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WARMER DOES NOT HAVE TO MEAN SICKER: TEMPERATURE AND PREDATORS CAN JOINTLY DRIVE TIMING OF EPIDEMICS

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Abstract. Ecologists and epidemiologists worry that global warming will increase disease prevalence. These fears arise because several direct and indirect mechanisms link warming to disease, and because parasite outbreaks are increasing in many taxa. However, this outcome is not a foregone conclusion, as physiological and community-interaction-based mechanisms may inhibit epidemics at warmer temperatures. Here, we explore this thermal-community-ecology-based mechanism, centering on fish predators that selectively prey upon *Daphnia* infected with a fungal parasite. We used an interplay between a simple model built around this system's biology and laboratory experiments designed to parameterize the model. Through this data–model interaction, we found that a given density of predators can inhibit epidemics as temperatures rise when thermal physiology of the predator scales more steeply than that of the host. This case is met in our fish–*Daphnia*–fungus system. Furthermore, the combination of steeply scaling parasite physiology and predation-induced mortality can inhibit epidemics at lower temperatures. This effect may terminate fungal epidemics of *Daphnia* as lakes cool in autumn. Thus, predation and physiology could constrain epidemics to intermediate temperatures (a pattern that we see in our system). More generally, these results accentuate the possibility that warmer temperatures might actually enhance predator control of parasites.

Key words: Daphnia; *global warming; host–parasite; persistence thresholds; thermal physiology*.

Introduction

Will an increasingly warmer world necessarily become a sicker world? Unfortunately, mounting evidence suggests that disease prevalence continues to increase among many groups of plant and wildlife species, and this increase likely ties directly and indirectly to global warming (Harvell et al. 1999, 2002, Lafferty et al. 2004, Ward and Lafferty 2004). Global warming links directly with disease prevalence because increased temperatures can accelerate the fitness of parasites, reduce recruitment bottlenecks for parasites during winter, and weaken hosts (Porter et al. 1989, Harvell et al. 2001, 2002, Mitchell et al. 2005). Furthermore, warmer temperatures may allow vectors of parasites to expand their range (Martens et al. 1999, Anderson et al. 2004). Such range expansion can indirectly introduce diseases to novel habitats.

These doom-and-gloom scenarios do not necessarily apply to all taxa or all situations, of course. Indeed, warming does not necessarily increase fitness of all parasites. For instance, virulence of parasites may not change, may decrease, or may respond unimodally to increasing temperatures (Stacey et al. 2003, Thomas and Blanford 2003). These various responses stem, in part, from the fact that vital rates of both hosts and parasites ultimately scale unimodally along broad temperature gradients (Huey and Stevenson 1979, Thomas and Blanford 2003). More specifically, vital rates increase with temperature until some optimum is reached; once temperature exceeds this optimum, vital rates decline gradually with increasing temperature for some taxa, but rapidly for others. In some host–parasite systems, a parasite's optimum occurs at cooler temperatures than the optimum of its host (e.g., fungus–grasshopper systems [Carruthers et al. 1992, Blanford and Thomas 1999, Blanford et al. 2003]). In such instances, a host can use warmer temperatures to help defeat its parasites through behavioral modification of its thermal environment. However, one cannot take too much comfort from these physiology- and behavior-based mechanisms because warmer temperatures can also select for shifts in temperature optima (Huey and Hertz 1984, Huey and Kingsolver 1989, 1993, Bennett et al. 1992). The exact evolutionary trajectory of host–parasite systems in a warmer world may depend sensitively upon underlying genetic correlation structures and interactions between host genotypes, parasite genotypes, and the environment (Blanford et al. 2003, Thomas and Blanford 2003, Stacey et al. 2003, Mitchell et al. 2004*a*). Thus, longer-

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term response of the physiology of host–parasite systems to global warming becomes difficult to predict.

Another major unknown variable has received considerably less attention but might prove to become quite important: how will other interactive but non-vector species respond to warming? Other species can profoundly shape the outcome of parasitism in host populations, and predators provide an important example. Predators can actually inhibit epidemics by selectively culling sick hosts and/or by maintaining host densities below levels required for parasites to persist (Hudson et al. 1992, Packer et al. 2003, Lafferty 2004, Ostfeld and Holt 2004, Duffy et al. 2005, Hall et al. 2005). The question thus becomes, will warmer temperatures enhance or hinder predator control of parasites? If both their per-capita feeding rates (i.e., physiological scaling with temperature [Kooijman 2003, Gillooly et al. 2001]) and density respond positively to temperature, predators might help prevent disease outbreaks as temperatures rise. Alternatively, if hotter regimes inhibit predator physiology or recruitment, warming may indirectly accelerate spread of disease by reducing or eliminating a potentially important, indirect source of parasite control.

Here, we consider these warming–food-web scenarios using a *Daphnia*-host–fungal-parasite–fish-predator system. This system is ideally suited for such questions because the vital rates of *Daphnia*, their parasites, and fish depend on temperature (Geller 1975, Mourelatos and Lacroix 1990, Kooijman 1993, Gillooly et al. 2001, Mitchell et al. 2004*b*, 2005). Additionally, fish selectively prey upon parasitized *Daphnia* (Duffy et al. 2005). Furthermore, the seasonal phenology of several parasites of *Daphnia* follows a similar, suggestive trajectory: epidemics start as lakes or ponds cool from their peaks in late summer or autumn but terminate as the habitat becomes cold later in autumn (Bittner et al. 2002, Mitchell et al. 2004*a*, Duffy et al. 2005, Cáceres et al. 2006). If coldness slows physiology of the parasite at faster rates than it slows physiology of the host, cold temperatures could inhibit epidemics. Warmer temperature might also accelerate the inhibitory effect of ectothermic predators on epidemics. Indeed, we argue both points below by developing quantitative predictions from a simple, relevant model.

General Modeling

Biology and equations

We have built our model around the biology of a particular *Daphnia*-host–fungal-parasite system, but many aspects of its biology are generic to other disease systems. The host, *Daphnia dentifera*, is a key crustacean zooplankton grazer that inhabits open waters of north-temperate lakes (Tessier and Woodruff 2002). Its parasite is the ascomycetous yeast *Metschnikowia bicuspidata*. Reproduction of the *Daphnia* host depends upon host density, but infection with *Metschnikowia* reduces fecundity and survival of the host (Ebert et al. 2000; M. A. Duffy and S. R. Hall *in review*). Transmission of the parasite occurs horizontally as hosts encounter spores of the fungus (Codreanu and Codreanu-Balcescu 1981). The fungus continues to multiply within an infected host, eventually filling its body with spores until the host dies, at which point spores are released into the water column (Ebert and Weisser 1997; see Plate 1). The host never recovers from infection (Ebert et al. 2000). However, infection renders the ordinarily translucent *Daphnia* more opaque, and hence more vulnerable to visually oriented predators such as the bluegill sunfish *Lepomis macrochirus* which consume infected hosts and spores (Mittelbach 1981, Duffy et al. 2005).

We used a differential equation model to capture the essence of this *Daphnia*–fungus–fish system. This system represents change in density of susceptible hosts (S), infected hosts (I), and spores (Z) as the balance between gains from production and losses from various sources (see Table 1 for meanings of symbols and Appendix A for more analytical details):

$$\frac{dS}{dt} = (bS + b_{\mathrm{I}}I)(1 - c[S + I]) - dS - \beta SZ - fPS \quad (1a)$$

$$\frac{dI}{dt} = \beta SZ - (d + v)I - \theta fPI \quad (1b)$$

$$\frac{dZ}{dt} = \sigma(d + v)I - mZ. \quad (1c)$$

Production of susceptible hosts (Eq. 1a) is the maximum birth rate of susceptible and infected hosts (at rates b and b_{I}, respectively, where $0 \leq b_{\mathrm{I}} < b$) multiplied by a term incorporating density dependence of reproduction (at strength c). This density dependence arises because both susceptible hosts and infected hosts consume resources. Losses of susceptible hosts include background mortality (at rate d), transmission of the parasite as susceptible hosts contact spores (at density Z and transmission rate β), and consumption by predators at density P who feed at rate f. Hosts become infected (Eq. 1b) as they contact spores, and infected hosts are lost due to background and parasite-induced mortality (at rate $d + v$) and selective mortality from predators (where $\theta > 1$ indicates that predators prefer infected to susceptible hosts). Finally, spores (Eq. 1c) are produced when infected hosts die (where σ is the number of spores released per dead host) but are lost by mortality or sinking at rate m. We assume that spores contained in consumed infected hosts are lost from the system, but we are currently working to verify or update this assumption.

Results

This model provides a simple rule determining when the parasite can persist in a system at equilibrium (see Appendix A for stability analyses). Parasite persistence (i.e., $I^* > 0$) requires that the density of susceptible hosts without parasites (the boundary equilibrium, S_{b}^*) ex-

TABLE 1. Response variables and parameters in the host–parasite-spore–predator model.

Symbol	Units	Meaning	Estimate (source)
I	no./L	density of infected hosts	
S	no./L	density of susceptible hosts	
Z	no./L	density of spores (sp.)	
t	no. days	time	
b	d^{-1}	maximal birth rate, susceptible hosts, at T_R	0.4 (a)
b_I	d^{-1}	maximal birth rate, infected hosts, at T_R	0.21 (b)
c	$(no./L)^{-1}$	strength of density dependence on birth rates	1/20 (c)
d	d^{-1}	background mortality rate	0.05 (c)
m	d^{-1}	loss rate of spores	0.033
f	$d^{-1}(no./L)^{-1}$	feeding rate of predators	200
P	no./L	density of predators	$0–2 \times 10^{-3}$
T	°C	temperature	7–27
T_A		Arrhenius coefficient for the host	6400 (d)
T_R	°C	reference temperature	20
v	d^{-1}	virulence mortality	0.05 (b)
β	$d^{-1}(no./L)^{-1}$	transmission rate at reference temperature (T_R)	3×10^{-6} (b)
θ		selectivity of predators on infected hosts	9 (c)
ρ		thermal scaling factor, parasite	2.7 (b)
ρ_P		thermal scaling factor, predator	1.75 (d)
σ		spores produced per host	6.4×10^4 (b)

Sources: a, Tessier and Woodruff (2002); b, this study; c, Duffy et al. (2005); d, Kooijman (1993).

ceeds their density when coexisting with parasites (the interior equilibrium, S_i^*). The intuition behind this rule is that S_i^* is the parasite's minimal "resource" requirement, while S_b^* represents the resource supplied to an invading parasite by the system. If resource available to the parasite (S_b^*) is lower than this minimum S_i^*, the parasite cannot maintain itself. For this model, these quantities are

$$S_b^* = \left(\frac{1}{c}\right)\left(1 - \frac{d + fP}{b}\right) \tag{2a}$$

$$S_i^* = \left[\frac{m}{\sigma(d + v)}\right]\left(\frac{d + v + \theta fP}{\beta}\right). \tag{2b}$$

Thus factors that increase S_b^* and/or lower S_i^* make it easier for the parasite to persist. As will become important below, the boundary equilibrium S_b^* is a negative function of predator density P, predator feeding rate f, and density dependence c (as determined by calculating the partial derivatives of the equilibria with respect to each parameter). Meanwhile, the interior equilibrium S_i^* is a positive function of predator density and feeding rate. This phenomenon occurs indirectly because predators consume sick hosts, thus decreasing infection from the host's other enemy (the parasite). The quantity S_i^* is also a negative function of transmission rate (β), spore production per host (σ), and virulence mortality (v), all of which increase the parasite's fitness.

We assume that vital rates and quantities can become temperature dependent using the Arrhenius function (following an approach related to Gillooly et al. [2001] and Savage et al. [2004]). It yields generalized rate k as a function of temperature, T (Kooijman 1993):

$$k(T) = k_R \exp\left[T_A\left(\frac{1}{T_R} - \frac{1}{T}\right)\right] \tag{3}$$

where k_R is the rate at a reference temperature, T_A is a scaling constant (called the Arrhenius temperature), and T_R is the reference temperature. With biologically relevant parameters (Kooijman 1993), this function accelerates as temperature warms (although at extremely high temperatures, it does plateau at $k_R \exp[T_A/T_R]$ [Gillooly et al. 2001]). Thus, it represents the increasing portion of the generalized unimodal response common in thermal biology (Huey and Stevenson 1979). This assumption seems reasonable for *Daphnia* because these animals die at temperatures just past their thermal optima (Kooijman 1993, Mitchell et al. 2004*a*). Additionally, vital rates of parasite and predator do not necessarily scale with the host's vital rates (Kooijman 1993, Mitchell et al. 2005). To incorporate this detail, one can replace the Arrhenius temperature (T_A) for parasite and predator rates with ρT_A or $\rho_P T_A$, respectively, where ρ and ρ_P are the ratio of Arrhenius temperatures of the enemies to that of the host (called "scaling factors" below). If these scaling factors become greater than one, vital rates of the particular enemy scale more steeply with temperature than do those of the host.

Once vital rates and quantities become functions of temperature, the equilibrial population sizes of the host with (S_i^*) and without (S_b^*) parasites can vary with temperature (T) and predator density (P). The direction of this change depends specifically on which parameters scale with temperature and whether vital rates of the enemies scale similarly with those of the host. To start, we consider a baseline case where the host traits of maximal birth rate (b) and non-specific loss rates (d), the parasite traits transmission rate (β), virulence mortality (v), host fecundity (b_I), and loss rates (m), and feeding rate of the predator (f) all scale with temperature according to the host's physiology (i.e., $\rho = \rho_P = 1$). Meanwhile, strength of density dependence (c), spore production per host (σ), and predator selectivity (θ) do

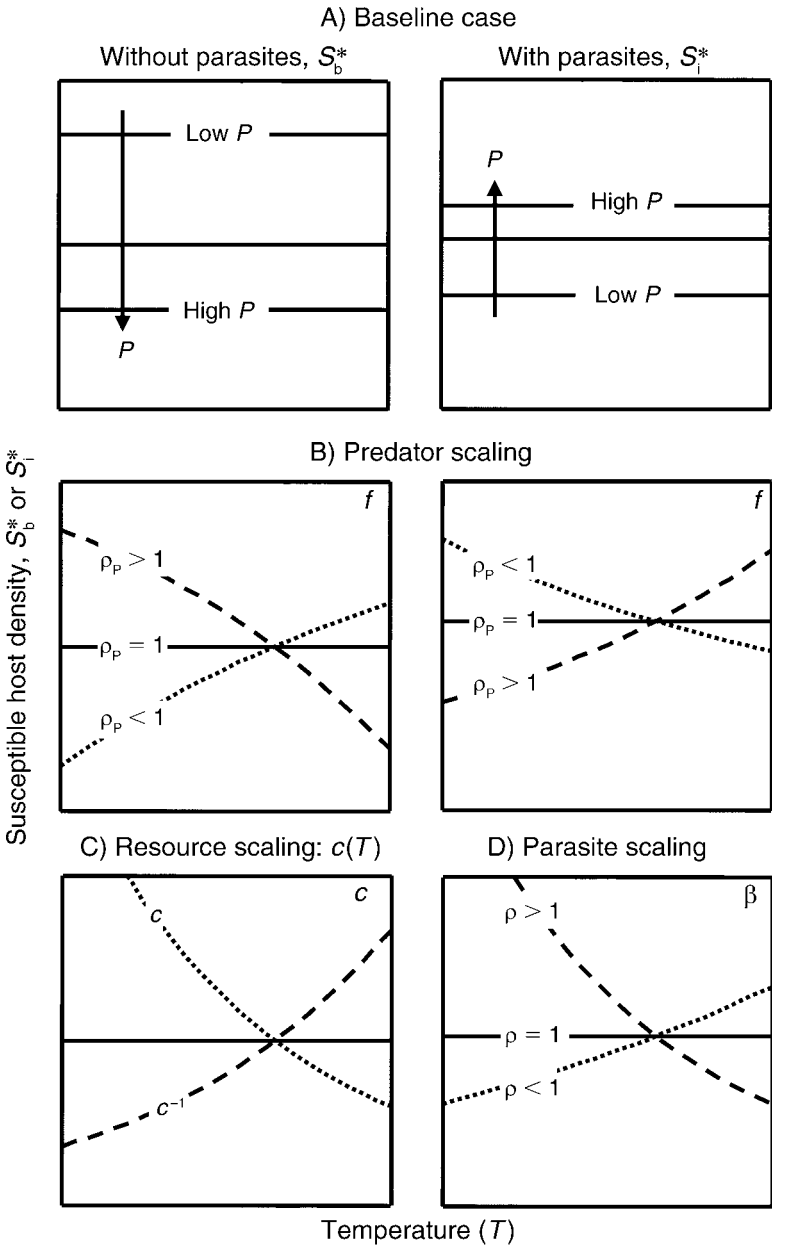

FIG. 1. Equilibrial density of susceptible hosts without (S_b^*) or with (S_i^*) parasites become functions of temperature (T) via several mechanisms (see text for details). Vital rates of parasite and predator scale differently with temperature than those of the host when scaling factors $\rho \neq 1$ (for parasites) and $\rho_P \neq 1$ (for predators), respectively. (A) In the baseline case ($\rho = 1$, $\rho_P = 1$), neither S_b^* nor S_i^* changes with temperature; these quantities only decrease (S_b^*) or increase (S_i^*) as predation density (P) moves from lower to higher levels (i.e., in direction of arrows). (B) Once the predator's feeding rate (f) scales more steeply than the hosts' ($\rho_P > 1$), a given density of predators becomes more lethal to S_b^* but indirectly beneficial to S_i^* with warming. The opposite pattern emerges when $\rho_P < 1$. (C) If strength of density dependence (c) scales proportionately with temperature, S_b^* decreases as temperature increases, but if the inverse of this strength scales proportionately with temperature, S_b^* increases. (D) Finally, if parasite-dependent vital rates (illustrated with transmission rate β) scale more steeply with temperate than do the host's vital rates ($\rho > 1$), S_i^* decreases with temperature. Conversely, if $\rho < 1$, S_i^* increases with temperature.

not vary with temperature. In this baseline case, neither S_i^* nor S_b^* vary with temperature (Fig. 1A). This result occurs mathematically because increases in parameters with T in numerators of the equilibria (Eq. 2) are offset by changes with temperature in parameters in their denominators. Instead, S_b^* decreases while S_i^* increases with increasing predator density (Fig. 1A).

The situation becomes more interesting if the vital rates of the enemies scale differently than those of the host ($\rho \neq 1$, $\rho_P \neq 1$) and when other parameters become

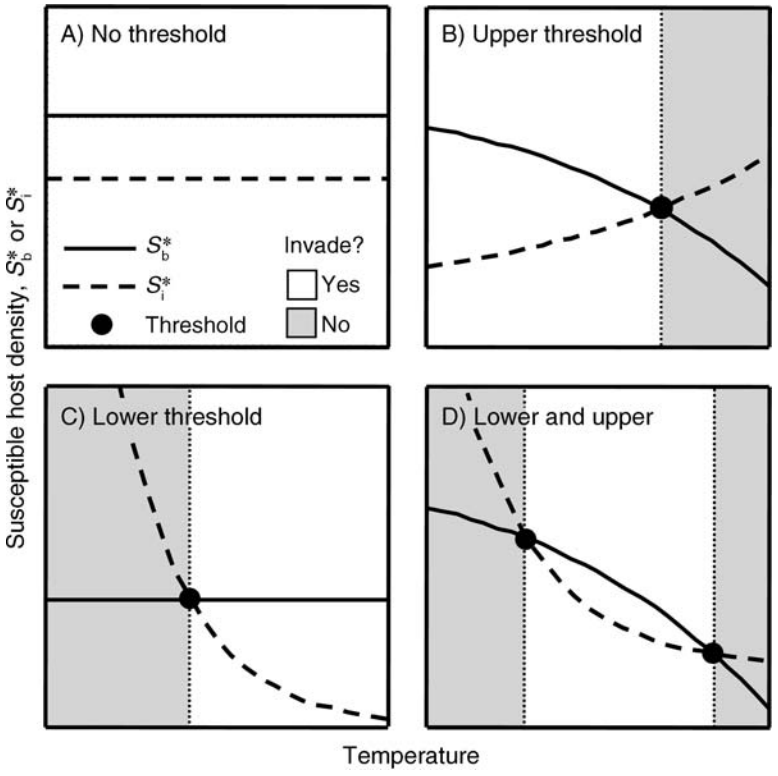

FIG. 2. Temperature-dependent thresholds for parasite persistence emerge once susceptible host density without (S_b^*) or with (S_i^*) parasites become functions of temperature. Parasites persist when $S_b^* > S_i^*$ (white regions), but cannot otherwise (shaded regions). Four different qualitative outcomes arise: (A) no temperature-dependent thresholds (because neither S_b^* nor S_i^* is a function of T); (B) an upper threshold emerges; (C) a lower threshold emerges; (D) both an upper and lower threshold emerge, confining epidemics to intermediate temperature.

functions of temperature (T). First consider the case where feeding rate of the predator (f) scales differently than the physiology of the host ($\rho_P \neq 1$; Fig. 1B). In this case, a given density of predators (P) becomes more lethal ($\rho_P > 1$) or less lethal ($\rho_P < 1$) to susceptible hosts at higher temperatures at the boundary equilibrium (S_b^*). Meanwhile, if they become more lethal at higher temperature, predators become indirectly "helpful" to susceptible hosts persisting with parasites (S_i^*), but less helpful when $\rho_P < 1$. This indirect effect occurs mathematically because S_i^* is a positive function of feeding rate of the predator (Eq. 2). Biologically, higher predation rates, driven by temperature, raise the minimal resource requirement for the parasites to persist because predators cull infected hosts, all else being equal. In another case, the strength of density dependence (c) may decrease with temperature if the inverse of c increases with temperature (Fig. 1C). Although parameter c is not a rate per se, it does phenomenologically represent dynamics of the host's resource. Thus, temperature dependence of c might emerge for *Daphnia* if the physiology of its algal food resources also scales with T (Alghren 1987, Kooijman 1993). In this case, S_b^* increases with temperature, but S_i^* does not change because it is not a function of temperature. Finally, if parasite traits such as transmission rate (β) scale more or less steeply with temperature than do the host's vital rates ($\rho \neq 1$), S_i^* decreases ($\rho > 1$) or increases ($\rho < 1$) with temperature (Fig. 1D).

Once density of hosts at the boundary (S_b^*) and interior (S_i^*) equilibria become functions of temperature, successful persistence of parasites can also depend on temperature. In fact, parasites may be inhibited at warmer, cooler, or both warmer and cooler temperatures (Fig. 2). In the baseline case (Fig. 2A), neither S_b^* nor S_i^* vary with temperature. Thus, as long as predator density is not too high, parasites persist with hosts and predators at any temperature (i.e., provided that $S_b^* > S_i^*$, following the rule sketched above). However, if feeding rate (f) of the predator increases more quickly with temperature than the vital rates of the host (i.e., $\rho_P > 1$), an upper temperature threshold might emerge. Once the system becomes warmer than this threshold, $S_b^* < S_i^*$ (Fig. 2B), so parasites cannot persist. A lower temperature threshold arises if, instead, parasite traits (such as transmission rate, β, and virulence mortality, v) scale more steeply with temperature than do the host's vital rates (i.e., $\rho > 1$; Fig. 2C). This inhibition at cooler conditions can occur with or without predators. However, if vital rates of predator and parasite both scale

PLATE 1. The host zooplankton *Daphnia dentifera* infected with the fungus *Metschnikowia bicuspidata*. (Left) Two infected hosts surround an uninfected host. Notice darker areas of infected *Daphnia* (body and head) where fungal spores have collected. Photo credit: A. J. Tessier. (Right) Fungal spores collected within the body of an infected host, observed using a scanning electron microscope. This view peers past the outer carapace of a *Daphnia* (lower left and upper right corners) to masses of cylindrically shaped spores accumulated within the animal. Photo credit: Carol Flegler.

steeply with temperature ($\rho_P > 1$ and $\rho > 1$), then the parasite might be able to persist at intermediate temperatures only (Fig. 2D). In this last case, predation effects create an upper threshold while parasite physiology creates the lower one.

Thus, this modeling shows how temperature-dependent physiology of hosts, parasites, and predators could constrain epidemics to warmer, colder, or intermediate temperatures. It may also explain the seasonal phenology of epidemics in our study system (Duffy et al. 2005, Cáceres et al. 2006). The next step for this problem involves making more quantitative predictions using the dynamical model (Eq. 1). To do so, one must collect information about relevant parameters and physiological scaling of vital rates of the three players. From literature surveys, we already know that *Daphnia*'s physiology scales with temperature (Arrhenius temperature $T_A = 6400$) and that physiology of fishes scales more steeply with temperature than does the *Daphnia* host (predator scaling factor $\rho_P \sim 1.75$; Kooijman 1993). Therefore, we need to estimate the scaling factor for vital rates of the fungal parasite.

PARAMATERIZATION

Methods

The experimental and statistical methods used to estimate parasite parameters and scaling factors are described in detail in Appendix B. Thus, those methods are presented very briefly here. To estimate transmission rate in the laboratory, we exposed five or six *Daphnia* to a gradient of spores (25, 75, 150, and 500 spores/mL) at four different temperatures (10, 15, 20, or 25°C) for 20 h, then incubated them at that particular temperature for 8–30 d before diagnosing them for infection. We then fit a simplified version of the model (Eq. 1) to the laboratory data and estimated the transmission rate (β) and parasite scaling factor (ρ) using maximum likelihood-based methods. We also conducted an analogous field experiment in a stratified lake using depth to create temperature gradients. In the laboratory, we estimated the virulent effects of the parasite on host fecundity and survival by noting offspring production of infected animals incubated at three temperatures (15, 20, or 25°C) and days until death for each animal. Using maximum-likelihood based methods again, we estimated birth rate of infected hosts (b_I), parasite-induced morality rate (v), and parasite scaling factor (ρ) for each of the two parameters. Finally, we estimated spore production from dead hosts by tracking spore release through time and fitting a non-linear time series model to the data.

Results

In both laboratory and field experiments, likelihood of infection varied greatly with temperature and spore concentration (Fig. 3). The response of infectivity to spore concentration follows the typical sigmoid dose response (see also Regoes et al. 2003). Infectivity was highest in the 25°C treatments, intermediate and similar among 20°C and 15°C treatments, and zero at 10°C treatments (Fig. 3A). This last result could arise through two different mechanisms, a statistical one or a biological one. The statistical mechanism assumes that parasite spores can infect hosts at 10°C, but the

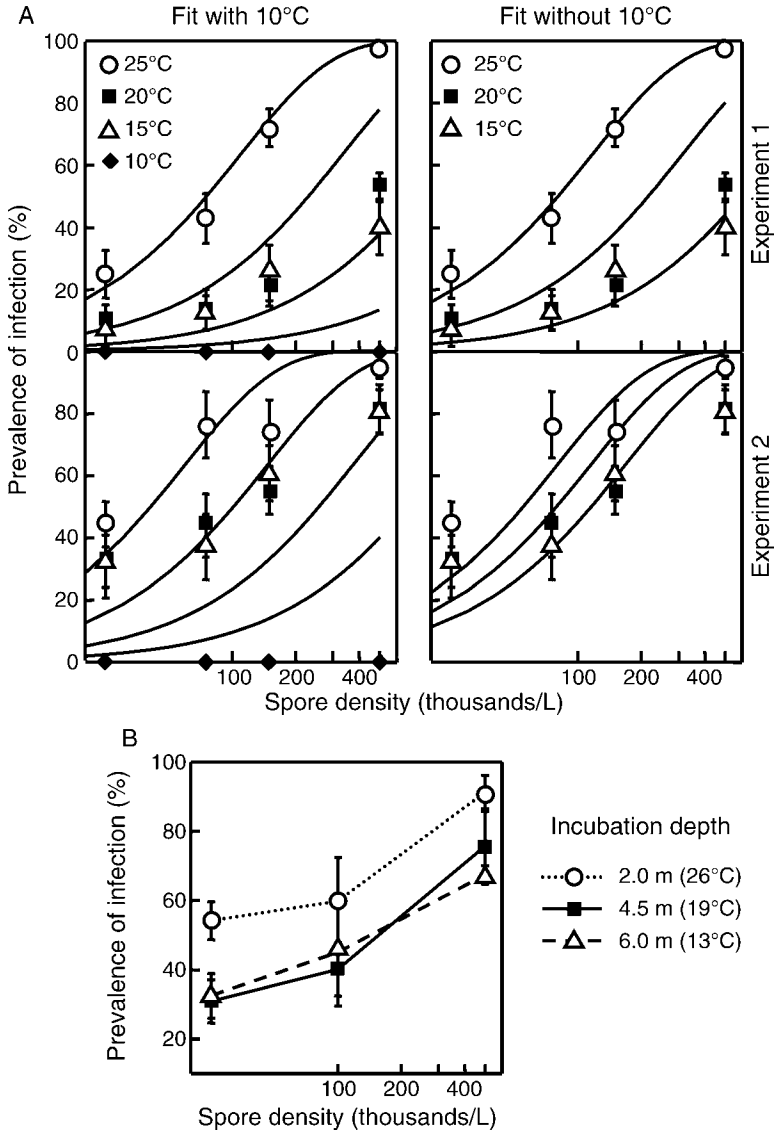

FIG. 3. Prevalence of infection from two laboratory and one field experiment quantifying transmission rate. (A) Prevalence of infection vs. spore density in the two lab experiments, incubated at four different temperatures. Lines represent predictions of an Arrhenius-based epidemiological model generated with maximum-likelihood estimated parameters, fit with or without the 10°C treatment (see Appendix B for details). (B) Results from a field experiment in thermally stratified Lawrence Lake, where jugs containing *Daphnia* and fungal spores were incubated at different depths that corresponded to different temperatures. Values are means ± SE.

probability of infection is so low that one is unlikely to see an infection among only five or six animals per beaker. This hypothesis suggests fitting the transmission rate model (Eq. 4) to all data (i.e., all 10–25°C treatments). The biological mechanism assumes that parasites spores become inactive at 10°C. The particular model we fit does not mathematically accommodate this scenario (although more complicated models could). Thus, we fit the transmission rate model again to only 15–25°C treatments. Then, we looked for major differences in parameter estimates between the 10–25°C and 15–25°C situations. In the first experiment, both scenarios yield similar parameter estimates (Appendix B: Table B1). Particularly noteworthy was that the parasite scaling factor (ρ) was greater than one in both cases. However, this consistency among results was not evident in the second experiment, where fits to all data yielded $\rho > 1$, while fits to the 15–25°C treatments yielded $\rho \approx 1$ (but fit worse in terms of R^2; see Table B1 [in Appendix B]). We used results from the first experiment to quantitatively explore the *S–I–Z* model with predation. We made this choice for several reasons: conceptually, the $\rho > 1$ result provides a greater challenge to explain lower temperature thresholds on parasite persistence than does the simpler parasite-inactivation mechanism; statistically, we found $\rho > 1$

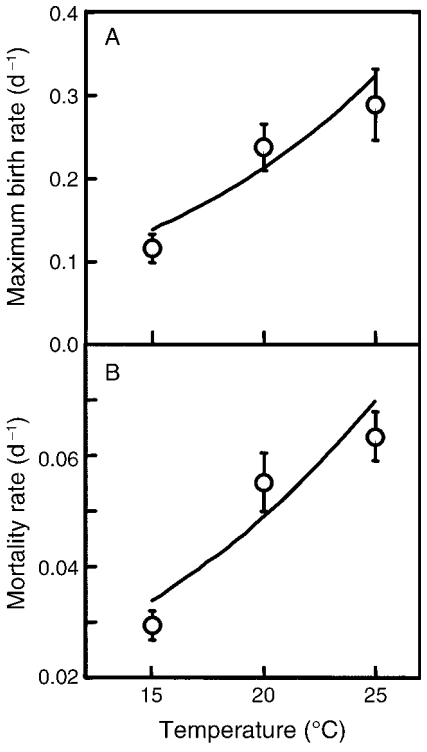

FIG. 4. Experimental data and results of fits to a biological model relating physiological rates to temperature (Appendix B): (A) maximum birth rates of infected hosts and (B) mortality rate of infected hosts, where the solid line is the Arrhenius-function-based model plotted with MLE estimates and data points are means ± SE.

in three out of four cases and the R^2 explained by the $\rho \approx 1$ result indicated worse fit.

Fits of maximal birth rate of infected hosts (b_I) and virulence (v) mortality to experimental data were more straightforward. In both cases, the parasite scaling factor (ρ) was approximately 1 (Fig. 4). This result implies that these fitness effects of the fungal parasite changed with temperature according to host physiology. Additionally, infection reduced birth rate of the *Daphnia* host by roughly one half. Although the accelerating portion of the Arrhenius model fit both data sets well ($R^2 > 0.72$; see Table B1 [in Appendix B]), the data hint that both maximal birth rate of infected hosts and virulence mortality may decelerate as temperatures become hotter (above 20°C). Unfortunately, the Arrhenius function cannot capture this possible deceleration using reasonable parameter values.

With these parameter estimates and others from the literature (Table 1), we used the model to make more quantitative predictions considering the interplay between temperature (T) and predator density (P). These predictions become readily understood when plotted as a persistence threshold curve (i.e., a map of where $S_b^* = S_i^*$, determined numerically; Fig. 5A). This curve compactly maps various threshold possibilities presented earlier (Fig. 2) in temperature–predator-density parameter space. The "standard" case (parameters following Table 1; density dependence and spore production per host do not depend on temperature) reveals the possibility that predation may constrain epidemics to intermediate temperatures (Fig. 5B), but the range of predator density to which this scenario applies is limited. However, variation in assumptions and parameter values can accentuate the temperature dependence of these thresholds. For instance, once either strength of density dependence (c) or spore production per host (σ) become functions of temperature (illustrated as scaling with host thermal biology), the threshold curve decreases more rapidly as temperatures decline (Fig. 5B). This dip means that lower predator density can inhibit parasite persistence in cooler conditions. In other examples, variation in spore loss rate (m), transmission rate (β, possibly caused by variation in resistance to infection among host populations), and strength of density dependence (c, possibly driven by variations in ecosystem productivity) produce qualitatively similar results. Changes in parameters which decrease host abundance without parasites, S_b^* (increasing strength of density dependence), or those which decrease host abundance with parasites, S_i^* (decreasing transmission rate or increasing loss rate of spores), tip the threshold curves downward toward colder temperatures (Fig. 5B). As a result, these changes increase the possibility that a given level of predator density will drive parasites extinct at lower temperature. Conversely, parameter shifts which increase S_b^* or decrease S_i^* tilt the threshold curves downward toward increasing temperature. Therefore, in these cases, inhibition of parasite persistence by a given predator density is more likely at higher temperature.

In a final variation, we acknowledge that our host, *Daphnia dentifera*, migrates vertically in thermally stratified lakes. This species moves between warmer, upper waters at night to cooler, lower waters during daylight (Leibold and Tessier 1997). Meanwhile, bluegill sunfish (the predators) remain in the warmer upper waters throughout the entire day (Hall and Werner 1977). Thus, the host experiences a different temperature (T) regime than the predator (at least while the lakes remain thermally stratified). The qualitative implications of this migration are represented simply here. Imagine that a host spends half of the day at 10°C (or 15°C, both are illustrated) and the other half at T°C, yet the fish predator remains at T°C. Between T and 10°C (or 15°C), the threshold curve tilts downward toward higher temperature (Fig. 5B). Consequently, migration increases chances that predator-driven extinction of parasites occurs at higher temperature.

DISCUSSION

The prospect of a warmer world becoming a sicker world should worry ecologists. Indeed, as temperatures climb, disease prevalence has apparently escalated in

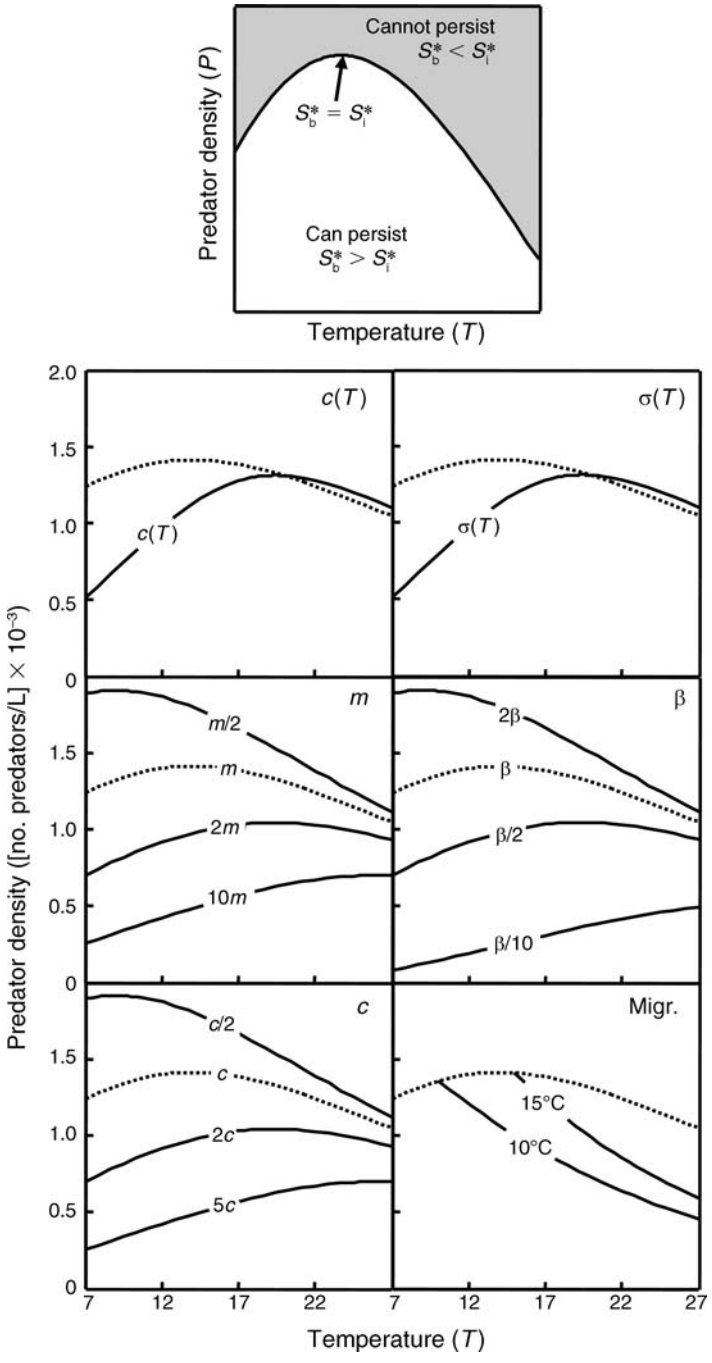

FIG. 5. Scenarios emerging from the temperature-dependent model, parameterized for the *Daphnia*–fungus–fish system with laboratory experiments and literature-based data. (A) In a generic example, a threshold line (solid) separates combinations of temperature (T) and predator density (P) above which the parasite cannot persist ($S_b^* < S_i^*$), and below which it can persist ($S_b^* > S_i^*$). Predation may always exclude parasites (high predator density), exclude them at higher, lower, or both higher and lower temperatures (intermediate predator density), or never exclude them (low predator density), depending on the shape of this curve. (B) Parameterized examples of these thresholds, where the dotted line in each panel represents the threshold for the "standard" scenario (see text for details; note that this "standard" case differs from the "baseline" of Fig. 1). If strength of density dependence (c) or spore production per host (σ) scales with host thermal biology, the threshold bends down toward lower temperature, accentuating predator-driven inhibition at lower temperature. Variations in magnitude of loss rate of spores (m), transmission rate (β), or strength of density dependence change the shape of these thresholds as well. These changes in shape accentuate either lower or upper temperature thresholds on parasite persistence. Finally, *Daphnia* hosts may experience different average temperatures during a whole day than predators if the hosts migrate between a colder, lower layer (10°C or 15°C) and an upper, warmer layer ($T >$ 10°C or $T >$ 15°C, respectively) and if fish predators stay in the warmer, upper layer. This migratory behavior tilts persistence thresholds down toward higher temperature, making extinction of parasites at warmer temperatures more likely.

many taxa (Harvell et al. 2002, Ward and Lafferty 2004). Warmer climates may facilitate disease spread through a variety of direct and indirect mechanisms, including acceleration of parasite fitness and range expansion of vectors (Martens et al. 1999, Harvell et al. 2002, Anderson et al. 2004). Although these and other mechanisms will likely promote spread of disease, other mechanisms may inhibit epidemics in other host–parasite systems. Direct inhibitors include physiological mismatches between the thermal optima of host and parasite (Blanford et al. 2003). Warmer climates may accentuate these mismatches to the host's benefit (i.e., may help the host thermally defeat the parasite [Carruthers et al. 1992, Blanford et al. 2003]). This possibility has received some attention, particularly in the applied entomology literature. Indirect inhibitors may include increased control of epidemics by predators that selectively cull parasitized hosts (Ostfeld and Holt

2004, Packer et al. 2003, Duffy et al. 2005). This prospect has more unknown potential.

Here, we explore the possibility that predation can inhibit epidemics at warmer temperatures. Can differences in thermal biology of host, parasite, and/or predator accentuate the inhibitory effect of selective predation on parasites? An affirmative answer could arise if warmer temperatures only increase recruitment of predators, of course. However, our study yields a more subtle result. A given density of predators can prevent persistence of parasites at higher temperatures if the predator's thermally biology scales more steeply with temperature than that of the host (Kooijman 1993). Such a situation seems more likely if the predator is a fish or amphibian while the prey is an invertebrate (Kooijman 1993, Gillooly et al. 2001). This result emerges because, in warmer conditions, a given biomass of predators becomes more lethal to the parasite's resource (uninfected hosts) as it tries to invade a host population. Additionally, once the parasite invades, this increased lethality on infected hosts increases the minimal number of susceptible hosts needed by the parasite to sustain the epidemic. Furthermore, predation-induced mortality, combined with thermal biology of the parasite, can terminate epidemics at colder temperatures, even if the parasite remains physiologically active at colder temperatures. This outcome becomes more likely when vital rates of the parasite (e.g., transmission) scale more steeply with temperature than do those of the host (Gillooly et al. 2001, Harvell et al. 2002, Mitchell et al. 2005), or if production of infective spores of the parasite per host decreases or density-dependence of the host increases with cooling temperatures.

These qualitative outcomes yield insight into our *Daphnia–Metschnikowia*–bluegill system. The seasonal phenology of epidemics in this and related systems (Bittner et al. 2002, Mitchell et al. 2004*b*, Duffy et al. 2005, Cáceres et al. 2006) suggests that epidemics begin as systems start to cool at some point after peak warmness in summer but end as systems become too cold. Can selective predation on infected *Daphnia* by bluegill sunfish constrain epidemics to intermediate temperatures in our model system? By coupling a minimal host-parasite-spore-predator model with parameter estimates derived from laboratory experiments and extant literature (Kooijman 1993, Tessier and Woodruff 2002, Duffy et al. 2005), we conclude that selective predation could indeed facilitate upper and lower persistence limits for the fungal parasite. This outcome seems more likely with certain parameter combinations than others. Indeed, fish predation becomes more likely to terminate epidemics at lower temperatures when parasites are less fit (e.g., lower transmission rate, higher loss rate of spores, stronger density-dependent controls on host reproduction, temperature-dependent spore production by infected hosts). Conversely, a given predator density is more likely to inhibit parasites at warmer temperatures when parasites become more fit or when hosts vertically migrate (Leibold and Tessier 1997). Thus, our results provide more mechanistic insight into our earlier proposal that predators can control epidemics in *Daphnia*-parasite systems (Duffy et al. 2005, Hall et al. 2005). However, more exact predictions would depend upon characteristics of the particular lake population (e.g., strength of density dependence) and upon the relative importance of other concurrent biological processes (e.g., the dynamical consequences of the evolution of resistance of host populations [M. Duffy and L. Sivars-Becker, *unpublished manuscript*]).

Of course, quantitative inquiries like this one often prompt as many questions as they answer. In this case, iterations between model and data yielded at least two important classes of uncertainty. The first class centers more on the biological details of our particular system. For instance, we do not know how the strength of density dependence of host reproduction responds to temperature in our lake systems. In fact, density dependence may scale non-monotonically as temperature, physiology, algal defenses, and resource limitation of algae interact (Alhgren 1987, Kooijman 1993, Tessier and Woodruff 2002). Additionally, predation intensity experienced by *Daphnia* likely changes from summer to autumn regardless of thermal biology because small bluegill often switch resources from *Daphnia* to other invertebrates during late summer (Hall and Werner 1977). Finally, we have abstracted the physical dynamics of spores in the water column. Spores released by dead hosts cannot propel themselves; thus, turbulence and mixing must somehow connect spore to host (Cáceres et al. 2006). Production of turbulence depends upon rate of cooling of a water body and could constitute an important factor starting these fungal epidemics.

A second class of uncertainty likely applies generically to this and other host–parasite–predator systems. First, how will predator recruitment respond to a warmer climate? In our model, we varied predator density as a parameter, not as a variable that responds to temperature. Thus, we did not consider how temperature might impact recruitment of predators. In the case of our fish predators, warmer winter temperatures can enhance survival of juveniles, but very warm temperatures in summer could possibly increase mortality or alter timing of reproduction during summer (Taylor et al. 1991, Garvey et al. 1998, Santucci and Wahl 2003). Furthermore, enhanced recruitment of predators with warming could outright eliminate the host (Moore and Folt 1993, Tessier and Woodruff 2002, Hall et al. 2005). Second, although we considered only smooth, slow changes in temperature, within-season climatic variation may also have pronounced effects on host–parasite dynamics (e.g., Pascual et al. 2000, Zhou et al. 2004). Third, increased warming can push host, parasite, or predator beyond their thermal optima (Huey and Stevenson 1977, Blanford et al. 2003), a possibility that we ignored here.

Despite these sources of uncertainty, our results do raise an important point: global warming does not necessarily mean that disease prevalence will increase in all systems. In fact, the interaction between warming and disease may depend substantially upon the response of the community in which host–parasite systems are embedded. In particular, warmer temperatures can enhance inhibition of epidemics by predators that selectively prey upon infected hosts. This conclusion seems likely for our *Daphnia*–fungus–fish system, and it stems from interplay between natural history observations, dynamical models, and temperature-dependent experiments designed to parameterize the models. One could readily apply this three-part protocol to other disease problems. Furthermore, we now emerge from this interplay armed with both a clearer understanding of critical uncertainties in our system's natural history and with a model template to which we can incorporate thermal (climatic) variability in a physiologically meaningful manner (Laakso et al. 2001). These fundamental issues are critically important to this and other systems if ecologists are to fully understand response of infectious disease to climate change.

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APPENDIX A

Description of the stability of the equilibria produced by modeling the dynamics of susceptible hosts (S), infected hosts (I), and free-floating spores (Z) (i.e., the S–I–Z model) with predators (P) (*Ecological Archives* E087-097-A1).

APPENDIX B

Details on the experiments used to parameterize the S–I–Z model with predation, along with statistical methods used to estimate these parameters (*Ecological Archives* E087-097-0A2).