, d, f) susceptibility of hosts (*u*). With *density-dependent* transmission (solid line), (a, b) the parasite reproductive ratio (R_0), (c, d) equilibrial prevalence of infection and (e, f) suppression of susceptible hosts all increase with disease-free host density (note the 1 : 1 line). Under the *constant foraging* model (dotted line), R_0 and equilibrial prevalence still increase with host density, but at a lower rate. However, the equilibrial density of susceptible hosts during the epidemic now increases with host density. With the *linear interference* model, R_0 and equilibrial prevalence become unimodal (hump-shaped) functions of host density. Suppression of the density of susceptible hosts by disease is weakened further.

focal hosts. Thus, parasite depletion by resistant species and maybe even more resistant genotypes within a focal host species could provide a mechanism for a dilution effect, the inhibition of disease spread in diverse communities (Keesing *et al.* 2006). Thus, parasite removal – by hosts and their competitors – merits increased attention in models and experiments.

The behavioural response of hosts to their own density also potently shaped transmission. Consumers often forage less efficiently at high density due to increases in territorial defence, physical interactions with other consumers or in response to infochemicals (Skalski & Gilliam 2001; Vahl *et al.* 2005; Hargrave *et al.* 2011). Interference competition has been repeatedly demonstrated for zooplankton grazers, such as *Daphnia*, through both chemical and physical mechanisms (Matveev 1993; Hargrave *et al.* 2011). Furthermore, interference among consumers can occur broadly across many taxa (Skalski & Gilliam 2001). Thus, it may be an important component of transmission whenever hosts contact their parasites while foraging – regardless of whether hosts substantially deplete parasites. Other ecological factors, such as resource density (Holling 1959), resource quality (Darchambeau & Thys 2005) and fear of predation (Rohr *et al.* 2009) can also modulate host foraging activity, and therefore exposure to parasites. Integrating interference competition with other ecological factors that influence exposure or immunity (e.g. Wilson *et al.* 2001, 2002) presents a promising avenue for

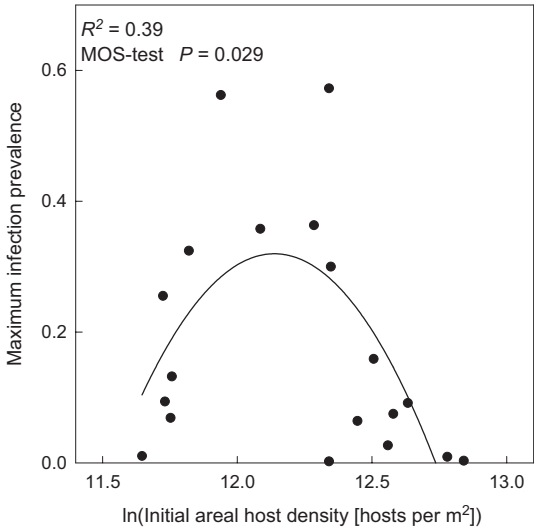

Figure 4 Results of the survey of natural epidemics among 19 lakes in southern Indiana, USA, in 2009. There was a significant unimodal relationship between maximum infection prevalence and the initial areal density of *Daphnia* hosts (MOS-test, $P = 0.029$). Epidemics grew largest in lakes with intermediate initial densities of *Daphnia*. Host density estimates are the average density from August 15 to September 15. Epidemics typically begin during early September. The fitted curve corresponds to a quadratic regression (Density^2: $P = 0.009$, $R^2 = 0.39$).

the further development of theory for transmission-while-foraging. As a pay-off, such theory may produce novel, testable insights regarding trophic cascades, indirect effects or ecosystem-level consequences for parasites embedded in food webs (Lafferty *et al.* 2008; Raffel *et al.* 2010).

The two focal components of foraging-based exposure – parasite depletion and host interference – together yielded novel implications for disease dynamics. The model with classic density-dependent transmission predicted that R_0, equilibrium prevalence, and suppression of susceptible hosts all increase monotonically with host density. Including parasite depletion by hosts reduced R_0 and equilibrium prevalence relative to density-dependent transmission. Still, the relationship between these quantities and host density remained qualitatively the same (i.e. they both increased with host density). However, foraging interference caused a qualitative change in the patterns between R_0 and host density and also prevalence and host density. Specifically, foraging interference caused these relationships to become unimodal (see Appendix S3 for theoretical support). These unimodal patterns may (or may not) occur in reasonable regions of parameter space for a given system. However, in zooplankton–fungus epidemics, the field survey qualitatively echoed this possibility: maximum infection prevalence responded unimodally to host density. These qualitative links between model prediction and field pattern suggest that parasite consumption and host interference could be important determinants of disease outbreaks in natural populations. The model also indicated that parasite removal and interference also substantially increase the equilibrium density of uninfected hosts after parasite invasion. This result could have implications for the conservation of species threatened by disease or the biological control of pests with parasites.

Disease dynamics hinge on the transmission process. Thus, we must model it more mechanistically. To uncover mechanisms that underlie transmission, we should scrutinise how hosts become exposed to parasites. In this study, transmission models that linked foraging ecology of hosts to disease transmission dominated a statistical competition. Foraging interference then provided a mechanism to qualitatively explain an unexpected field pattern of disease (a unimodal prevalence–density relationship in fungal epidemics in *Daphnia*). Ultimately, further integration of foraging ecology and transmission may catalyse deeper understanding of disease spread, host persistence and control strategies when parasites infect foraging hosts.

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AUTHORSHIP

DC and SH designed and analysed the infection experiment, DC and SP performed the experiment, SH and MD designed the field survey, DC and SH collected and analysed field survey data and all authors contributed to writing the manuscript.

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