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ARTICLE

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A healthy but depleted herd: Predators decrease prey disease and density

Laura K. Lopez[1] | **Michael H. Cortez**[2] | **Turner S. DeBlieux**[3] | **Ilona A. Menel**[4] | **Bruce O'Brien**[1] | **Carla E. Cáceres**[4] | **Spencer R. Hall**[3] | **Meghan A. Duffy**[1]

[1]Department of Ecology and Evolutionary Biology, University of Michigan, Ann Arbor, Michigan, USA

[2]Department of Biological Science, Florida State University, Tallahassee, Florida, USA

[3]Department of Biology, Indiana University, Bloomington, Indiana, USA

[4]School of Integrative Biology, University of Illinois Urbana-Champaign, Urbana, Illinois, USA

Correspondence
Meghan A. Duffy
Email: duffymeg@umich.edu

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Abstract

The healthy herds hypothesis proposes that predators can reduce parasite prevalence and thereby increase the density of their prey. However, evidence for such predator-driven reductions in the prevalence of prey remains mixed. Furthermore, even less evidence supports increases in prey density during epidemics. Here, we used a planktonic predator–prey–parasite system to experimentally test the healthy herds hypothesis. We manipulated density of a predator (the phantom midge, *Chaoborus punctipennis*) and parasitism (the virulent fungus *Metschnikowia bicuspidata*) in experimental assemblages. Because we know natural populations of the prey (*Daphnia dentifera*) vary in susceptibility to both predator and parasite, we stocked experimental populations with nine genotypes spanning a broad range of susceptibility to both enemies. Predation significantly reduced infection prevalence, eliminating infection at the highest predation level. However, lower parasitism did not increase densities of prey; instead, prey density decreased substantially at the highest predation levels (a major density cost of healthy herds predation). This density result was predicted by a model parameterized for this system. The model specifies three conditions for predation to increase prey density during epidemics: (i) predators selectively feed on infected prey, (ii) consumed infected prey release fewer infectious propagules than unconsumed prey, and (iii) sufficiently low infection prevalence. While the system satisfied the first two conditions, prevalence remained too high to see an increase in prey density with predation. Low prey densities caused by high predation drove increases in algal resources of the prey, fueling greater reproduction, indicating that consumer–resource interactions can complicate predator–prey–parasite dynamics. Overall, in our experiment, predation reduced the prevalence of a virulent parasite but, at the highest levels, also reduced prey density. Hence, while healthy herds predation is possible under

some conditions, our empirical results make it clear that the manipulation of predators to reduce parasite prevalence may harm prey density.

KEYWORDS
consumer–resource, density mediated indirect effects, healthy herds, host–parasite, infection prevalence, parasitoid, pathogen, predation, predator spreader

INTRODUCTION

Attack by multiple natural enemies seems like it should increase harm to a population. However, a joy of ecology is that unexpected outcomes can occur when we put different interactions together. This premise underlies the "healthy herds hypothesis," which argues that adding predators to a system can reduce parasite prevalence in their prey, thereby potentially increasing prey density (Packer et al., 2003). If higher predation in natural populations routinely decreases parasitism and increases prey density, predators could perhaps be used to manage disease in vulnerable prey populations (Packer et al., 2003; Rohr et al., 2015) or to reduce the risk of spillover of disease to other populations, such as humans. However, the generality of the predictions of the healthy herds hypothesis has been questioned recently (Richards et al., 2022). Indeed, predators can increase disease prevalence in their prey (Duffy et al., 2019; Richards et al., 2022). Moreover, in some systems, higher predation intensity decreases prey density during epidemics (e.g., Gallagher et al., 2019; Mohammed, 2018; Shang et al., 2019)—indicating a major cost of lower prevalence via predators. Both patterns raise uncertainty about the promise of predators to control disease and protect prey populations.

The appeal of the healthy herds hypothesis lies in the alignment of multiple conservation goals—simultaneous conservation of predators, reduction of parasitism, and protection of vulnerable populations—as well as the potential to reduce spillover risk to other populations, including humans. The original mathematical model for it proposed that healthy herds (i.e., predators decreasing parasitism and increasing prey density) is most likely with highly virulent parasites, long-lived host-prey species (hereafter "prey"), selective predation on infected prey, and, when applicable, high aggregation of macroparasites in individual prey (Packer et al., 2003). The well-studied system of red grouse prey, parasitic nematodes, and fox predators meets these conditions (Hudson et al., 1992). In that system, predators reduce parasitism in prey. Additionally, reduced parasitism stabilizes population densities, avoiding major population declines and increasing average density (Hudson et al., 1998). Thus, in the grouse system, adding predators reduces parasitism and thereby increases prey density—supporting the healthy herds hypothesis and showing that predator conservation can reduce parasitism and protect vulnerable prey.

However, this grouse–predator–parasite pattern is not ubiquitous (Duffy et al., 2019; Richards et al., 2022), and a recent meta-analysis concluded that reduction of parasitism in prey by predators is "far from universal" (Richards et al., 2022). Predation often has no influence on parasitism (e.g., Duffy, 2007; Flick et al., 2020; Malek & Byers, 2016) or is associated with greater parasitism (e.g., Cáceres et al., 2009; Shang et al., 2019; Tan et al., 2016; Trandem et al., 2016; Yin et al., 2011). Similarly, in systems with parasites, predators sometimes do not affect prey density (e.g., Duffy, 2007; Laundon et al., 2021; Laws et al., 2009; Strauss et al., 2016) and other times decrease it (e.g., Gallagher et al., 2019; Mohammed, 2018; Shang et al., 2019). Furthermore, in predator–prey–parasitoid interactions, a meta-analysis found that predators reduced prey density as much as they increased it (Rosenheim & Harmon, 2006).

Thus, 20 years after formalization of the healthy herds hypothesis, it is clear that predators do not always protect their prey, even during epidemics of virulent parasites. With more models and experiments, we might mechanistically sort out these disparate responses. These experiments should track prey and parasite dynamics along predation gradients (rather than with just two levels, as is currently most common; Richards et al., 2022). They should also interweave other factors that might indirectly influence prey dynamics such as the resources of prey (Murdoch et al., 2003). For example, if predators depress prey abundance well below carrying capacity, prey reproduction may increase, leading to population recovery. In addition, prey with short generation times may evolve rapidly during epidemics (Hairston Jr. et al., 2005), potentially influencing healthy herds dynamics. For example, if prey populations rapidly evolve resistance to a parasite, predators might depress prey abundance without reducing parasitism. Thus, a robust test of the impacts of predation on disease and prey density should integrate a gradient of predation with other ecological and evolutionary processes that occur concurrently.

We used a planktonic predator–prey–parasite (midge–zooplankton–fungus) system to test the healthy herds hypothesis. This system possesses some features that should favor healthy herds predation (i.e., predation that reduces parasitism and increases prey density): The parasite virulently suppresses survival and fecundity (Clay et al., 2019), and the predator selectively culls infected prey (although not as intensively as fish, and not in all scenarios: Cáceres et al., 2009; Duffy & Hall, 2008; Appendix S1: Section S3.2). At the same time, the short-lived prey can strongly interact with resources and rapidly evolve during epidemics via clonal selection, both of which might interfere with healthy herds dynamics. To evaluate the net outcomes of these processes, we stocked mesocosms with nine clonal genotypes of prey that varied in susceptibility to both natural enemies to capture the range of trait variation that we know exists in natural populations. We created four levels of predation (from none to high) and added parasite spores to half the populations. After multiple prey generations, predation reduced infection prevalence, but, contrary to healthy herds expectations, also reduced prey density at the highest predation levels. At lower predation levels, predators neither increased nor decreased total prey density (as compared to the no-predation treatment). A mathematical model parameterized for our system specifies that, in order for predation to increase prey density at equilibrium, first, predators must feed selectively on infected prey, second, infected prey that are consumed by predators must release fewer infectious propagules (as compared to infected prey that are not consumed), and, third, infection prevalence must be sufficiently low. Our system meets the first two of these conditions but not the third, suggesting that we did not see healthy herds dynamics in our experiment because infection levels were too high.

METHODS

Study system

Daphnia dentifera is a dominant zooplankton species in stratified lakes in Midwestern North America (Tessier & Woodruff, 2002). It hosts the fungal parasite *Metschnikowia bicuspidata*, becoming infected after incidentally ingesting spores while grazing (Stewart Merrill & Cáceres, 2018). Infection shortens life span and decreases fecundity (Clay et al., 2019). Host death releases infectious spores into the water column, where other *Daphnia* can ingest them.

Larvae of the phantom midge, *Chaoborus* spp., including *C. punctipennis*, commonly prey on *Daphnia* in North American temperate lakes (Garcia & Mittelbach, 2008; Tessier & Woodruff, 2002). Lakes with abundant *Chaoborus* tend to have higher levels of disease (Cáceres et al., 2009; Strauss et al., 2016), likely because they release spores in the water column when feeding on infected *Daphnia* (Cáceres et al., 2009). This is important because the lakes in which these interactions occur are stratified for much of the year, with limited resuspension of spores from sediment spore banks and decomposing *Daphnia* during periods of stratification. However, in unstratified environments such as the one used in this study, *Chaoborus* may not spread disease (Cáceres et al., 2009); in these mixed mesocosms, spores released from dead prey will still come in contact with new prey.

Mesocosm experiment

We experimentally manipulated predator density and parasite presence/absence to assess the impacts of predation and parasitism on ecological and evolutionary prey–parasite dynamics. We crossed the presence/absence of the parasite (*M. bicuspidata*) with four levels of predation (0, 0.1, 0.5, and 1 *C. punctipennis* per liter, using third or fourth instar larvae) to mimic realistic predation levels in Midwestern United States (Garcia & Mittelbach, 2008). This design resulted in eight treatment combinations replicated six times each (48 mesocosms total). One low (0.1 L^{-1}) predation treatment tank was excluded from analyses due to very high abundances of *C. punctipennis*. Each replicate was housed within a 75-L polyethylene tank filled to 50 L with a 20:80 combination of filtered lake water and treated tap water. Water that was lost due to evaporation was replaced with treated tap water weekly. At the start of the experiment, we added nitrogen (300 μg L^{-1} N as $NaNO_3$) and phosphorus (20 ug L^{-1} P as K_2HPO_4) to each tank. Nutrients were replenished in tanks weekly (assuming 5% daily loss rate). Two days prior to the addition of *D. dentifera* prey, tanks were inoculated with 50 mg dry weight of the green alga *Ankistrodesmus falcatus*. Tanks were housed in a 16:8 light:dark cycle.

We stocked tanks with nine genotypes of *D. dentifera* that differed in susceptibility to infection by *M. bicuspidata* and susceptibility to predation by *C. punctipennis*. These genotypes span a wide range of phenotype space for these traits but do not experience a trade-off between susceptibility to infection and susceptibility to predation (see Appendix S1: Figure S1a). To generate animals for the experiment, we raised single-genotype monocultures in the same conditions as experimental tanks. To add equal densities of each clone, we sampled each monoculture in triplicate to estimate prey density. We then added a fixed volume from each monoculture tank to each experimental tank to yield 70 individuals per genotype of all nine isoclonal lines (Week 0). Then *M. bicuspidata* spores (5000

spores L^{-1} based on Hite et al. [2016] and Strauss et al. [2017]) and *C. punctipennis* (third and fourth instar, collected from a nearby lake) were introduced 7 days after adding *D. dentifera* (Week 1). We checked tanks twice a week, replacing any pupating or dead *C. punctipennis* observed. Our sampling methods did not accurately quantify predator densities—given that the two intermediate predation treatments were 0.1 and 0.5 predators per liter, we would expect zero or one predator individual in the 2-L sample for these two intermediate predation treatments. However, we know that predator densities dropped in all treatments during the experiment. By the end, we recovered no predators from 46 of the 47 mesocosms. We did not routinely record predator densities in the subsamples during the experiment but have notes indicating the predator was seen in subsamples up to Week 4. Thus, while the predation treatments strongly differed in infection prevalence and prey density (see following discussion), predation levels likely converged beginning midway through the experiment. We did not anticipate this prior to doing this experiment; as a result of this experience, we modified our protocols for this type of experiment in the future to allow us to better track predator densities over time.

Following the addition of predators and parasites (Week 1), we sampled tanks weekly for 56 days. During the weekly sampling in Weeks 2–9 (July–August 2019), we quantified infection prevalence and prey density to test the healthy herds hypothesis. We mixed tanks and collected prey samples by sieving 2 L of water (80 μm mesh). We chose this volume because we anticipated that it would provide enough animals to accurately quantify infection levels without providing a substantial source of mortality; this destructive sampling (no animals were returned to the tanks) resulted in a mortality rate on the population of 4% per week. This entire sample was counted within 24 h, and infections were visually diagnosed (at 50× magnification, focused on late-stage [terminal] rather than earlier-stage infections [Stewart Merrill & Cáceres, 2018]). We also recorded the densities of infected and uninfected adult and juvenile prey in the sample. In addition, for up to 20 adult *Daphnia* from each replicate, we measured the number of eggs (technically embryos) contained in the brood chamber ("egg ratio"). The average sample size for the egg ratio analyses for the treatments with 0, 0.1, and 0.5 predators per liter was 11.5–15.0 adult *Daphnia* per 2-L sample per week; however, for the highest predation treatment, average sample sizes were lower due to very low densities (3.4–5.3 adult *Daphnia* per 2-L sample per week). We then stored these adults in 95% ethanol at 2°C. We also collected a sieved water sample to quantify a biomass proxy for the algal resource, chlorophyll a, using narrowband filters on a Trilogy fluorometer (Turner Designs, San Jose, CA, USA), following a chilled ethanol extraction (Welschmeyer, 1994).

To track the evolution of the prey population, we genotyped the preserved (adult) individuals at Weeks 2, 6, and 9. The average sample size for the 0- to 0.5-predators-per-liter treatments was 9.3–14.5 adult *Daphnia* per 2-L sample per week; however, for the highest predation treatment, average sample sizes were again lower (4.6–6.2 adult *Daphnia* per 2-L sample per week); see Appendix S1: Section S1.3 for genotyping methods (after Allen et al., 2010). We did not estimate parasite evolution because (a) we only added a single parasite genotype, (b) the parasite possesses surprisingly little genetic variation (Shaw et al., 2021), and (c) attempts to experimentally evolve it have failed (Auld et al., 2014; Cuco et al., 2020; Duffy & Sivars-Becker, 2007).

Statistical analyses

To test the healthy herds hypothesis, we analyzed data on infection prevalence, infected prey density, and total prey density for Weeks 2–9. A generalized linear model (GLM) with binomial error was overdispersed. Instead, we calculated the average for each of these metrics by tank. For density metrics, we took the natural log of the density plus one prior to calculating averages. For average infection prevalence and infected prey density, we performed an ANOVA with predator treatment as a fixed effect. Given the likely shift in predation regimes over the course of the experiment, as described earlier, we also tested to see whether there was an effect of predation in the middle of the experiment; because of overdispersion, we calculated the average across the different replicates for each predation treatment at Week 5, then regressed this against predation level. For natural log-transformed average density of total prey density, we performed an ANOVA with predator treatment, parasite presence/absence, and their interaction as fixed effects. We then used the emmeans package (Lenth, 2022) to compare specific treatments.

We found a strong reduction in parasitism in some treatments. To test whether evolution of resistance to parasitism could explain this reduction, we combined data on the genotypic composition of each prey population with estimates of infection susceptibility of each genotype. The infection rate of clone i, $\beta_i = p_i f_{S_i}$, is the product of filtering rate (f_{S_i}) and per-spore probability of infection (p_i). Thus, the mean infection rate for a population is the weighted average, $\sum_i \beta_i q_i(t)$, where $q_i(t)$ is the frequency of clone i at time t. We computed this mean at Weeks 2, 6, and 9. We then analyzed evolution (changes in mean β) using a linear mixed-effects model with time (Week

2, 6, or 9), predator treatment, parasite presence/absence, and all two- and three-way interactions and tank as random effects (using the nlme package; Pinheiro et al., 2022).

As shown in what follows, prey density declined sharply in high predation treatments over the first half of the experiment. To test whether this decline drove changes in prey–resource dynamics, we analyzed data on chlorophyll a and prey reproduction (egg ratio). We averaged natural log (LN) chlorophyll a and egg ratios from the first half of the experiment (Weeks 2–5) and fit ANOVAs with predator treatment, parasite presence/absence, and their interaction as fixed effects. We did not analyze data on chlorophyll a or egg ratio from the second half of the experiment because of uncertainty about predator densities (see earlier discussion). All analyses used R version 4.1.2 (R Core Team, 2022).

Theoretical methods overview

To gain additional insight about the observed dynamics, we analyzed a mathematical model parameterized to our system. We used it to answer two main questions: First, why did outbreaks occur in the lower predation treatments, but not the highest predation treatment? Second, what biological conditions prevented increased predation from leading to increased total prey density?

Multiclone model of prey–parasite dynamics

Our model describes the dynamics of multiple prey clones, an environmentally transmitted parasite, and predators held at a fixed density. The model equations are

$$\frac{dS_i}{dt} = \overbrace{G_i(\cdot)}^{\text{reproduction}} - \overbrace{m_i S_i}^{\text{nondisease mortality}} - \overbrace{\beta_i S_i Z}^{\text{infection}} - \overbrace{\alpha_i S_i P}^{\text{predation}} - \overbrace{\lambda S_i}^{\text{sampling}}, \tag{1}$$

$$\frac{dI_i}{dt} = \overbrace{\beta_i S_i Z}^{\text{infection}} - \overbrace{(m_i + \mu_i) I_i}^{\text{mortality}} - \overbrace{\omega \alpha_i I_i P}^{\text{predation}} - \overbrace{\lambda I_i}^{\text{sampling}}, \tag{2}$$

$$\frac{dZ}{dt} = \overbrace{\sum_i \chi_i (m_i + \mu_i + x_i \omega \alpha_i P) I_i}^{\text{spore release}} - \overbrace{\sum_i \left(f_{S_i} S_i + f_{I_i} I_i\right) Z}^{\text{ingestion}} - \overbrace{\delta Z}^{\text{degradation}} - \overbrace{\lambda Z}^{\text{sampling}}, \tag{3}$$

where S_i and I_i are the densities of susceptible and infected individuals of clone i, respectively, and Z is the density of infectious propagules (spores; see Table 1 for a complete list of model state variables and parameters). In

TABLE 1 Model parameters and state variables for multiclone model (Equation 1).

Parameter or state variable	Unit	Description
S_i	Individual/L	Density of susceptible prey of clone i
I_i	Individual/L	Density of infected prey of clone i
Z	Spores/L	Density of infectious propagules (spores)
p_i	Individual/spore	Per-spore probability of infection of clone i
f_S, f_I	L/h/individual	Filtering rates of susceptible and infected individuals, respectively, of clone i
β_i	L/h/spore	Infection rate for clone i, defined as $p_i f_S$
m_i	1/h	Prey mortality rate due to factors other than disease for clone i
μ_i	1/h	Disease-induced mortality rate for clone i
a_i	L/h/predator	Predator attack rate on susceptible individuals of clone i
ω	Unitless	Increase in attack rate on infected individuals
P	Predator/L	Predator density
χ_i	Spores/individual	Spore burst size (i.e., spores released from a dead infected individual) for clone i
x_i	Unitless	Fractional reduction in spore burst size of consumed individuals
δ	1/h	Spore degradation rate
λ	1/h	Liquid removal rate (during destructive sampling)

Note: Specific estimates for each of the clone-specific parameters are given in Appendix S1: Table S3.

Equation (1), susceptible individuals of clone i increase due to reproduction, $G_i(\cdot)$, and decrease due to mortality from nondisease sources ($m_i S_i$), infection ($p_i f_{S_i} S_i Z$), predation ($\alpha_i S_i P$), and destructive sampling (λS_i). The reproduction rate $G_i(\cdot)$ is left unspecified because we did not collect the density-dependent growth rates needed to parameterize it; however, that information is not needed for our equilibrium-based analyses. Infection rate ($\beta_i = p_i f_{S_i}$) is the product of the per-spore probability of infection (p_i) and the filtering rate of susceptible individuals (f_{S_i}). The predation term assumes fixed predator density (P) (based on the experimental design) and predators have a linear functional response with attack rate α_i. In Equation (2), infected individuals increase due to infection ($\beta_i S_i Z$) and decrease due to mortality from disease ($\mu_i I_i$) and nondisease sources ($m_i I_i$), predation ($\omega\alpha_i I_i P$), and destructive sampling (λI_i). The parameter ω allows for predators to have higher attack rates ($\omega > 1$) on infected prey. In Appendix S1, we also consider nonselective predation ($\omega = 1$); the results differ only modestly (see Appendix S1: Sections S4.1 and S4.2). In Equation (3), spores increase when released by infected prey, $\sum_i \chi_i (m_i + \mu_i + x_i \omega \alpha_i P) I_i$, and decrease due to ingestion, $\sum_i (f_{S_i} S_i + f_{I_i} I_i) Z$, degradation, δZ, and destructive sampling, λZ. Release rate upon host death is the product of the spore burst size (χ_i) and mortality rates of infected prey. Predators reduce burst size ($x_i < 1$) when they kill hosts before parasites reach the maximum within-host density (Appendix S1: Section S3.2). Ingestion removes spores, with susceptible individuals having higher filtering rates than infected ones ($f_{S_i} > f_{I_i}$) (e.g., Penczykowski et al., 2022).

Details about estimation of parameters from smaller, ancillary experiments and their values are given in Appendix S1: Sections S1 and S3.2. As indicated earlier, susceptibilities to predation (predator attack rates, α_i) and susceptibilities to infection (infection rates, β_i) were uncorrelated (Appendix S1: Figure S1a).

Predicting the impact of predation on prey density

We identified conditions under which predators increased total prey density by calculating the response of total prey density at equilibrium (N^*) to increased predator density (P). Specifically, the partial derivative $\partial N^*/\partial P$ determines whether higher predation increases ($\partial N^*/\partial P > 0$) or decreases ($\partial N^*/\partial P < 0$) prey density. This analysis focused on a single-clone version of Equations (1–3) because analysis of the full version requires parameterization of the reproduction rates, $G_i(\cdot)$ (Appendix S1: Section S4.2).

Defining and computing R_0 and R

To explore why outbreaks occurred in the lower, but not the highest, predation treatments, we used the multiclone model (Equation 1) to estimate the parasite's basic reproduction number (R_0). R_0 is the average number of new infections produced by a single infected individual in a completely susceptible population (analogous to our no-parasite treatment). Outbreaks are predicted to occur if $R_0 > 1$. To make comparisons between treatments with and without parasites, we also computed the parasite's reproduction number (R). The reproduction number is the average number of new infections produced by an infected individual in a population made up of both susceptible and infected prey (analogous to our treatment with the parasite). Assuming prey densities remain fixed, an infected individual infects more than one prey in its lifetime if $R > 1$.

We calculated R_0 and R with the next-generation matrix approach (Diekmann et al., 2010; van den Driessche & Watmough, 2008):

$$R_0 = \sum_i \frac{\chi_i (m_i + \mu_i + x_i \omega \alpha_i P)}{m_i + \mu_i + \omega \alpha_i P} \cdot \frac{\beta_i q_i N}{\delta + \sum_j f_{S_j} q_j N}, \quad (4)$$

$$R = \sum_i \frac{\chi_i (m_i + \mu_i + x_i \omega \alpha_i P)}{m_i + \mu_i + \omega \alpha_i P} \cdot \frac{\beta_i q_i (N - I)}{\delta + \sum_j f_{S_j} q_j (N - I) + f_{I_j} q_j I}, \quad (5)$$

where N is the total prey density, I the total density of infected prey, $S = N - I$ the total density of susceptible prey, and q_i the frequency of clone i (Appendix S1: Section S3.3). Note that because Equation (4) assumes all prey are susceptible, the total density N is equal to the total density of susceptible prey ($S = N$). In both sums, the first fraction is the production rate of spores by infected individuals of clone i multiplied by the average lifespan of an infected individual of clone i ($1/[m_i + \mu_i + \omega\alpha_i P]$). This ratio defines the average lifetime production of spores by an infected individual of clone i. The second fraction in both sums is the infection rate of susceptible individuals of clone i multiplied by the average lifespan of a spore ($1/[\delta + \sum_j f_{S_j} q_j N]$ or $1/[\delta + \sum_j f_{S_j} q_j (N - I) + f_{I_j} q_j I]$). It defines the average lifetime production of newly infected individuals of clone i by a spore. We computed R_0 and R using the estimated parameter values and measured prey densities and clone frequencies at Weeks 0 and 2; Weeks 6 and 9 were not analyzed because of possible changes in predator density.

RESULTS

Empirical result: Predation reduced infection prevalence and infected prey density without increasing total prey density

Predation reduced infection prevalence (Figure 1a,b) and the density of infected prey (Figure 1c,d). After Week 2, infection prevalence dropped to zero in all prey populations experiencing the highest levels of predation. Conversely, infections persisted throughout the experiment in all populations without predation. Predation significantly impacted average infection prevalence ($F_{3,20} = 8.46$, $p = 0.0008$; Figure 1b) and average density of infected prey ($F_{3,20} = 15.2$, $p < 0.0001$; Figure 1d), with a significant negative effect of predator density treatment on infection prevalence ($t_3 = -8.0$, $p = 0.015$) and average density of infected prey ($t_3 = -10.2$, $p = 0.0096$) at Week 5. This reduction did not arise due to the evolution of resistance to infection. Prey populations became significantly more resistant (lower mean infection rate) by the end of the experiment (Figure 1g; time: $F_{1,71} = 112.0$, $p < 0.0001$). Resistance evolved even in populations not exposed to parasites, but more so in those with them (Figure 1g,h; parasitism: $F_{1,31} = 4.86$, $p = 0.033$). Importantly, susceptibility to infection was increasing when parasites disappeared from the high predation populations (Figure 1a,g), and predation did not significantly influence the evolution of infection rate (predation: $F_{3,39} = 2.16$, $p = 0.108$). For this analysis, all interactions were not significant (Appendix S1: Table S1). Overall, the reduction in parasitism cannot be attributed to the evolution of resistance to infection.

Reduction of parasite prevalence did not increase prey densities (Figure 1e,f). Instead, the highest predation treatment cleared infection but had much lower prey density. Higher predation decreased prey density (predation: $F_{3,39} = 37.3$, $p < 0.0001$) while parasitism did not change it (parasitism: $F_{1,39} = 2.54$, $p = 0.12$, predation × parasitism: $F_{3,39} = 0.82$, $p = 0.49$; Figure 1f). Comparing across treatments, the highest predation treatments with and without parasites did not differ from one another ($t_1 = 1.54$, $p = 0.78$), but these two treatments (i.e., 1.0 predator L^{-1}, with and without parasites) differed significantly from all of the other treatments; none of those other treatments differed significantly from one another (Appendix S1: Table S1). Thus, the highest predation treatments had lower prey densities than the other predation treatments, and the extent of density reduction in prey did not depend on whether the population was parasitized.

Theoretical result: High predation lowers parasite reproduction number to near or below 1

Consistent with the experiment, predation lowered the basic reproduction number, R_0, and the reproduction number, R. More specifically, R_0 and R were highest without predation and lowest in the highest predation treatment (Figure 2a,b). The reason is that high predation levels mean that more infected prey die from predation (with reduced burst size) than from infection (with full burst size). This reduction in burst size reduces R_0 and R.

The decreasing values of R_0 and R with increased predation provide indirect support for the first prediction of the healthy herds hypothesis (that predation should reduce disease in prey populations). In our experiment, the parasite did not persist in the highest predation treatment (black lines in Figure 1a,c), indicating that R_0 and R were less than 1. In partial agreement with this, about half of the predicted values of R_0 and R were less than 1 for the highest predation treatment at all times (black points in Figure 2). The other values remained near 1. Hence, the R_0 and R calculations qualitatively agree with how infection prevalence changed across treatments in the experiment.

Additionally, R_0 and R increased for all low predation treatments between Weeks 0 and 2, but only for some of the high predation treatments (Figure 2a,b). As described in Appendix S1: Section S4.1, we used the Geber method (Hairston Jr. et al., 2005) to show that the changes in R_0 and R were primarily driven by changes in prey densities rather than changes in clone frequencies (i.e., evolution). Specifically, large increases in prey density elevated R_0 and R in the low predation treatments (blue lines in Figure 1e). The smaller changes in the highest predation treatment were due to decreases or smaller increases in prey density (black lines in Figure 1e).

Theoretical result: High infection prevalence prevented predators from increasing prey density

Our analysis of a single-clone version of the model (Equation 1) in Appendix S1: Section S4.2 shows that higher prey density with increased predator density, $\partial N^*/\partial P > 0$, requires that (i) predators have sufficiently higher attack rates on infected prey than susceptible prey ($\omega > 1$) and that (ii) consumed infected prey have sufficiently smaller burst sizes than infected prey that were not consumed ($x_i < 1$). These two conditions were met (Appendix S1: Sections S3.2 and S4.2). The third condition is that (iii) the proportion of infected prey (I/N) must

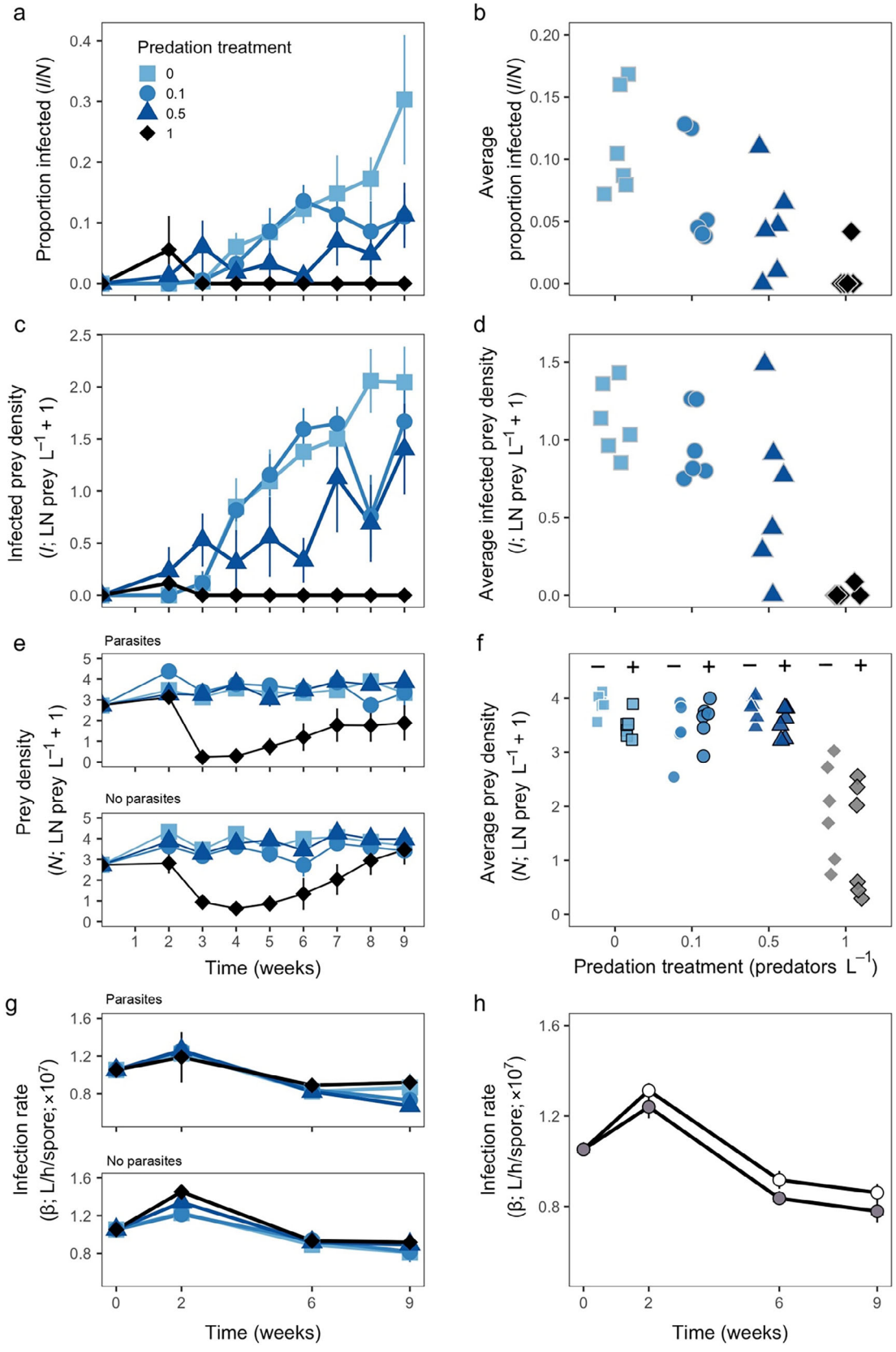

FIGURE 1 Legend on next page.

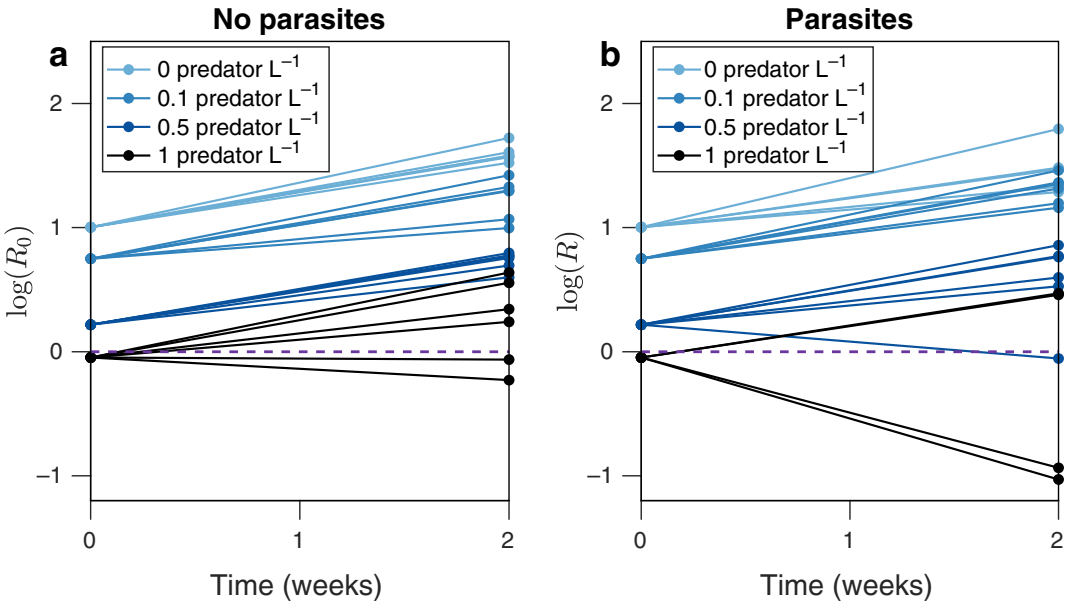

FIGURE 2 Predation reduced (a) the parasite's basic reproduction number (R_0) and (b) reproduction number (R). Values of R_0 and R were computed using Equations (4) and (5), estimated parameter values, and the measured clone frequencies and prey densities at Weeks 0 and 2. Each point connected by lines represents an estimated value of R_0 or R for a particular tank. Line coloring indicates the predation treatment. Some replicates are missing points because very low prey density eliminated estimation of clone frequencies. The dashed line indicates $R_0 = R = 1$.

be sufficiently low. Under these conditions, prey density is highest in the absence of the predator and parasite, lower in the presence of just the predator, even lower in the presence of the predator and parasite, and lowest in the presence of just the parasite. These conditions result in stronger regulation of the prey population by the parasite than by predators.

Our empirical results (Figure 1e) show that prey density decreased from the lower to highest predation treatments. This suggests that $\partial N^*/\partial P < 0$, and because conditions (i) and (ii) were met in our system, we inferred that predators decreased prey density because infection prevalence was too high. To verify this inference, we parameterized the single-clone version of the model using averaged parameter values computed from the clone frequencies observed at Weeks 0 and 2 of our mesocosm experiments (Appendix S1: Section S4.2). The parameterized single-clone model predicted that increased prey density with increased predation required an infection prevalence of approximately 5% or less (Appendix S1: Figure S6)—a condition rarely met in the experiment (Figure 1a). Thus, despite satisfying conditions about selectivity and burst size, predators likely did not increase prey densities because infection prevalence remained too high.

Why does infection prevalence need to be sufficiently low for predators to increase prey density? Increased predator density has a negative direct effect on prey density because it increases mortality for infected and susceptible prey. At the same time, predators have positive indirect effects on prey density because increased predator density (i) reduces intraspecific competition for resources (by reducing density) and (ii) decreases rates of infection (and, thus, rates of disease-induced mortality) by reducing spore burst sizes of consumed infected prey. If infection prevalence is low, then the negative direct effect of increased mortality from predation is

FIGURE 1 Predation decreased the prevalence of infection (a, b), the density of infected prey (*D. dentifera*) (c, d), and total prey density (e, f). Prey evolved resistance to infection (i.e., lower mean weighted infection rate) (g, h) after the parasite went extinct in the high predation treatments. Panels (a), (c), (e), and (g) show time series data averaged across replicates, whereas panels (b), (d), and (f) show the averages across replicates and time; for panels (c)–(f), the *y*-axis is the natural log (LN) of infected or total prey density per liter plus 1. Error bars on panels (a, c, e, g, and h) represent SEs. In panels (b), (d), and (f), individual replicates are shown, jittered horizontally to increase visibility. In panel (f), the points are grouped by whether they were the no-parasite treatment ("−" label in upper left set of symbols for each predation treatment) or whether they were the + parasite treatment ("+" label in upper right set of symbols for each predation level, black outlines around symbols). Panel (h) shows the same data as in panel (f) averaged across predation treatments; lower infection rate means higher infection resistance.

counteracted by the positive indirect effects of decreased intraspecific competition and decreased infection rates. The net result increases prey density with higher predation. Alternatively, with higher infection prevalence, decreased intraspecific competition and burst sizes cannot counteract the increased mortality from predation.

Empirical result: Predator-driven reductions in prey influenced prey–resource dynamics

High predation prevented epidemics but inflicted major density costs on prey (Figure 1e). After prey density dropped, chlorophyll increased, especially in the highest predation treatment (Figure 3a; analysis of average LN chl in Weeks 2–5: predation: $F_{3,39} = 7.32$, $p = 0.0005$, parasitism: $F_{1,39} = 0.88$, $p = 0.35$, predation × parasitism: $F_{3,39} = 1.47$, $p = 0.24$). This increase fueled higher reproduction of prey (egg ratios) (Figure 3c,d; analysis of average egg ratios in Weeks 2–5: predation: $F_{3,39} = 18.5$, $p < 0.0001$, parasitism: $F_{1,39} = 0.53$, $p = 0.47$, predation × parasitism: $F_{3,39} = 0.20$, $p = 0.90$).

DISCUSSION

The healthy herds hypothesis suggests that increasing predation can reduce parasitism and, as a result, increase densities of prey populations. However, a recent meta-analysis questioned the generality of healthy herds dynamics (Richards et al., 2022). In our study manipulating predation levels in a predator–prey–parasite system, we found partial support for healthy herds. Increasing predation reduced parasitism (both prevalence and infected prey density). Thus, if a management goal centers on low(er) parasitism in a population (e.g., because of concerns about spillover of parasites to humans or other populations), adding predators can help. The theoretical analysis supports this conclusion: High enough predation decreased the reproductive number of the parasite to near or below 1, inhibiting parasite spread. However, predation greatly decreased prey population sizes at the highest predation levels, despite eliminating the virulent parasite. This result arose in both the mesocosms and the theoretical analysis. Thus, if our primary concern is overall population size (e.g., to conserve genetic diversity or avoid stochastic extinctions), adding high levels of predation that eliminate disease could be detrimental. Interestingly, intermediate predation levels reduced parasitism without incurring a cost in terms of overall prey density—a situation that would reduce spillover risk without harming prey density.

The experiment supported the first but not second part of the healthy herds hypothesis: Predation reduced infection prevalence, but prey density did not increase as a result. Why did epidemic suppression not increase prey density? In its original formulation (Packer et al., 2003), the healthy herds effect of decreased parasitism and increased prey density was most likely for (1) highly virulent parasites, (2) highly aggregated macroparasites, (3) long-lived prey, and (4) selective predation on infected prey. Our plankton system satisfies Conditions 1 and 4. Our theoretical analysis revealed a fifth condition: sufficiently low infection prevalence (see Appendix S1: Section S4 for details). This fifth condition occurs because, at low prevalence, enhanced reproduction by susceptible hosts can compensate for the mortality imposed by selective predators; however, if prevalence becomes too high, mortality from predation becomes too high for such compensation. Therefore, our analysis reveals that increased prey density with increased predation can arise only if infection prevalence is sufficiently low.

In our experiment, intermediate levels of predation reduced parasitism but not prey density. This result does not meet the full healthy herds prediction yet remains of interest because it suggests predation can reduce infection levels (and, therefore, risk of spillover to nearby populations) without harming prey density. However, too much predation (as at the highest level here) can greatly deplete prey. Hence, lower spillover risk can come at a severe density cost in prey, depending on the exact level of predation. Therefore, any management decisions would need to weigh the potential costs and benefits associated with increasing predation. The result from the intermediate predation levels also shows how qualitative results can differ along a predation gradient. Unfortunately, most studies of the healthy herds hypothesis use only two predation levels (presence/absence or high/low; Richards et al., 2022). We recommend that future work at the predation–parasitism interface span predation gradients instead.

The healthy herds hypothesis has similarities with another dominant topic in disease ecology, the dilution effect: Both of these community modules of disease highlight how adding a species can reduce disease prevalence (Civitello, Cohen, et al., 2015; Johnson et al., 2015; Rohr et al., 2020). For instance, both can reduce disease encounter (i.e., removal of propagules), via direct consumption of propagules or selective removal of infected hosts. However, work on the dilution effect and healthy herds hypothesis has proceeded largely independently. To develop a more robust understanding of the factors driving infection levels in natural populations, we must build toward studies recognizing that focal hosts play a

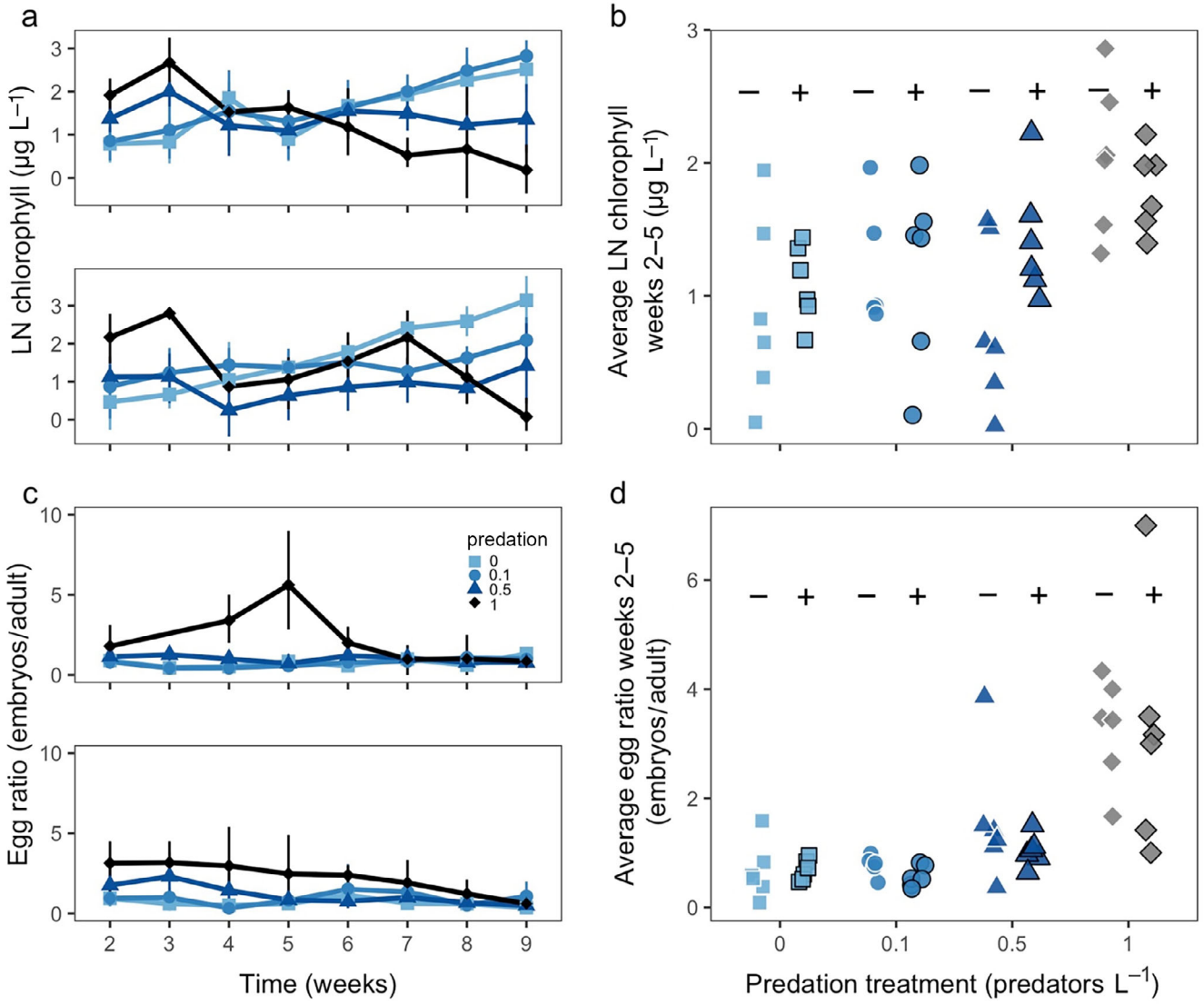

FIGURE 3 Algal abundance (as measured by chlorophyll a) increased in the highest predation treatments early in the experiment, driving higher egg ratios in the first half of the experiment. Panels (a) and (b) show chlorophyll data, while panels (c) and (d) show egg ratio (number of embryos per adult *D. dentifera*) data. Panels (a) and (c) show time series data; error bars represent SEs. We could not estimate egg ratio in any population of the high predation + parasitism treatment in Week 3 because prey densities reached such low levels. Panels (b) and (d) show averages for the first half of the experiment (Weeks 2–5) for each replicate, jittered to increase visibility and with the points grouped by whether they were the no-parasite treatment ("−" label in upper left set of symbols for each predation treatment) or the + parasite treatment ("+" label in upper right set of symbols for each predation level, black outlines around symbols).

multitude of roles in food webs. We require studies that combine food web modules (as in Rohr et al. [2015] and Strauss et al. [2016]), allowing us to better integrate the multiple roles that species play simultaneously (hosts, competitors, prey). Doing so will allow better management of populations where there are multiple, potentially competing, goals (e.g., reducing disease levels vs. maintaining high densities).

Our experiment did not measure resources through time, but resources likely varied over time because resources were replenished weekly. While we know that resource levels have the potential to strongly influence host–parasite dynamics (Civitello, Penczykowski, et al., 2015; Johnson et al., 2007; Pedersen & Greives, 2008) and the effects of predators on parasitism (Hall et al., 2005), our model suggests that variation in resource availability is unlikely to qualitatively affect the observed reduction in total prey density due to predation in our experiment. The way equilibrium prey density is affected by changes in predator density is given by Appendix S1: Equation (S26). Variation in resources causes variation in prey growth rate and variation in prey growth rate would qualitatively alter our results only if Appendix S1: Equation (S26) were to change signs. As explained in more detail at the end of

Appendix S1: Section S4.2, Equation (S26) can change signs only if (1) the prey per capita growth rate is an increasing function of prey density or (2) infection prevalence drops below 5%. The former is unlikely because at the high prey densities in our experiment, the variation in prey growth rates caused by variation in resource availability is unlikely to alter the negative relationship between prey density and prey per capita growth rate. The latter is also unlikely because infection prevalence was greater than 10% at the end of the experiment and variation in resources is unlikely to cause a large enough decrease in prey density that the infection prevalence drops by more than half. In total, our model suggests that the variation in resource availability is unlikely to have affected the negative relationship between total prey density and predator density level.

An interesting finding of our experiment was that parasitism was reduced in the intermediate predation treatments, but prey density was not, which would mean reduced risk of disease spillover to neighboring populations without the host population suffering reduced densities. However, we know that predation levels declined to low levels in all treatments midway through the experiment, meaning that the predation effects we measured are likely conservative. If predation levels had stayed at the intended levels, it is possible that we would have seen an impact on prey density in these intermediate predation treatments. This uncertainty—along with the challenges associated with trying to maintain particular predation levels, even in relatively controlled settings such as our environment—mean that caution is warranted for managers seeking to manipulate predation levels. Achieving and maintaining a predation level that reduces parasitism without harming density might be equivalent to threading the proverbial needle.

Here, we found that increased predation reduced the prevalence of a virulent parasite, illustrating the potential for predation to lower disease in prey. However, even though this virulent parasite could not persist in the presence of high predation, prey population size did not benefit, contrary to the healthy herds hypothesis. Instead, high predation led to healthy but depleted herds. Together, the prevalence-versus-density results showcase the pros and cons of disease control by predators: Predation could reduce spillover risk but also harm prey population sizes. Interestingly, a different type of interaction—that between prey and their resources—was clearly impacted by the variation in predation, reminding us that predator–prey–parasite interactions do not occur in isolation. Expanding our focus to include a broader perspective on the many roles that individual species play in a food web will allow us to better understand—and hopefully even predict—how populations will respond to changing predation regimes and along broad predation gradients.

AUTHOR CONTRIBUTIONS

Carla E. Cáceres, Meghan A. Duffy, and Spencer R. Hall initiated the study. The experiment was designed by Carla E. Cáceres, Turner S. DeBlieux, Meghan A. Duffy, Spencer R. Hall, and Laura K. Lopez and carried out by Laura K. Lopez, Turner S. DeBlieux, Bruce O'Brien, and Spencer R. Hall. Genotyping was carried out by Ilona A. Menel and Carla E. Cáceres; trait measurements were carried out by Laura K. Lopez, Ilona A. Menel, and Carla E. Cáceres. Model development and analysis were led by Michael H. Cortez, with feedback from Meghan A. Duffy, Laura K. Lopez, and Spencer R. Hall. Meghan A. Duffy, Michael H. Cortez, and Laura K. Lopez wrote the initial draft of the manuscript; all authors contributed to editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

All data and code (Duffy et al., 2023) used for the analyses and figures are available in Dryad at https://doi.org/10.5061/dryad.w3r2280tm.

ORCID

Meghan A. Duffy https://orcid.org/0000-0002-8142-0802

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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