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SYMPOSIUM

Predators and Patterns of Within-Host Growth Can Mediate Both Among-Host Competition and Evolution of Transmission Potential of Parasites*

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ABSTRACT: Parasite prevalence shows tremendous spatiotemporal variation. Theory indicates that this variation might stem from life-history characteristics of parasites and key ecological factors. Here, we illustrate how the interaction of an important predator and the schedule of transmission potential of two parasites can explain parasite abundance. A field survey showed that a noncastrating fungus (*Metschnikowia bicuspidata*) commonly infected a dominant zooplankton host (*Daphnia dentifera*), while a castrating bacterial parasite (*Pasteuria ramosa*) was rare. This result seemed surprising given that the bacterium produces many more infectious propagules (spores) than the fungus upon host death. The fungus's dominance can be explained by the schedule of within-host growth of parasites (i.e., how transmission potential changes over the course of infection) and the release of spores from "sloppy" predators (*Chaoborus* spp., who consume *Daphnia* prey whole and then later regurgitate the carapace and parasite spores). In essence, sloppy predators create a niche that the faster-schedule fungus currently occupies. However, a selection experiment showed that the slower-schedule bacterium can evolve into this faster-schedule, predator-mediated niche (but pays a cost in maximal spore yield to do so). Hence, our study shows how parasite life history can interact with predation to strongly influence the ecology, epidemiology, and evolution of infectious disease.

Keywords: parasitic castrators, virulence evolution, parasite competition, *Chaoborus*, obligate killers.

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Introduction

Parasites exhibit pronounced spatiotemporal variation in abundance, both within and among species (Schall and Marghoob 1995; Duffy et al. 2010). It remains challenging yet pressing to explain this variation, given increases in disease prevalence in a variety of systems. Theoretical studies of competition for hosts between parasites tell us that both life-history strategy and ecological constraints can determine competitive success and community structure of parasites (O'Keefe and Antonovics 2002; Holt et al. 2003). For instance, life-history strategies can grant certain parasites competitive superiority over others. One interesting strategy (pertinent to our argument below) is castration (sterilization), which is common among parasites of vertebrates, invertebrates, and some plants (Antonovics 2009; Lafferty and Kuris 2009). Parasitic castration is favored if it allows parasites to enhance their production of infectious propagules (Jaenike 1996; O'Keefe and Antonovics 2002; Ebert et al. 2004). Under some conditions, this propagule-production strategy could grant castrators a competitive advantage over other parasites (O'Keefe and Antonovics 2002). However, factors other than parasite life history also influence competitive outcomes. Notably, ecological forces can constrain or enhance the abundance of a given parasite. For instance, both abiotic factors, such as solar radiation, and biotic ones, such as selective predation, might reduce prevalence of a parasite (e.g., Packer et al. 2003; Overholt et al. 2012). If these ecological forces differentially affect fitness of one parasite versus another, they too could modulate competition between parasites. Thus, the spatiotemporal variation that we see in parasite abundance can reflect the outcome of competition, which, in turn, might be influenced by life-history strategy and/or ecological factors.

Here, we use a case study to argue that the interplay between parasite life history and ecological context can

govern competition between parasites (and, therefore, structure parasite communities). More specifically, interactions between life-history strategies and predation can explain a striking pattern in the prevalence of two obligately killing, spore-producing parasites. In Midwestern US lakes, a noncastrating fungus (*Metschnikowia bicuspidata*) dominates the assemblage of parasites infecting a common zooplankton host (*Daphnia dentifera*; Duffy et al. 2010; this study); meanwhile, a castrating bacterium (*Pasteuria ramosa*) remains starkly less prevalent. This result seemed surprising. As shown previously (Ebert 2005) and illustrated below with data and models, the castrating bacterium in our case study can enjoy an immense propagule-production advantage over the fungus. Thus, the bacterium might be expected to outcompete the fungus, since castrators can dominate parasite assemblages through competitive advantages stemming from their propagule-production strategy (Jaenike 1996; O'Keefe and Antonovics 2002). To resolve this discrepancy, we focus on how a key invertebrate predator and life-history schedules of parasites can jointly influence competition. Both factors, when combined, can reverse competitive outcomes and explain the dominance of the fungus.

We make this argument using three parameterized models that infuse key aspects of ecology (predators) and life history of parasites into a competition framework. The first two models act as a foil for the resolution-producing third model. We built this mechanistic yet general obligate killer version of the model for both parasites (Hall et al. 2006). It was parameterized using laboratory data that quantified parasite production and transmission rate of both parasites. This first model confirmed the anticipated superiority of the bacterial castrator: if hosts can release their maximal yield of spores upon death from infection, the castrating bacterium always outcompetes the noncastrating fungus. The second model changed a key assumption about spore release from infected hosts to better capture underlying natural history. In lakes, hosts dying from infection sink out of the system before releasing spores—an environmental trap facing both parasites (Cáceres et al. 2009). However, midge larvae (*Chaoborus* spp.) release spores of both parasites into the water column through "sloppy" predation on infected hosts (i.e., partial regurgitation of infected hosts after predation; Cáceres et al. 2009). Consequently, sloppy predators allow parasites to avoid the environmental trap. In our second model, these predators mechanically release only a fixed portion of the maximal spore production (i.e., this model does not take into account parasite life-history schedule.) Despite this new assumption about spore release, the second model still predicted dominance by the castrating bacterium. In other words, sloppy predation on its own does not grant a competitive edge to the fungus. Thus, it alone cannot explain the field pattern documented here.

The third model connected sloppy predation with a key aspect of parasite life history: the schedule of within-host growth of parasites. Many parasites differentially increase propagule density within hosts during the course of infection (Holt and Barfield 2006). These differences in time trajectories (schedule) matter because predators can truncate parasite growth within infected hosts. Here, differences in schedule between the competing parasites created a predator-mediated niche for the faster-schedule fungus to dominate over the slower-schedule bacterium. This differential schedule among parasites, however, did not stem from differences in maximal growth rate between the parasites. Instead, it arose from the time trajectory of transmission potential (spore density weighted by infectivity of spores). Since spores of the fungus are more infective (Auld et al. 2012, 2014), the fungus can enjoy higher transmission potential when sloppy predation truncates bacterial spore production within hosts. This difference provides a window of opportunity, mediated by sloppy predation, during which the noncastrating fungus can outcompete the otherwise superior castrating bacterium.

This fusion of predation and life history proves crucial for the fitness and competitive success of the parasites. It also prompted an obvious follow-up question: Does predation select on either parasite—but especially the slower-schedule, castrating bacterium—to evolve toward a faster schedule of transmission potential? In theory, increased mortality rate of hosts should select for more rapid replication of parasites growing within hosts (Anderson and May 1982; Kakehashi and Yoshinaga 1992; Lenski and May 1994; Ebert and Weisser 1997; although, see also Choo et al. 2003). Furthermore, more general theory predicts that high adult mortality selects for earlier investment in reproduction (Law 1979; Charlesworth 1980). Thus, higher intensity of sloppy predation might select for more rapid spore growth in the bacterium, enhancing its transmission potential and reducing the temporal window in which the fungus can dominate. A lab-based experimental evolution study supported this prediction: the bacterium, but not the fungus, produced spores more rapidly but at lower maximal yield in selection lines mimicking higher predation rate. Therefore, the bacterium showed the capacity to evolve into the faster-schedule niche, but with a cost (see also Paterson and Barber 2007; Nidelet et al. 2009). More broadly, this evolution result, coupled with the competition outcomes in model 3, shows how predators and life history of parasites can jointly shape the abundance, distribution, and evolution of parasites.

Methods and Results

Overview

This study integrates field data, experiments designed to parameterize a suite of models, analysis of the models, and an experimental evolution study. We first present the results of a field survey showing that the fungal parasite dominates host populations in two locations. Next, we used laboratory studies to quantify within-host growth rate and transmission potential of the two parasites. These experiments showed that, while the bacterium can ultimately produce many more spores, the fungus has a transmission potential advantage early in infections. We then used these data to parameterize three models (a standard obligate killer model, a model incorporating sloppy predation but not patterns of within-host growth, and a model incorporating both sloppy predation and patterns of within-host growth). These models revealed that sloppy predation creates a niche in which the fungus (the parasite with the faster schedule of transmission potential) can dominate over the castrating bacterium. Finally, a controlled natural selection experiment shows that the bacterium can evolve to better exploit this fast-schedule niche created by sloppy predators, though at a cost of lowered maximal production of spores.

Study System

Our focal host is the cyclically parthenogenetic freshwater crustacean, *Daphnia dentifera*, a common zooplankter in stratified lakes in the Midwestern United States (Tessier and Woodruff 2002). *Daphnia dentifera* (hereafter, "*Daphnia*") populations are infected by multiple parasite species, including the bacterium *Pasteuria ramosa* (hereafter, "bacterium") and the fungus *Metschnikowia bicuspidata* (hereafter, "fungus"; Duffy et al. 2010). A single host is rarely coinfected with both parasites (M. A. Duffy and S. R. Hall, unpublished data). Both of these parasites are obligate killers (i.e., spore release follows host death). However, they differentially affect host fitness: the fungus lowers fecundity and causes early host death, whereas the bacterium sterilizes early in infection (Auld et al. 2012). Overall, the bacterium is more virulent. Infection success of the bacterium depends on genetic specificity (i.e., infection rates depend on the pairing of host genotype and parasite isolate; Auld et al. 2012). In contrast, the fungus shows no specificity (Duffy and Sivars-Becker 2007). The fungus also shows no significant variation in traits related to disease spread (Duffy and Sivars-Becker 2007; C. L. Searle et al., unpublished manuscript). Furthermore, isolates from different states and continents do not vary genetically at several markers that are typically variable in fungi (Wolinska et al. 2009; C. L. Searle et al., unpublished manuscript).

Field Survey: Methods and Results

We surveyed epidemics of the bacterium and fungus in two geographic locations. In Indiana, we sampled host populations in 17 lakes in Greene, Sullivan, and Monroe Counties every week from August to December during the years 2009–2011 (see Civitello et al. 2013 for a list of lakes with geographic coordinates). In Michigan, we sampled 15 lakes every other week in Barry and Kalamazoo Counties from 2003 to 2006 (see Cáceres et al. 2006 for more details on the lakes). Surveys in both areas followed the same general protocol. During each visit, we collected zooplankton with three vertical tows of a Wisconsin bucket net (13.5-cm diameter, 153-μm mesh) at sampling stations more than 25 m apart. We then estimated infection prevalence on live *Daphnia* using a dissecting microscope (Hall et al. 2009). Here, we summarize maximal prevalence of infection during each year; maximal prevalence represents epidemic size well (Overholt et al. 2012). We arcsine square root–transformed prevalence data from the field surveys and fitted two linear mixed models (LMMs; one for Indiana lakes and one for Michigan lakes). Both models included parasite species as a fixed effect and both survey year and lake as random effects. The fungus was much more common than the bacterium in both Indiana (fig. 1*A*; LMM: $F_{1,49} = 66.50$, $P < .0001$) and Michigan (fig. 1*B*; LMM: $F_{1,59} = 10.88$, $P = .0017$).

Parameterization: Within-Host Growth and Transmission Potential

We used epidemiological models to connect life history (within-host growth) with disease transmission and an ecological factor (sloppy predation) to qualitatively explain dominance of the noncastrating fungus over the castrating bacterium in the field. We parameterized these models with experiments designed to quantify parasite production (hereafter, "spore yield," σ) and transmission rate (β). As shown below, their product ($\sigma\beta$, which we refer to as "transmission potential") is a central driver of competitive ability of each parasite j.

Parameterization Methods. To measure spore production through time, $\sigma_j(t)$, we created an experimental sacrifice series for each parasite. Clones used, food quantities, rearing temperatures, spore doses, and other experimental details can be found in the appendix (available online). Most importantly here, individual hosts were exposed as neonates for a 24-h period to a controlled dose of spores (different doses for each parasite). After the exposure period, animals were kept individually in favorable conditions until they either died or were sacrificed. Spore densities were estimated from each individual by homogenizing *Daphnia* in 100 μL

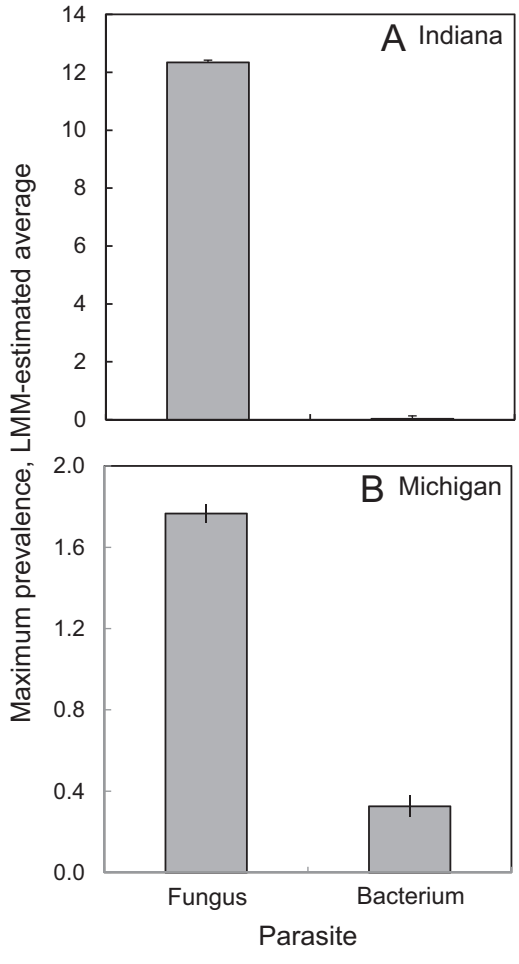

Figure 1: Maximum prevalence of infection by the noncastrating fungus (*Metschnikowia bicuspidata*) and the castrating bacterium (*Pasteuria ramosa*) in two regions of the Midwestern United States: Indiana (17 lakes, sampled 3 years; *A*) and Michigan (15 lakes, sampled 4 years; *B*; see text for more details). This estimate of the mean (with standard error) of peak prevalence of infection among lakes and years comes from the fit of linear mixed models (LMM) treating parasite as a fixed effect and lake and year as random effects.

of water, followed by counting on a hemocytometer using a compound microscope. (See table A1 for samples sizes and sacrifice dates; tables A1, A2 are available online.)

Using these data, we characterized within-host growth of the parasite using the logistic model. This model describes density-dependence growth of parasites, Z_j, as a function of the rate of maximal growth (r_j) and a carrying capacity (here, maximal spores, σ_j, yielded upon death of host from infection):

$$\frac{dZ_j}{dt} = r_j Z_j\left(\frac{1 - Z_j}{\sigma_j}\right), \tag{1}$$

where Z_j is the population density of parasite j within hosts. To fit this model, we used its integrated form, which predicts spore yield (i.e., the number of spores contained within the infected host) at any time t, $\sigma_j(t)$, as

$$\sigma_j(t) = \left[\frac{\sigma_j \sigma_{0,j}}{\sigma_{0,j} + (\sigma_j - \sigma_{0,j})\exp(-rt)}\right]\varepsilon, \tag{2}$$

where ε are log-normally distributed errors. (Note, here, we multiplied the numerator and denominator of the typical logistic equation by the initial density of spores [$\sigma_{0,j}$].) We then estimated parameters (r, σ_j, $\sigma_{0,j}$, and variance of the errors) for each parasite using a normal distribution as the likelihood function and log-transformed spore densities. We also bootstrapped 95% confidence intervals on these estimates.

Then, to estimate mean transmission rate, β_j, for each parasite, we used previously published data (see Auld et al. 2012 for details). Briefly here, individual neonate hosts were exposed to a controlled dose of spores (500 or 2,000 spores/mL for the fungus and bacterium, respectively, chosen to achieve similar prevalence of infection among parasites) in 40 mL of water for 1 day. A total of 168 hosts were exposed to the fungus, and 149 hosts were exposed to the bacterium. After exposure, we maintained hosts for up to 25 days, visually diagnosing hosts using a dissecting microscope. We then estimated transmission rate from the binomial infection data. Assuming that change in susceptible hosts during the infection assays follows a simple model, $dS/dt = -\beta_j S Z_j$, estimates of β_j readily arise from data on infection prevalence in the assay and the integrated form of this model,

$$p = \frac{1 - S_t}{S_0} = 1 - \exp(-\beta_j Z_{0,j} t), \tag{3}$$

where p is the predicted prevalence of infection, S_t is the density of uninfected hosts at the end of exposure time t, S_0 is their initial density (one animal), $Z_{0,j}$ is the initial starting density of spores (500 or 2,000 spores/mL), and exposure time t is 1 day. We assumed that infection prevalence followed a binomial distribution; the binomial, therefore, served as the likelihood function used to estimate β_j for each clone (see Civitello et al. 2012). With these estimates for each clone, we calculated the among-clone mean and bootstrapped confidence intervals around it (using 5,000 random draws, with replacement, within each clone).

We also bootstrapped 95% confidence envelopes around two sets of relationships. First, we generated envelopes for the logistic model of within-host growth (eq. [2]) for each parasite, based on bootstrapped replicates of the curve at fixed intervals (0.1 days). We also generated 95% confidence envelopes for the transmission potential of each

parasite though time by bootstrapping over both spore yield ($\sigma_j(t)$) and infectivity (β_j) data sets for each parasite.

Parameterization Results. Both parasites grew (produced spores) within hosts at a similar maximal rate, r_j (~0.5 day^{-1} for each; fig. 2*A*; table 1). However, the maximal spore yield (carrying capacity, σ_j) of the bacterium was more than 20 times that of the fungus (fig. 2*B*; table 1). The per-spore transmission rate of the fungus was higher than that of the bacterium, though only by ~2.5 times (fig. 2*C*; table 1; 95% confidence intervals do not overlap, indicating a significant difference).

We combined temporal trajectories of within-host growth of both parasites (fig. 2*D*, 2*E*) with the estimates of transmission rate (fig. 2*C*) to predict changing transmission potential ($\sigma_j(t) \times \beta_j$) through time. Two key find-

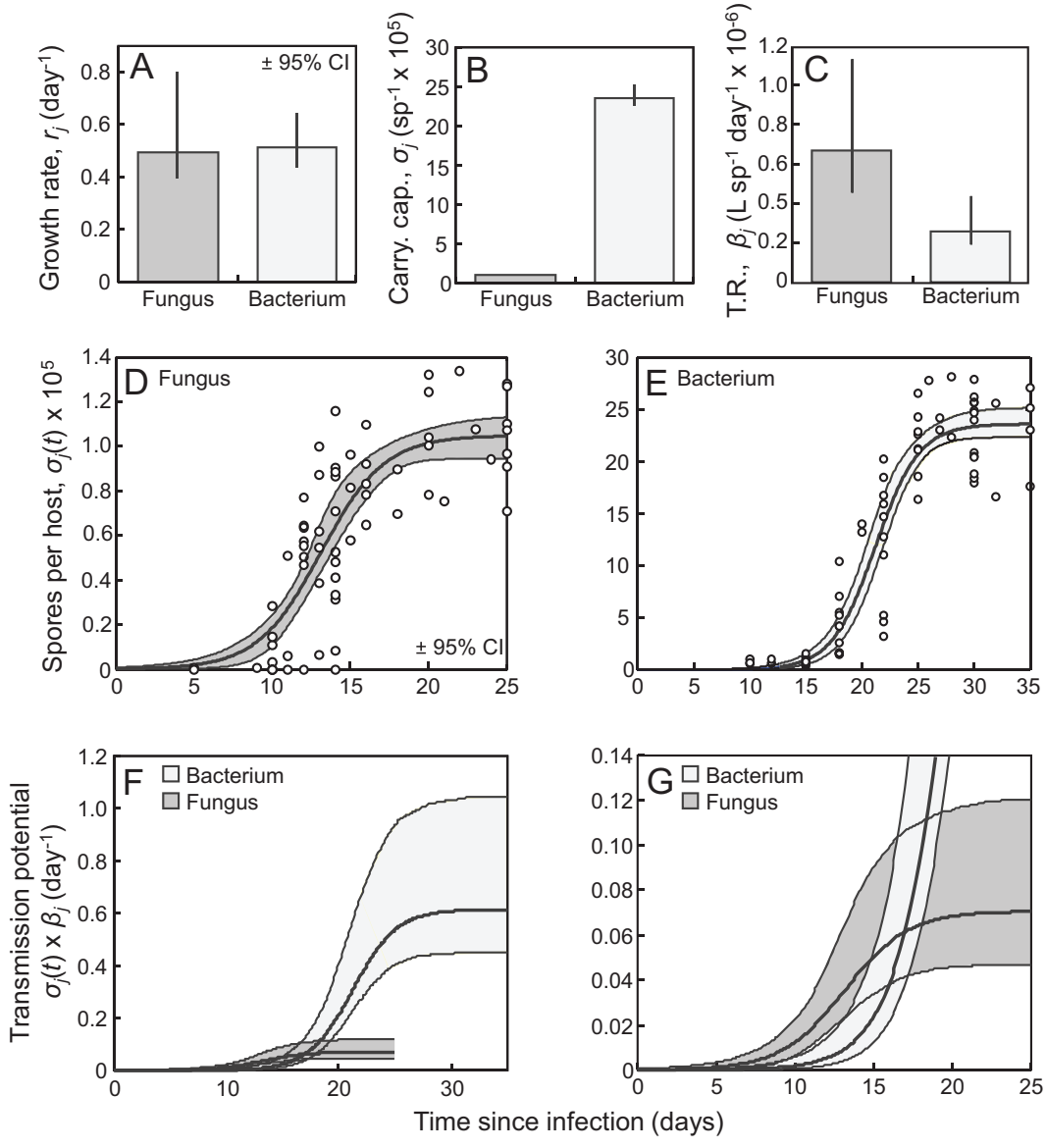

Figure 2: Within-host growth and infectivity of a fungal (*Metschnikowia bicuspidata*) or a bacterial (*Pasteuria ramosa*) parasite in zooplankton hosts (*Daphnia dentifera*). Parameter estimates: maximal per capita growth rate (r; *A*) and carrying capacity (σ; *B*) of parasites growing logistically; transmission rate (T.R., β; *C*). Within-host growth: both the fungus (*D*) and the bacterium (*E*) show logistic growth (each point is an individual, with the best-fitting curve plotted). Transmission potential: the product of spore yield through time, $\sigma(t)$, and transmission rate, b, yields differences in transmission potential between parasites, viewed over 35 days (*F*) or over a shorter interval (*G*). All bootstrapped error bars and envelopes correspond to a 95% level.

Table 1: Key quantities (variables, parameters, etc.) for the epidemiological models (eqq. [4]–[8]) of disease with the two parasites j

Quantity	Units	Description	Parameter value/range
Variables:			
I_j	Host/L	Density of infected hosts	...
S	Host/L	Density of susceptible hosts	...
Z_j	Spores/L	Density of parasite propagules (spores)	...
t	Days	Time	...
Parameters:			
b	Day^{-1}	Maximal birthrate of uninfected hosts	.3[a]
$b_{I,j}$	Day^{-1}	Maximal birthrate of infected host	.25, .05[a]
c	L/host	Strength of density dependence on birthrate	.0025
d	Day^{-1}	Background mortality rate of hosts	.02[a]
f_C	Day^{-1}	Predation from sloppy predators (*Chaoborus*)	0–.3
f_F	Day^{-1}	Predation from fish predators	0–.3
m	Day^{-1}	Loss rate of parasite spores	.1
r_j	Day^{-1}	Maximal within-host growth rate of parasites	.49[b], .51[b]
v_j	Day^{-1}	Virulent effects of infection on survivorship	.05[a], 0[a]
β_j	L $spores^{-1}$ day^{-1}	Transmission rate	6.75×10^{-7}[b], 2.60×10^{-7}[b]
θ	...	Selectivity of fish predation	5[c]
λ	...	Proportion of spores released from infected hosts	.6[d]
σ_j	Spores/host	Maximal within-host spore density	1.04×10^{5}[b], 2×10^{6}[b]
$\sigma_{0,j}$	Spores/host	Initial within-host density of spores	161[b], 43.3[b]
Compound parameters/key quantities:			
$R_{0,j}$	...	"Reproductive ratio"; invasion threshold (eq. [A2])	...
S_b^*	Hosts/L	Disease-free boundary equilibrium, hosts (eq. [A1])	...
S_j^*	Hosts/L	Epidemic equilibrium for susceptible hosts (e.g., eq. [A3]); the minimal host requirement	...
$\sigma_j(f_c)$	Spores/host	Within-host growth of parasite spores, scaled by sloppy predation rate, f_C (eq. [8])	...

Note: For parasite parameters, value for the fungus (*Metschnikowia bicuspidata*) is listed first, followed by that for the bacterium (*Pasteuria ramosa*).

[a] Reasonable parameter values, not generated from this study. For b, see Hall et al. (2010). Values of $b_{I,j}$ assume little effect of infection by fungus on fecundity but strong effects of bacterial infection. Value of d assumes hosts live about 50 days without predation or infection, as in the lab. Combined with estimates of v, hosts infected with the fungus live about 15 days; the bacterium does not elevate mortality.

[b] Estimates from this study (fig. 2). The following are 95% confidence intervals, first for the fungus and then the bacterium. β_j: $(4.58 \times 10^{-7}, 1.14 \times 10^{-6})$, $(1.93 \times 10^{-7}, 4.41 \times 10^{-6})$; r_j: (0.38, 0.80), (0.44, 0.64); σ_j: $(0.95 \times 10^{5}, 1.14 \times 10^{5})$, $(2.24 \times 10^{6}, 2.51 \times 10^{6})$; $\sigma_{0,j}$: (3.3, 640), (5.2, 215).

[c] A reasonable value—perhaps an underestimate—from field data (Duffy and Hall 2008).

[d] A reasonable value estimated for the fungus based on experiments (Cáceres et al. 2009).

ings emerged. First, if infected hosts live sufficiently long (>17–18 days), then the bacterium should enjoy higher transmission potential (fig. 2*F*). All else equal, this difference should give the bacterium a distinct competitive advantage over the fungus (in contrast to the field data; fig. 1; see also results of models 1 and 2 below). However, if bacteria-infected hosts die relatively early from consumption by sloppy predators, then they release many fewer spores than they would if infections were allowed to mature. Given the time trajectories (schedules) of within-host growth (fig. 2*D*, 2*E*), if death rates are relatively high (hosts live less than ~13 days), then the fungus will have a higher transmission potential (fig. 2*G*) than the bacterium (i.e., the fungus has a faster schedule of transmission potential). In contrast, if death rates are intermediate (infected hosts live ~13–17 days), then the fungus and bacterium have roughly equivalent transmission potential (fig. 2*G*). Overall, patterns of within-host growth of parasites might confer an advantage to the fungus when mortality rates of infected hosts from sloppy predation are higher—that is, when hosts live less time before parasite spores are released (highlighted in the results of model 3, below).

Population-Level Modeling

Building and Analyzing the Model Variations. We used these parameters (summarized in fig. 2)—including or ignoring the rate of within-host growth—to try to explain the field patterns (presented in fig. 1). We modeled three pertinent variations that differ in their assumptions about release of infectious propagules (spores) into the environment (see also table 1). (We studied other combinations of model assumptions, but these three presented here compactly convey the essence of our argument.) In model 1 (standard obligate killer model), we used a traditional representation of an obligate killer for both parasites. Here, spore release follows only death of hosts from infection (fungus) or nonconsumptive mortality (e.g., senescence, the assumption used for the castrating bacterium, which has little effect on longevity of infected hosts). Spore release in this model is maximal for both parasites. In model 2 (simple sloppy predation), sloppy predators release a fixed proportion of maximal spore yield (Cáceres et al. 2009). In model 3 (sloppy predation and within-host growth), sloppy predators release a fraction of spore yield from hosts, but spore yield depends on dynamics of within-host growth and host mortality rate due to sloppy predation. Each of these models is described in more detail below. All variations represent dynamics of the susceptible host, S, and infected stages, I_j, similarly:

$$\frac{dS}{dt} = \Big(bS + \sum_j b_{I,j} I_j\Big)(1 - cN) - dS \tag{4a}$$

$$- (f_F + f_C)S - \sum_j \beta_j Z_j S, \tag{4b}$$

$$\frac{dI_j}{dt} = \beta_j Z_j S - (d + \nu_j)I_j - \theta f_F I_j - f_c I_j.$$

Density of susceptible hosts (eq. [4a]) increases due to density-dependent births. Susceptible hosts give birth at maximal rate b, while hosts infected with parasite j have lower maximal fecundity ($0 \le b_{I,j} \le b$). All hosts ($N = S + I_j$) exert similar density-dependent effects on birthrate (governed by strength c). Susceptible host density then decreases due to background losses (at rate d), selective predation (by fish, at rate f_F), and predation by a nonselective sloppy predator (*Chaoborus* midge larvae, at rate f_C). Susceptible hosts also become infected through exposure to environmentally distributed propagules (spores, Z_j) at transmission rate β_j, and then move into the infected class (eq. [4b]). These hosts are lost due to death from infection at rate $d + \nu_j$, where ν_j represents the added virulent effects of the parasite on survival. Infected hosts are also consumed by the selective predators, at rate θf_F (where $\theta > 1$ denotes selectivity on infected prey), and by the nonselective ($\theta = 1$) sloppy predator, at rate f_C.

The three model variants differentially represent spore release from infected hosts. In model 1 (standard obligate killer model), change in spore density is

$$\frac{dZ_j}{dt} = \sigma_j(d + \nu_j)I_j - mZ_j, \tag{5}$$

where hosts release the maximal spore yield (σ_j) after death from infection ($\nu_j > 0$; fungus) or background, nonconsumptive mortality (for the castrating bacterium: $\nu_j = 0$). This model takes a more traditional view on spore release for obligate killers (i.e., it follows host death from infection). This version might apply best to pond *Daphnia*, where spores released from dead, infected hosts can contact new hosts (i.e., seasonal stratification does not pose an environmental trap in ponds as it does in lakes). Spores are lost at a constant background rate (m, assumed equivalent for both parasites for parsimony). In contrast, model 2 (simple sloppy predation model) builds in ecological realism for stratified lake habitats concerning spore release. It envisions spore release following sloppy predation only; hosts dying from infection are assumed to sink out of the host habitat before they can release spores (based on Cáceres et al. 2009). In addition, we assume that spores in hosts dying from fish predation settle out of the water column and are thus lost (a reasonable assumption given density of fecal pellets, which contain ingested spores; S. Auld and M. A. Duffy, unpublished data; Duffy 2009). Thus, the dZ_j/dt equation becomes

$$\frac{dZ_j}{dt} = \lambda f_C \sigma_j I_j - mZ_j. \tag{6}$$

Note that hosts eaten by sloppy predators (at rate f_C) still release a proportion (λ) of the maximal yield of spores (σ_j); that is, in model 2, spore yield does not take into account patterns of within-host growth. Like model 2, model 3 (sloppy predation and within-host growth model) assumes that spore release for each parasite follows only sloppy predation. However, now spores released from predation depend on within-host growth of parasites, $\sigma_j(f_C)$:

$$\frac{dZ_j}{dt} = \lambda f_C \sigma_j(f_C) I_j - mZ_j. \tag{7}$$

This $\sigma_j(f_C)$ function is the integrated logistic curve fit above (eq. [2]); however, now time t is scaled as the inverse of mortality rate from sloppy predators, f_C (i.e., $t = 1/f_C$):

$$\sigma_j(f_C) = \frac{\sigma_j \sigma_{0,j}}{\sigma_{0,j} + (\sigma_j - \sigma_{0,j}) \exp(-r_j/f_C)}, \tag{8}$$

where, again, $\sigma_{0,j}$ is the (estimated) initial starting density of parasite with hosts, r_j is the maximal growth rate of the parasite within the host, and σ_j is the asymptotic density of spores. Spore yield decreases nonlinearly with sloppy predation, f_C.

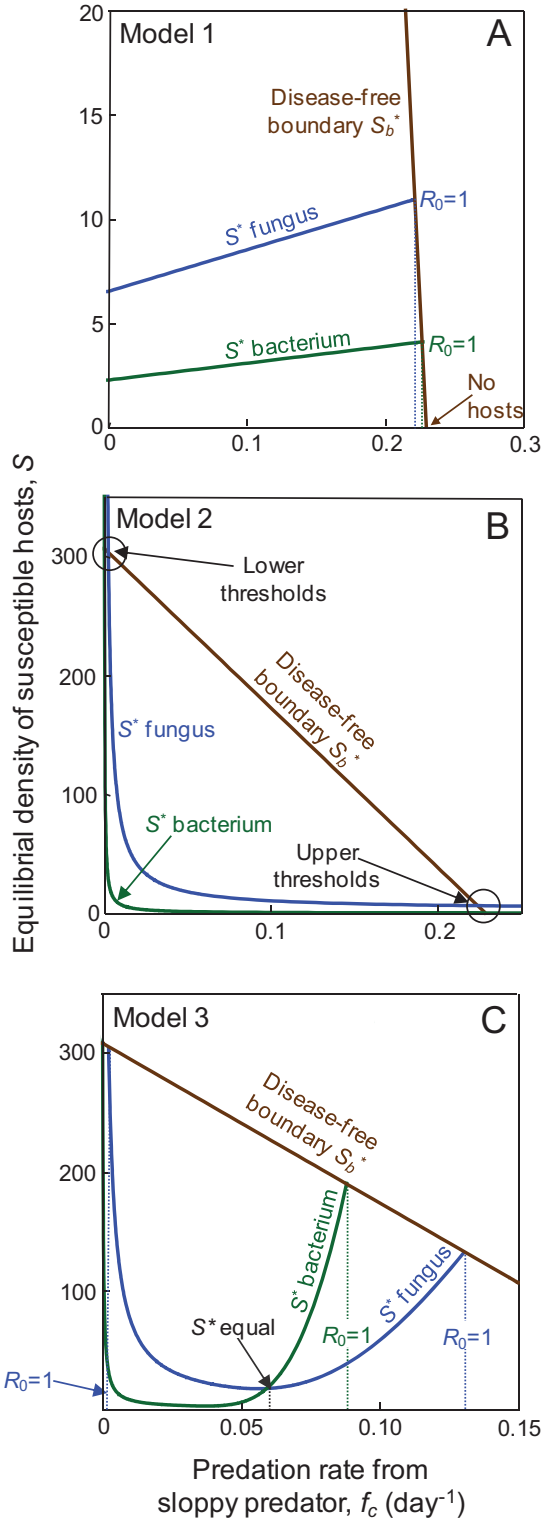

Figure 3: Origin of key invasion ($R_0 = 1$) and competition thresholds in the three model variations along gradients of sloppy predation (f_C). These thresholds hinge on density of hosts in disease-environments (S_b^*) and with parasites (S_j^*), that is, the minimal host requirement of the parasite. *A*, In model 1 (standard obligate killer), f_C imposes only mortality, not spore release. Thus, the minimal host requirement S_j^* for each parasite increases with f_C until the invasion threshold is crossed. *B*, In model 2 (simple sloppy predation), S_j^* decreases with f_C because predators provide the only successful release of spores. Now, two invasion thresholds arise, an upper and a lower. In both *A* and *B*, the bacterium has a lower host requirement (S_j^*)—hence, it is a superior competitor. *C*, Model 3 (sloppy predation and within-host growth), combines spore release from predation and within-host growth. It also shows two invasion thresholds, but now S_j^* first decreases and then increases with f_C (see text). Because this curve increases more steeply for the bacterium than the fungus, the minimal host requirements shift ranking. As a result, the fungus can dominate at intermediate to high f_C.

Modeling Results. Competition between parasites depends on relationships between three key densities of hosts. The following section describes the key results (while the mathematical details are presented in the appendix). Each parasite has a minimal host requirement (S_j^*). Traits governing host-parasite interactions—for example, transmission potential, $\sigma_j\beta_j$—determine S_j^*, and lower S_j^* confers competitive superiority. But before they can compete, parasites must first invade a disease-free host population. For a given parasite, when host density without disease (S_b^*) exceeds the parasite's minimal host requirement, S_j^*, it can invade a host population (i.e., net reproductive ratio $R_0 > 1$). For model 1, this invasion threshold arises once, when sloppy predation (f_C) becomes sufficiently intense. Since sloppy predators do not release spores in model 1 (standard obligate killer), increasing f_C only depresses available host resources for the parasite (i.e., S_b^* declines with f_C) while increasing the minimal demands of the parasites for hosts (i.e., S_j^* increases with f_C; fig. 3*A*. Eventually, predation is too intense to maintain either parasite. If sloppy predators release a proportion of maximal spore yield (model 2, simple sloppy predation), then two thresholds emerge (fig. 3*B*). The minimal host requirement now decreases with intensity of sloppy predation. Therefore, a system can have too few sloppy predators to support the parasite, creating an additional invasion threshold at low f_C. Despite these differences, the bacterium is competitively dominant over the fungus in both models as parameterized because it always has a lower minimal host requirement. However, when spore release depends on within-host growth (model 3, sloppy predation and within-host growth model), competitive outcomes can reverse (fig. 3*C*). Now, the minimal host requirement of each parasite (S_j^*) first decreases with intensity of sloppy predation (f_C, due to positive effects of spore release) but then increases with further f_C (due to negative effects of higher mortality coupled to decreased spore yield; eq. [8]). This increase in

S_j^* is sharper for the bacterium than for the fungus. As a result, the fungus now becomes competitively dominant (has lower S_j^*) at intermediate f_C; at higher sloppy predation, only the fungus can persist with the sloppy predator.

These thresholds govern parasite invasion and competition along broad predation gradients and in epidemiological trait space. Despite very different assumptions about spore release between models 1 and 2, both make the same point about competition: the bacterium, due to its immense transmission potential at maximal spore yield, should competitively displace the fungus along broad gradients of selective (f_F) and sloppy (f_C) predation (fig. 4*A*, 4*B*). (Other model variants that combine the two modes of spore release in models 1 and 2 yield the same conclusion [not shown].) In other words, even when the fungus could invade in f_F–f_C space, it is displaced by the bacterium. (The different shapes of these thresholds between models are discussed in the appendix.) Thus, models that ignore within-host growth of parasites are discordant with our field results. However, once spore yield becomes a joint function of sloppy predation and within-host growth in model 3, the fungus can dominate at intermediate–high intensity of sloppy predation (fig. 4*C*). Again, relatively high f_C means that hosts infected with either parasite die before they maximally produce spores. This predator-mediated truncation grants the faster-schedule, noncastrating fungus a transmission potential–based advantage over the slower-schedule, castrating bacterium (fig. 2*G*). Thus, the fungus dominates higher f_C environments, while the bacterium dominates lower f_C—even if selective (nonsloppy) fish predation becomes intense (i.e., at high f_F; fig. 4*C*). Furthermore, the fungus can dominate environments with even lower intensity of sloppy predation if the bacterium has a lower transmission rate than estimated here (fig. 4*D*; this scenario seems possible but less likely, given the transmission rates of other bacterial strains; appendix; fig. A2; figs. A1–A4 are available online). Competitive outcomes change little with variation in maximal spore yield (σ_j) unless the bacterium's σ_j drops more than two orders of magnitude (fig. 4*E*). Such a drastic drop seems unlikely. However, these competitive outcomes do hinge on the assumption that spore release follows only sloppy predation. If the castrating bacterium can successfully release full spore loads following death from senescence, it can regain/retain competitive advantage over the noncastrating fungus—always, over all intensities of sloppy predation (results not shown). Overall, our modeling results demonstrate that sloppy predation, coupled with within-host growth of parasites, creates a niche in which the noncastrating fungus can dominate competition and displace the castrating bacterium (fig. 4*C*–4*E*).

Selection on Within-Host Growth

These modeling results suggest that, at present, the sloppy predator can constrain the castrating bacterium's realized niche in favor of the noncastrating fungus. In essence, sufficiently high sloppy predation favors parasites with a faster schedule of transmission potential (e.g., the fungus here). As a follow-up, we used a controlled natural selection experiment to test whether either parasite could evolve to better exploit this predator-mediated fast-schedule niche. We evaluated the potential for both components of transmission potential (spore production and per spore transmission rate) to evolve, using selection lines that mimicked high- and low-predation environments. High-predation environments were simulated by killing hosts 13 days after exposure to parasites, while low-predation environments were simulated by killing them 20 days post-exposure. We had 8 replicate selection lines for each parasite × predation treatment (i.e., 32 selection lines in total), each of which consisted of 15 *Daphnia*. On sacrifice, hosts were homogenized, and those spores were used to start a new round of infections, maintaining independence of our replicate selection lines. (See appendix for additional empirical and statistical details.) After five rounds of selection on the bacterium and six on the fungus, we conducted an additional infection assay to compare transmission rates between lines. Furthermore, using post-selection spores, we measured density of parasites produced in hosts reared in environments with short infection duration (i.e., high predation; killed at day 13, when fungus spore densities are higher than bacteria spore densities within infected hosts) and long duration (i.e., low predation; killed at day 20, when bacteria spore densities are higher than fungus spore densities within infected hosts). These assays evaluated the potential trade-off between early and later parasite production.

High predation resulted in the evolution of faster growth of the castrating bacterium (fig. 5). Hosts in these lines produced spores more rapidly than did those in low-predation lines when assayed in high-predation conditions (planned contrast: $z = -3.07$, $P = .0021$; compare filled squares in fig. 5*A*). However, this more rapid proliferation of the bacterium came with a cost, as indicated by the selection line × assay environment interaction (table A2); in low-predation environments, high-predation lines of the bacterium produced fewer spores than did low-predation lines (planned contrast: $z = 2.70$, $P = .0070$; compare open squares in fig. 5*A*). Spore production of the noncastrating fungus was influenced only by the length of the experimental assay (significant assay environment effect in table A2, as expected given fig. 2*D*). It did not respond to selection (fig. 5*A*; table A2). Furthermore, the transmission rate of neither the bacterium nor the fungus

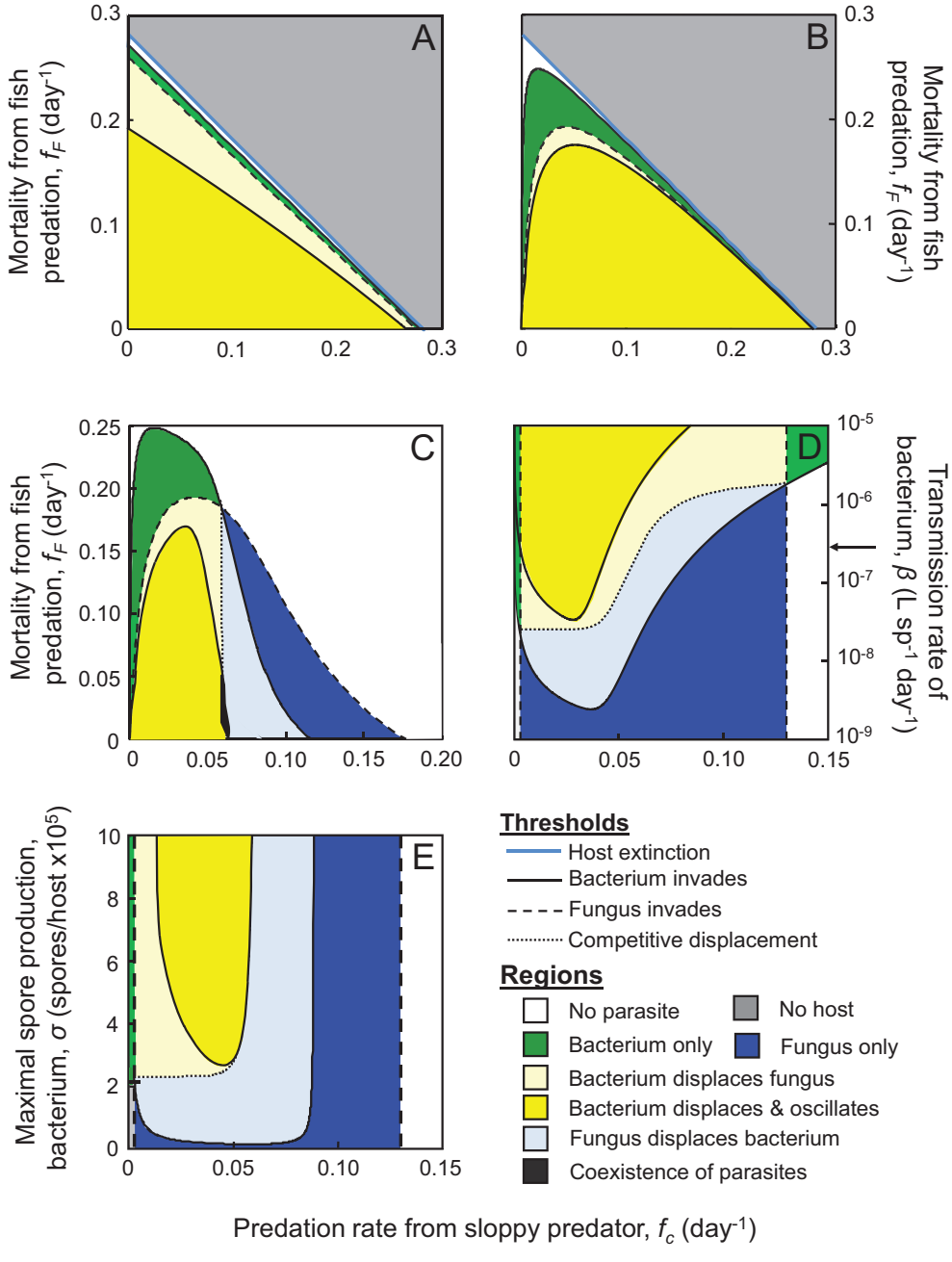

Figure 4: Outcomes of competition between a fungal parasite and a bacterial parasite in three variations of a model. Five thresholds (one for host extinction; two denoting successful invasion of each parasite, $R_0 = 1$; one marking shift in competitive dominance based on minimal S^* requirements; one mapping host-bacterium oscillations) break parameter space into eight possible dynamical outcomes: host extinction (dark gray); neither parasite can persist (white); the bacterium persists where the fungus could not (green); the bacterium displaces the fungus (stable dynamics: light yellow; oscillations: dark yellow); the two parasites coexist in oscillations (black); the fungus competitively displaces the bacterium (light blue); or the fungus persists where the bacterium could not (royal blue). *A*, Model 1: when sloppy predators do not disperse spores, the bacterium is always the competitive dominant. *B*, Model 2: the same outcome arises when sloppy predators release a fixed proportion of maximal spore production. *C–E*, Model 3: within-host growth creates a niche for the fungus to dominate, as shown along gradients of fish predation, f_F (*C*), transmission rate of the bacterium, β_B (*D*), or maximal spore production, σ_B (*E*). The arrow in *D* denotes the mean estimate among several clones (fig. 2*C*). In *D–E*, $f_F = 0.05$; other parameter values follow table 1.

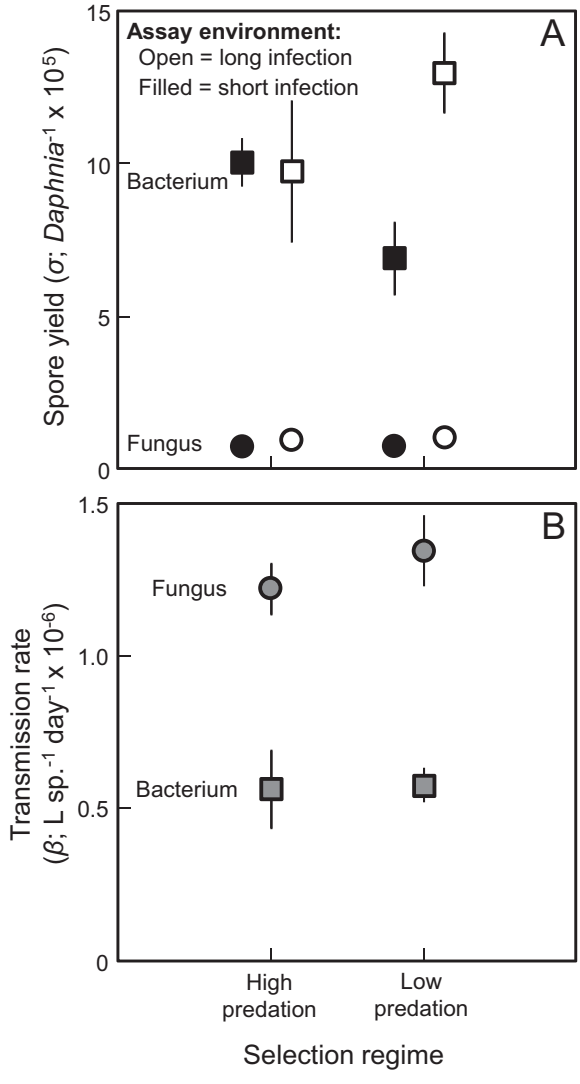

Figure 5: The effects of selection regime (high predation vs. low predation) on the two components of transmission potential: spore yield (σ; *A*) and transmission rate (β; *B*). In *A*, filled symbols = short infection duration (hosts killed after 13 days), open symbols = long infection duration (hosts killed after 20 days). Circles = fungus; squares = bacterium. Error bars are standard errors calculated across replicate selection lines; error bars for fungal spore yield are obscured by the symbols.

responded to selection (fig. 5*B*; bacterium: $t = 0.11$, df = 4.01, $P = .92$; fungus: $t = 0.89$, df = 9.90, $P = .39$). All field-collected and experimental data are deposited in the Dryad Digital Repository: http://dx.doi.org/10.5061/dryad.3ht1p (Auld et al. 2014).

Discussion

Ecologists and epidemiologists strive to explain and predict spatiotemporal variation in parasite abundance (Anderson and May 1979, 1981; Keesing et al. 2010). Existing theory for disease suggests that the ecology and life history of parasites could shape their fundamental and realized niches and thus explain patterns of abundance in nature (Jaenike 1996; O'Keefe and Antonovics 2002; Bonds 2006). For instance, parasitic castrators can outcompete other parasites with similar epidemiology for their shared resource (susceptible hosts) if castration increases spore production sufficiently (O'Keefe and Antonovics 2002; Ebert et al. 2004; Hall et al. 2007). We looked for the signature of this prediction among two obligate killer parasites (Ebert and Weisser 1997). In multiyear, multilake surveys in two regions (Indiana and Michigan), we found quite the opposite pattern. A noncastrating fungus (*Metschnikowia bicuspidata*) was much more abundant than a castrating, gigantism-causing bacterium (*Pasteuria ramosa*) in populations of the shared zooplankton host (*Daphnia dentifera*; see appendix for evidence of gigantism; see also Duffy et al. 2010). This field observation contrasted with predictions from a general but parameterized model for these two obligate killers (model 1); the model predicted that the bacterium should have dominated (figs. 3*A*, 3*B*, 4*A*, 4*B*).

What could explain the model-observation discordance? At least two possibilities arise. One is that the general model (model 1) represents parasite biology well but that our parameter estimates are wrong. For instance, our estimates come from lab assays. It seems possible that environmental variation (e.g., in temperature) could differentially affect fungal and bacterial transmission potential. Additionally, even using lab assays, we might overestimate the transmission potential of the castrating bacterium. The bacterium, while having the capacity to produce huge numbers of transmission spores (high σ, in our model), also shows genetic specificity in the infection process (Carius et al. 2001; Luijckx et al. 2011; Auld et al. 2012). A given strain of the bacterium can infect some but not all host genotypes, likely lowering overall infection risk (transmission rate, β). Thus, specificity might undermine the bacterium's transmission potential and invasion success (Lively 2010). Currently, we lack among-lake data of genetic specificity of infection to robustly evaluate this possibility. However, when looking at five isolates of the bacterium over six host clones in one lake (Auld et al. 2012), our β estimate here seems reasonable (see appendix). Thus, using our lab-based estimates, the general model (model 1) likely lacks some key biology of these parasites that can reverse competitive outcomes.

Another possibility involves the mechanism of spore release from infected hosts. The general model (model 1) assumes that hosts release the maximal number of spores upon death from infection. This assumption may capture the scenario in European ponds where the castrating bac-

terium dominates (Stirnadel and Ebert 1997; Ebert et al. 2001; Mitchell et al. 2004; Duncan and Little 2007). In these ponds, hosts likely contact spores released from dead, infected hosts in bottom sediments (Decaestecker et al. 2002). However, in deeper lakes, hosts dying from infection likely release spores after sinking to anoxic lake bottoms that are devoid of hosts (Cáceres et al. 2009). Instead, relevant, epidemic-fueling spore release more likely stems from sloppy predation (Cáceres et al. 2009). Larvae of a midge (*Chaoborus* spp.) release about half of the spores contained in their parasite-infected prey during feeding. Importantly, these spores enter a region of lake habitat (the epilimnion) where they can readily contact hosts. Thus, in stratified lakes, sloppy predators kill infected hosts (a negative effect on parasite fitness), but they also spread spores, enabling the parasites to avoid the environmental trap created by lake habitat (a positive effect on parasite fitness). Through this release, sloppy predators can differentially affect the competitive ability of the parasites and create a niche for dominance of the noncastrating fungus (as shown in model 3; fig. 4*C*–4*E*). This outcome resembles the predator-mediated switch of competitive ranking between consumers of a shared resource (i.e., keystone predation theory: Leibold 1996; Grover 1997). However, the switch here involves an intricate mechanism—the combination of mortality, release of infectious propagules through sloppy feeding into a key region of habitat, and within-host growth of parasites.

Indeed, high levels of sloppy predation can grant competitive advantage to the noncastrating fungus due only to the temporal dynamic of spore accrual within hosts. The fungus has a faster schedule of transmission potential (spore yield × transmission rate) than the castrating bacterium. Therefore, the fungus spreads more readily when sloppy predation is more intense. When infections can develop for longer (at lower intensity of sloppy predation), the slower-schedule, castrating bacterium enjoys a competitive advantage because it can then produce many more spores, granting it much higher maximal transmission potential. Thus, given the right natural history (here, spore release from sloppy predation), dynamics of within-host growth can strongly shape the ecology and epidemiology of parasites (Holt and Barfield 2006). Models that assume that parasites quickly reach carrying capacity miss this pertinent point (also see Holt and Barfield 2006), especially for obligate killers, which need to disperse from hosts following host death. Here, the combination of life-history schedule and ecology (sloppy predation) helps to resolve discrepancy between more general models and field patterns (fig. 1).

The niche created by sloppy predators and within-host growth creates an evolutionary opportunity for both parasites. Can the slow-schedule castrating bacterium evolve toward this niche by becoming more like its fast-schedule fungal competitor? In the field, bacterial populations can evolve over the course of a single epidemic (Auld et al. 2013). Thus, the bacterium has the capacity to evolve quickly in nature. In the selection experiment here, the bacterium evolved faster parasite production in treatments that simulated high predation. However, in these high-predation lines, the bacterium evolved to produce fewer spores later during infection when compared to the low simulated predation treatment. This costly evolutionary response echoes previously developed theory (Anderson and May 1982; Kakehashi and Yoshinaga 1992; Lenski and May 1994; Ebert and Weisser 1997) and earlier experimental studies (nematode-rats: Paterson and Barber 2007; bacterium-*Paramecia*: Nidelet et al. 2009). Thus, costly evolution of faster growth occurs in diverse host-parasite systems. However, transmission rate of the evolved lines did not differ from each other. Therefore, the bacterium's ability to grow responded distinctly from its ability to infect (on a per-spore basis). In contrast, neither the schedule of spore production nor the transmission rate of the fungus demonstrated a significant response to selection (consistent with previous selection experiments and assays with it; Duffy and Sivars-Becker 2007; C. L. Searle et al., unpublished manuscript). Thus, the castrating bacterium can potentially evolve into this fast-schedule niche occupied by the noncastrating fungus in systems with higher levels of sloppy predation. We must note, however, that this evolutionary response arose for one host genotype paired with one bacterial isolate. Given strong host genotype × parasite genotype interactions ($G_H \times G_P$) between *D. dentifera* and the bacterium (Auld et al. 2012), it remains to be seen if evolution of a faster life-history schedule in one host genotype begets a faster schedule in other host genotypes. If it does not, $G_H \times G_P$ interactions might constrain the bacteria's rapid evolutionary response shown here.

This study grappled with discordance between the predictions of a general (but parameterized) epidemiological model and the dominance of parasites in the field. Rooted in theory for parasite competition, our general but parameterized model (model 1) anticipated dominance of a castrating bacterium over its competing fungus. However, we observed the opposite pattern: the fungus was much more abundant than the bacterium in North American lakes. We found that integrating the schedule of within-host growth of the parasites with a predator-driven mechanism of spore release can explain the fungus's dominance in these stratified lakes. This combination of the parasite's life history, an ecological player (the sloppy predator), and a habitat constraint provided opportunity for the fast-schedule fungus to overturn dominance of the castrator. Thus, seemingly subtle aspects of ecology (sloppy preda-

tion of infected hosts), when combined with variation in life-history schedules among competing parasites, can strongly influence the ecology, epidemiology, and evolution of infectious disease.

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