Variation in Resource Acquisition and Use among Host Clones Creates Key Epidemiological Trade-Offs

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abstract: Parasites can certainly harm host fitness. Given such virulence, hosts should evolve strategies to resist or tolerate infection. But what governs those strategies and the costs that they incur? This study illustrates how a fecundity-susceptibility trade-off among clonally reared genotypes of a zooplankton (*Daphnia dentifera*) infected by a fungal parasite (*Metschnikowia*) arises due to variation in resource acquisition and use by hosts. To make these connections, we used lab experiments and theoretical models that link feeding with susceptibility, energetics, and fecundity of hosts. These feeding-based mechanisms also produced a fecundity-survivorship trade-off. Meanwhile, a parasite spore yield–fecundity trade-off arose from variation in juvenile growth rate among host clones (another index of resource use), a result that was readily anticipated and explained by the models. Thus, several key epidemiological trade-offs stem from variation in resource acquisition and use among clones. This connection should catalyze the creation of new theory that integrates resource- and gene-based responses of hosts to disease.

Keywords: control-fecundity trade-off, consumer-resource, *Daphnia*, host-parasite, resistance-fecundity trade-off, *Metschnikowia*.

Introduction

Parasites exert virulent effects on their hosts and can harm host populations (May and Anderson 1983; Anderson and May 1991). However, host genotypes can vary considerably in susceptibility to infection (e.g., May and Anderson 1983; Ebert 2005; Duffy et al. 2008; Elderd et al. 2008). Thus, not all hosts are harmed equally. These virulent effects of parasites on host fitness provide a strong selective force that can promote evolution of defense strategies, such as resistance (i.e., avoiding or fighting infection), control (i.e., reducing replication of parasites within hosts, sensu Miller et al. 2005), and tolerance (i.e., living and reproducing with infection). In response to infection, then, the genetic distribution of defense traits within host populations can change, ultimately promoting or degrading genetic diversity of hosts (Boots et al. 2009). This diversity of defense traits might determine ecoevolutionary dynamics of epidemics.

What factors, then, drive genetic variation in hosts to resist, tolerate, or control infection by parasites? One major idea stems from the gene-for-gene and matching-alleles models (Agrawal and Lively 2002). Some genotypes of parasites more readily infect all or particular host genotypes; conversely, some host genotypes can better resist infection by all or some genotypes of parasites. The interactions, then, depend solely on genetic specificity mechanisms for infection and resistance and associated costs with higher infectivity or resistance to infection. Both models predict that negative frequency-dependent selection ("rare advantage") can promote host diversity (Agrawal and Lively 2002). Alternatively, epidemiology–life-history trade-offs critically shape diversity of host response to infection through density-dependent feedbacks (Boots and Haraguchi 1999; Miller et al. 2005; Boots et al. 2009). Host genotypes that resist, control, or tolerate parasites may experience fecundity or growth rate costs. As a result, these trade-offs then influence densities of hosts and parasites during epidemics and modify the type and strength of parasite-mediated selection (Boots et al. 2009; Duffy and Forde 2009). Trade-offs for resistance versus fecundity can even promote diversity of hosts via disruptive selection on host resistance. This occurs even without coevolutionary response of parasites, because disruptive selection maintains both highly susceptible and resistant genotypes.

These schools of thought apply to two well-studied *Daphnia*-microparasite systems. Both the bacterium *Pasteuria ramosa* and the fungus *Metschnikowia bicuspidata* exhibit roughly similar epidemiologies: both produce free-living spores released only upon host death, and both replicate within host hemolymph after inadvertent spore consumption by hosts. The *Pasteuria–Daphnia magna* system shows strong host-parasite genetic specificity (Carius et al. 2001; Decaestecker et al. 2003) and local adaptation (Ebert

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1994) that signal a matching-alleles mechanism. As a result, selection during epidemics can promote rapid host evolution (Haag and Ebert 2004; Duncan and Little 2007) and long-term coevolutionary Red Queen dynamics (Decaestecker et al. 2007). In contrast, in the *Metschnikowia–Daphnia dentifera* system, host genotypes differ in susceptibility to infection, yet parasite strains seem comparatively invariant in infectivity (Duffy and Sivars-Becker 2007). Hosts can evolve rapidly during epidemics via parasite-mediated directional or disruptive selection (Duffy and Sivars-Becker 2007; Duffy and Hall 2008; Duffy et al. 2008, 2009). The disruptive-selection result in particular suggests trade-offs between epidemiological parameters and life-history traits (Boots et al. 2009).

This study combined models and experiments to reveal several sets of such trade-offs among clonal host genotypes in the *D. dentifera*–fungus system. More specifically, we uncovered trade-offs between susceptibility and fecundity of uninfected hosts, between survivorship of infected hosts and fecundity, and between spore yield from dead hosts and fecundity. Moreover, we show that variation in feeding rate and resource use among host clones produce and interconnect these trade-offs. We anticipate these connections for two reasons. First, hosts become infected by eating free-living parasitic spores (Ebert 2005; Hall et al. 2007*a*). Thus, variation in feeding rate among clones should correlate with variation in susceptibility among clones. Second, variation in the rate of resource acquisition and use influences the flow of energy within hosts. The fungal parasite, growing inside the host, uses this energy to replicate itself. Thus, energy drawn by parasites from hosts causes virulent reductions in growth, survival, and reproduction of hosts (Hall et al. 2007*b*, 2009*b*). Therefore, variation in resource acquisition and use among host clones should have predictable effects on survival, fecundity, and spore yield from hosts.

Models: An Overview

Two of our previously developed models predict that variation in resource acquisition and use among host clones drives variation in epidemiology parameters that then create key trade-offs. Both models were published elsewhere, so here we sketch out the core features and direct interested readers to those articles (Hall et al. 2007*a*, 2009*b*) for more details.

Model 1: A Feeding Metric Predicts Host Susceptibility

We use the first model to link variation in a metric of feeding rate with host susceptibility. In a previous study, we used a model to explain why variation in body size and food quantity should drive variation in susceptibility to infection of a single host clone. That model focused on "clearance rate" as defined by resource ecologists (e.g., Grover 1997), not epidemiologists. Resource-based clearance is the habitat volume per unit time from which food is removed. However, to avoid confusion with immunological clearance of infection, we will refer to this as a "feeding metric," F_M. For consistency with the dynamic energy budget model below, we derive this F_M from feeding rate on an algal resource, X, based on a Type II functional response, $F_{II}(X)$. Since the feeding metric equals the feeding rate divided by the resource density (Grover 1997; Hall et al. 2007*a*),

$$F_M = \frac{F_{II}(X)}{X} = \frac{fL^2X/(h + X)}{X} = \frac{fL^2}{h + X}, \quad (1)$$

where L is body length (such that L^2 is proportional to surface area), f is the surface area–specific feeding rate, and h is the half-saturation constant of the functional response. However, a previous model-selection exercise (Hall et al. 2007*a*) showed that host susceptibility depended on another factor proportional to L^2. On the basis of those model-selection results and the infection biology of the fungus, we assume that this factor is gut surface area, S_g. If S_g equals length squared times a proportionality constant (i.e., $S_g = g_{SA}L^2$; Kooijman 1993), then the per capita, per-spore host infectivity rate (β) becomes (when combined with eq. [1])

$$\beta = u \times F_M \times S_g = \frac{ufg_{SA}L^4}{h + X}, \quad (2)$$

where u is per-spore infectivity once contacted. Thus, all else being equal, this model (eq. [2]) predicts a direct connection between the size-specific feeding rate metric, f_M (which is itself a function of maximal, size-specific feeding rate, f) and host susceptibility (β).

Model 2: A Dynamic Energy Budget (DEB) Model Predicts Other Disease Parameters

Another model (Hall et al. 2009*b*) links variation in the feeding metric and host energetics to other epidemiological parameters. It is more complicated than the model for host susceptibility (eq. [2]), but it makes important connections in a physiologically justifiable manner. This dynamic energy budget (DEB) model, based on Kooijman (1993), tracks the flow of energy from ingestion and assimilation to storage in a "reserve" pool. This reserve energy is then used, or "catabolized," for growth, reproduction in adults, reproductive development in juveniles, and associated metabolic costs. We assume that parasites then deplete energy from the host reserve and replicate within

hosts. Through this energy consumption, parasites exact virulent costs on growth and reproduction of their hosts. Furthermore, the parasite kills its host once parasite mass reaches a certain threshold: specifically, a fraction of the structural mass of the host (Hall et al. 2009*b*). Before killing the host, however, the parasite can inflict energetic stress by reducing internal energy reserves. The DEB model predicts how this reduction in reserves will affect growth, reproduction, and survival of hosts.

The DEB model tracks energy flow through hosts and parasites. The flow of this energy can be used to derive the core differential equations of the DEB model. These equations track changes in structural mass (dW/dt), changes in energy reserve (dE/dt), and changes in reproductive output (dR/dt). To begin this derivation, hosts first eat food and then assimilate some fraction of it. Assimilation rate (A), then, is

$$A = \frac{aL^2X}{h + X}. \tag{3}$$

Assimilation rate A depends on size-specific assimilation rate, a, which is itself the product of size-specific maximal feeding rate, f, and conversion efficiency, ε. Assimilation rate A also depends on surface area of the host (proportional to L^2) and algal food (X), following a Type II functional response with a half-saturation constant (h). Assimilated energy is then put into a reserve energy pool (E). Reserve energy (E), in turn, is modeled as the product of energy density (e) and structural mass (W), that is, $E = eW$. The change through time of this energy pool, then,

$$\frac{dE}{dt} = \frac{d(eW)}{dt} = W\frac{de}{dt} + e\frac{dW}{dt}, \tag{4}$$

involves two components. First, the reserve density per unit structural mass changes (involving the de/dt term), and then the host grows more structure (the dW/dt term). Following Kooijman (1993), we assume homeostasis of reserves, meaning that the animal regulates the reserve density at a level related to its feeding rate. Change in reserve density through time (de/dt) increases with assimilation and decreases linearly with e (i.e., according to first-order kinetics):

$$\frac{de}{dt} = \frac{A}{W} - \left(\frac{aL^2}{e_{\mathrm{M}}W}\right)e, \tag{5}$$

where e_{M} is the maximum density of energy. When equations (3)–(5) are combined, utilization rate (C) of energy becomes defined as

$$C = A - \frac{dE}{dt} = E\left(\frac{aL^2}{e_{\mathrm{M}}W} - \frac{dW}{Wdt}\right). \tag{6}$$

Under normal circumstances, the host allocates these catabolized energy reserves toward growth versus reproduction if mature or toward maturation if juvenile, following the kappa (κ) rule. According to this rule, a fixed proportion κ of utilized energy is allocated to growth and a proportion $1 - \kappa$ is allocated to reproduction. In mathematical terms, the host devotes utilized energy to growth at rate

$$\kappa C = g\left(\frac{dW}{dt}\right) + mW, \tag{7}$$

where the first term on the right-hand side denotes growth of structural mass (dW/dt) with the associated cost of growing (g) and the second term represents costs to maintain current mass (at rate m). We solved equations (6) and (7) for C, set them equal to each other, and then solved for the dW/dt term, to yield

$$\frac{dW}{dt} = W\left[\frac{\kappa aL^2E/(e_{\mathrm{M}}W) - mW}{\kappa E + gW}\right]. \tag{8}$$

The rest of the catabolized energy reserve, $(1 - \kappa)C$, is used for reproduction and associated costs. The rate of reproduction, dR/dt, is then

$$\frac{dR}{dt} = \frac{q}{E_0}\left[(1 - \kappa)C - \frac{1 - \kappa}{\kappa}mW_{\mathrm{P}}\right], \tag{9}$$

where q is the cost of converting the energy reserve of the mother into the energy reserve of the offspring ($0 < q < 1$), and E_0 converts energy to offspring. This equation also includes a second term (in brackets) for "maturity maintenance" (see Kooijman 1993; W_{P} denotes size at maturation). The DEB model for the host, then, consists of equations (4), (8), and (9).

We then add the parasite growth within the host. The parasite (N) feeds on the energy reserves of its host (E) according to its own saturating or Type II functional response. Thus, reserve dynamics change (from eq. [4]) to

$$\frac{dE}{dt} = W\frac{de}{dt} + e\frac{dW}{dt} - \frac{a_{\mathrm{N}}}{\varepsilon_{\mathrm{N}}}\frac{E}{h_{\mathrm{N}} + E}N, \tag{10}$$

where consumption by parasites (last term) is governed by the half-saturation constant h_{N}, the maximal assimilation rate a_{N}, and the conversion efficiency ε_{N} of the parasite. The parasite then grows according to a classic equation for a resource consumer (Grover 1997):

$$\frac{dN}{dt} = a_N \frac{E_N}{h_N + E_N} N - m_N N, \tag{11}$$

where m_N combines maintenance costs and death rate of the parasite into a single parameter.

This model requires a few more biological details (see Hall et al. 2009*b*). First, an equation for food dynamics follows our experimental protocol (below): the algal food consumed by hosts does not reproduce but is replenished daily. Second, parasite growth within a host can inflict both moderate and severe energetic stress on the host. As parasites draw down energy within a host, they can first stop growth of the host (moderate energetic stress) and then stop reproduction (severe energetic stress). These changes alter the kappa rule for allocation of utilized energy. Third, the parasite kills the host after parasite mass N crosses a physical threshold $N = \rho W$. Once this threshold is crossed, the host stops eating (i.e., $f = 0$). Then the energy reserve (E) drops to 0, and the host dies. The parasite cannot drop E to 0 itself, because its own minimal energy reserve requirements exceed 0. Finally, the initial parasite density (P_0) within a host of an initial size (L_0) was assumed to equal that consumed over a 24-h period. Thus, hosts with higher rates of the feeding metric started with more parasites internally than did those with lower rates. Parameter values are summarized in table A1 in the online edition of the *American Naturalist*.

Empirical Methods

We used several experiments aimed at estimating epidemiological and resource-based parameters and revealing the focal trade-offs. These experiments quantify susceptibility of hosts, as estimated from infection assays, and fecundity, as gleaned (with several other parameters) from a life-table experiment. We characterized resource acquisition using radiotracer experiments designed to estimate the feeding metric (see the appendix in the online edition of the *American Naturalist* for data and details). Then, a growth rate assay provided another indicator of resource use. Unless stated otherwise, experiments were performed under similar, favorable conditions (20°C, 16L : 8D cycle, ample levels of algal food [2.0 mg dry weight of chemostat-reared *Scenedesmus*] per L, filtered lake water). *Daphnia* clones ($N = 10$–11) came from several lakes in southwestern Michigan (Kalamazoo and Barry counties) and were collected during 2004–2005. These clones have been raised in standardized conditions in lab culture since the collection. Our experiments are thus designed to isolate genetic effects from maternal and environmental effects as much as possible. The parasite strain was collected from Baker Lake (Barry County) in 2003. It has been reared in vivo in one *Daphnia* clone ever since, passing through hosts ~20 times per year. Thus, the culturing methods likely reduced genetic variation in the parasite (if much variation exists in nature; see Duffy and Sivars-Becker 2007). Furthermore, since we did not collect and use parasite strains from multiple locations, the experiments here were not designed to evaluate the possibility of local adaptation. For all parameter estimates, we present bootstrapped 95% confidence intervals using 1,000 draws. Relationships with fecundity scaled instantaneously appear in the appendix.

Experiments: Epidemiological Parameters

Estimation of Susceptibility (Assays of Host Infectivity). We used a simple infection assay to estimate the susceptibility of host clones. We placed five 6-d-old *Daphnia dentifera* into 100 mL of filtered lake water containing 2.0 mg of dry *Scenedesmus* per L and one of two spore levels (50 or 200 spores mL^{-1}), and we incubated them for ~24 h (six to eight replicates). Additionally, we saved 10 separate animals for initial length measurements (eye to base of tail, using a micrometer at × 50; clonal mean sizes ranged from 1.36 to 1.52 mm). After exposure, we transferred animals from beakers into fresh, spore-free water and fed them for 10 d before performing visual diagnosis (Green 1974). Infection status was used to calculate prevalence of infection (see prevalence data in the appendix).

This prevalence and size information was then used to calculate the size-specific host infectivity rate (β; often called the "transmission rate"), our metric of host susceptibility. To estimate this parameter, we assumed that it depended on body length (L) raised to the fourth power (i.e., L^4), as described above in eq. (2), but not food density. The changes in susceptible (S) and infected (I) host classes, given spore densities (Z), then became $dS/dt = -\beta L^4 SZ$ and $dI/dt = -dS/dt$. We estimated β using maximum likelihood, with the beta-binomial distribution serving as the likelihood function. The beta-binomial distribution accommodates overdispersion problems that can arise using the related binomial distribution (Bolker 2008).

Estimation of Virulent Effects on Survival and Fecundity, and Spore Production (Life Table). We used a life-table experiment to estimate effects of infection on host survival and fecundity, size at death, and the spores produced. Using 4-d-old juveniles (~1.2 mm) of each clone, we exposed "infection" treatment animals (10 per clone) to a high spore dose (1,500 spores mL^{-1} for 24 h at room temperature, yielding four to eight infected animals per clone). Uninfected animals ($N = 5$–6) from each clone received a similar treatment, but without spores. Then we placed individual *Daphnia* in clean water to start the experiment. During

daily changes of water, we noted the number of offspring produced, the date of death, and the size reached at death. Size matters because larger hosts typically yield more spores at death (Hall et al. 2009*a*, 2009*b*). To estimate spore yield, we measured infected animals, placed them into 0.25 mL of water in plastic tubes, gently smashed the corpses using tweezers, and counted the spores in the slurry with a hemocytometer at × 200. With the reproduction data, we estimated fecundity (birth rate), that is, total number of offspring divided by date of death or termination of the experiment (day 23). We then calculated proportional fecundity of infected relative to uninfected hosts. Values of this fecundity metric that were closer to 1 signaled more benign effects of infection on fecundity.

Juvenile Growth Rate. Juvenile growth rate (JGR) combines variation in the feeding metric with other factors that jointly determine growth rate of hosts (i.e., parameters of the dynamic energy budget model). The JGR was measured for all clones as mass accrual by neonates during a 4-d assay (Lampert and Trubetskova 1996). To provide initial, day 0 measurements ($\overline{W}_0$), 15 neonates (<24 h old) were dried at 55°C and weights were estimated using a Mettler microbalance and averaged. Then, 10–15 neonates per clone were transferred individually into beakers for 4 d ($d = 4$) and were similarly dried and weighed individually. This procedure yielded mass estimates on day 4 (W_4). Thus, JGR was calculated as $\gamma = [\ln(W_4) - \ln(\overline{W}_0)]/d$.

Results

Variation in feeding rate among host clones had predictable consequences for three epidemiological parameters. Host susceptibility increased with the feeding metric, a result predicted by the mechanistic model of host infectivity (eq. [2]; fig. 1*A*). Furthermore, host clones with higher feeding rates died more quickly once they became infected. This result was also predicted from the dynamic energy budget (DEB) model (fig. 1*B*), for two reasons. First, hosts with higher rates of the feeding metric contact more spores (eq. [2]), and higher initial spore doses cause faster death in the model (Hall et al. 2009*b*). Second, hosts with higher feeding rates, a major driver of the feeding metric, also consume more food per unit time. After assimilation, these food resources promote faster growth of hosts. Larger, faster-growing hosts then acquire even more resources, since assimilation rate increases with surface area (eq. [3]). These assimilated resources promote faster replication of parasites within hosts. Finally, higher feeding rate correlates positively with fecundity (fig. 1*C*). All else being equal, hosts with fast feeding rates should grow more quickly, thereby acquiring more resources for reproduction.

Three relationships arose from these feeding-based

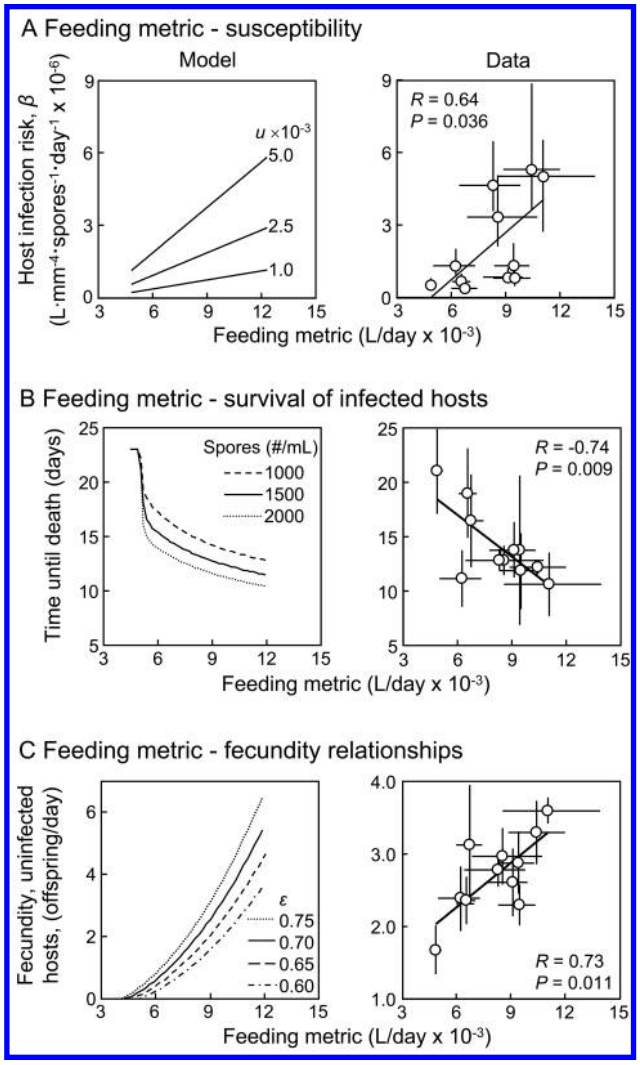

Figure 1: Origins of several life history–epidemiology trade-offs: relationships between a metric of feeding rate and three epidemiological components. Left column: predictions from a feeding-susceptibility model and a dynamic energy budget (DEB) model; right column: data from lab-based experiments, where each point is a *Daphnia* host clone. *A*, Susceptibility (host infectivity) rate. Variation in the feeding metric among different host clones (standardized to a 1.5-mm *Daphnia*, approximately the size of hosts in infectivity assays; see the appendix in the online edition of the *American Naturalist*) correlated positively with size-independent susceptibility, as estimated in assays and a model for susceptibility. The contours correspond to different levels of per-spore infectivity, *u*, in that model (eq. [2]). *B*, Survival of infected hosts. Clones with higher values of the feeding metric or higher exposure to parasites died faster when infected. (The different contours correspond to different doses of parasites to which animals were exposed in the simulations.) *C*, Uninfected fecundity. Fecundity of uninfected hosts increased with the feeding rate metric. In the plots showing model predictions here, contours correspond to different values of conversion efficiency (ε). Data panels: points are means ± 95% bootstrapped confidence intervals. Pearson correlation coefficients (*R*) with associated *P* values qualitatively confirmed the empirical relationships that were predicted by the models.

mechanisms. More susceptible host clones died faster from infection (fig. 2*A*). However, higher susceptibility was also positively correlated with fecundity of the clones when uninfected (fig. 2*B*). Furthermore, hosts that died more quickly from infection also gave birth at higher rates when uninfected (fig. 2*C*). Thus, hosts suffering from higher susceptibility and higher mortality due to infection enjoyed higher birth rates when uninfected. Survival and susceptibility, however, did not correlate with the fecundity of infected hosts (time until death: $R = -0.22$, $P = .51$; infectivity: $R = 0.42$, $P = .20$).

The DEB model also predicted that variation in the feeding metric among host clones should produce a trade-off between fecundity and spore yield. This prediction arose because high feeding rates (again, a major driver of the feeding metric) produced both high spore yield from dead, infected hosts and high fecundity of uninfected hosts. Thus, due to energetic reasons, hosts producing large amounts of spores when infected should also produce more offspring when uninfected. Additionally, these relationships with feeding rate imply that spore yield, host susceptibility, and time until death of infected hosts should all be correlated. More susceptible hosts should produce more spores and should die faster. The experimental data qualitatively followed these model predictions, but the various relationships were not statistically significant (fig. A6 in the online edition of the *American Naturalist*).

However, a trade-off between spore yield and fecundity of infected hosts arose from a shared relationship with juvenile growth rate (JGR). The DEB model predicted that variations in the feeding rate, conversion efficiency, and maintenance costs can all produce variation in JGR. However, in the data, growth rate did not correlate significantly with the feeding metric (fig. A4 in the online edition of the *American Naturalist*). Still, JGR positively correlated with spore yield per dead host and size at death of infected hosts, as predicted by the DEB model (fig. 3*A* and 3*B*, respectively). Thus, faster-growing host clones became larger and were filled with more spores. The model predicted that clones with higher JGRs should have higher fecundity when infected, a result that was also observed in the data (marginally significant; fig. 3*C*). Furthermore, proportional fecundity also increased with growth rate roughly as predicted (fig. 3*D*). Thus, fast-growing clones retained most of their reproductive capacity when infected. Meanwhile, slower-growing clones suffered higher proportional fecundity loss (i.e., more virulent effects on reproduction). These results produced a detectable spore yield–fecundity trade-off. Spore yield correlated positively with fecundity of clones when infected (fig. 4*A*) and proportional fecundity (fig. 4*B*).

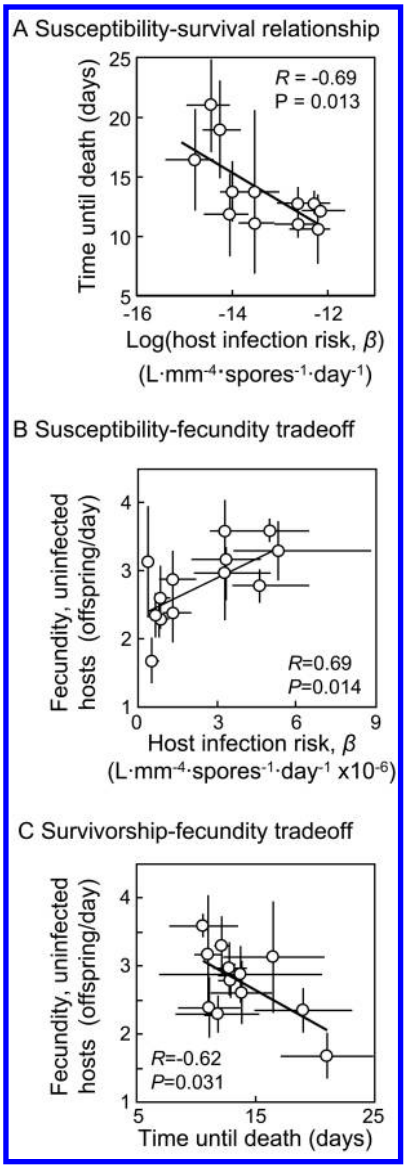

Figure 2: Three pertinent epidemiological correlations among host clones. *A*, The index of host susceptibility (host infectivity rate) and survival of infected hosts correlated negatively; that is, more susceptible host clones died faster when they were sick. *B*, Susceptibility and uninfected fecundity were negatively related: host clones that became infected more easily also gave birth at a higher rate when uninfected. *C*, Similarly, host clones that died more quickly from infection also reproduced at higher rates; conversely, hosts that survived a long time during infection reproduced at lower rates when uninfected. Points are clonal means ± 95% bootstrapped confidence intervals. Pearson correlation coefficients (R) and P values are also provided.

Discussion

Variation among host clones in resource acquisition and juvenile growth rates linked with variation in epidemiological traits (susceptibility, fecundity, survivorship of in-

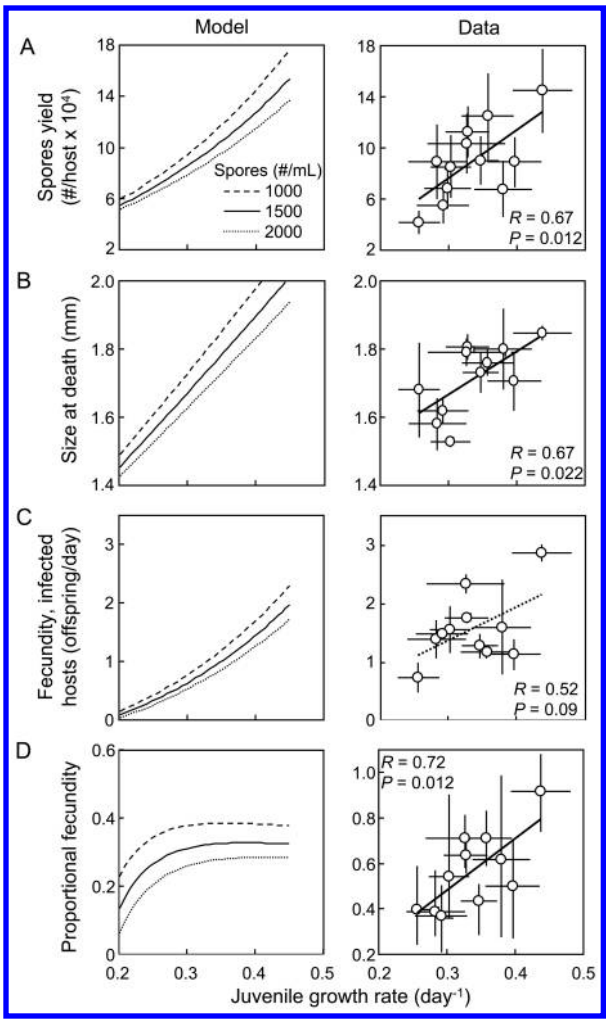

Figure 3: Juvenile growth rate among host clones and its connection to spore yield from dead hosts, body size of hosts, and fecundity of infected hosts. Juvenile growth rate correlated positively with spores yielded from dead, infected hosts (*A*), and those hosts reached larger body sizes at death (*B*). Both results were anticipated by the dynamic energy budget (DEB) model. Juvenile growth rate correlated positively (but marginally significantly: *dashed lines*) with fecundity of host clones when infected (*C*) and also increased with proportional fecundity (*D*). Growth rate values (*X*-axis) were calculated from the model along a gradient of maximal feeding rate; similar gradients are created by manipulating conversion efficiency or maintenance rates (not shown). Contours correspond to densities of spores to which hosts were initially exposed. Data panels: points are clonal means ± 95% bootstrapped confidence intervals. Pearson correlation coefficients (*R*) and *P* values are provided to qualitatively confirm these empirical relationships that were predicted by the DEB model.

fected hosts, and spore yield per infected host). Such connections between feeding and disease are striking because, as in many host species, *Daphnia* clones vary in resource acquisition, growth, and fecundity (Yampolsky and Ebert 1994; Hairston et al. 2001). Thus, factors that promote or degrade variation among clones in feeding and resource-related traits via processes unconnected to disease (i.e., power-efficiency trade-offs: Tessier and Woodruff 2002) can influence variation in epidemiological traits. These connections contrast with other drivers of variation in susceptibility. More locus-based models (gene-for-gene and matching-alleles models) emphasize variation in genes that code for susceptibility of hosts and infection ability of parasites, likely through immune function/defense. Here we focus on other steps in the infection process.

Variation in feeding rate among host clones imposed several relationships with epidemiological traits. The feeding rate–susceptibility connection arose because *Daphnia* eat infective stages (spores) that are dispersed in their habitat (Hall et al. 2007*a*). Thus, variation in susceptibility among clones should increase with variation in feeding rate among clones (Hall et al. 2007*a*). Similar feeding-susceptibility links might occur whenever hosts contact parasites while eating (e.g., snails and trematodes, forest insects and viruses, meal moths and viruses, grazing mammals and worms, vertebrate host and tick vector: Fenton et al. 2002; Wobeser 2006). Additionally, feeding rate and time until death were negatively related: fast-eating clones died more quickly once they became infected. The dynamic energy budget model predicted this result because fast-eating clones consume more spores and a larger initial spore dose promotes faster death (data: Ebert et al. 2000; model: Hall et al. 2009*b*; this article). Furthermore, hosts that eat and grow faster create a greater internal energy reserve. Since parasites use this reserve, a greater reserve enhances parasite replication within hosts, thereby catalyzing host death from infection (Hall et al. 2009*b*). Finally, hosts with a faster feeding rate became more fecund (as predicted by the model: Kooijman 1993; Hall et al. 2009*b*).

Variation in feeding rate among clones then imposed three important epidemiological relationships. First, more susceptible clones died faster when they became infected, and they produced more spores when they died. The DEB model-data combination implies a correlation structure among these parameters that could be built into models of host evolution (Boots et al. 2009). Second, an important trade-off arose: more susceptible hosts experienced higher fecundity (see also Boots and Begon 1993). Theory predicts that such trade-offs matter for host evolution during epidemics because they can facilitate parasite-mediated disruptive selection (Boots and Haraguchi 1999; Hoyle et al. 2008; Boots et al. 2009). This trade-off may explain the disruptive selection that was observed during a fungal epidemic (Duffy et al. 2008). Notice, however, that the "cost" of low susceptibility in our model simply reflects slow feeding rate and not costs of defense, costs of maintaining immune systems, etc. Third, feeding rate imposed a

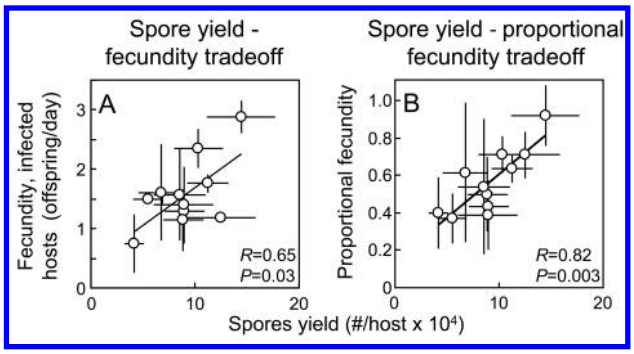

Figure 4: More trade-offs involving spore yield and fecundity of infected hosts. *A*, Host clones that yielded more spores when dead reproduced at a higher rate when infected. *B*, Clones that produced more spores when infected reproduced more when infected relative to uninfected individuals (i.e., higher proportional fecundity). These results signal a spore yield–fecundity trade-off. Points are clonal means ± 95% bootstrapped confidence intervals. Pearson correlation coefficients (R) and P values are also provided.

fecundity-survivorship trade-off: clones that died faster from infection enjoyed higher fecundity when uninfected. This result suggests a fecundity-tolerance relationship (Miller et al. 2005); "tolerance" here refers to the ability of a host to reduce parasite-inflicted damage on survivorship (Miller et al. 2005; Read et al. 2008; Boots et al. 2009). Theory predicts that such fecundity-survival relationships can enhance epidemics and degrade host diversity (Miller et al. 2005; Boots et al. 2009).

Our dynamic energy budget model of disease also predicts that variation in feeding rate among clones should impose a trade-off between spore yield and fecundity. A high feeding rate should promote both high spore yield and high fecundity. In theory, such spore yield–fecundity trade-offs can also enable parasite-mediated disruptive selection and promote host diversity (i.e., Miller et al.'s [2005] "control-fecundity" trade-off). Thus, our DEB model unites two trade-offs promoting disruptive selection (Boots et al. 2009) through the same underlying, feeding-based mechanisms. Although they trended correctly, our data were too noisy to support these predicted connections with statistical significance. However, another spore yield trade-off arose: clones producing high numbers of spores experienced higher birth rates when infected and suffered smaller reductions in fecundity. In the data, these relationships came from a shared correlation with another resource-use indicator, juvenile growth rate (JGR). Host clones with higher JGRs produced more spores from bigger hosts upon dying (also observed when food quality or quantity varies: Hall et al. 2009*a*, 2009*b*). Yet clones with fast JGRs enjoyed higher fecundity when infected. This trade-off might also yield disruptive selection during epidemics (Miller et al. 2005).

The trade-offs highlighted in this study can be explained parsimoniously by taking a resource-based approach. Of course, other factors may also be involved. For instance, the DEB model (Hall et al. 2007*b*, 2009*b*) currently ignores the immune system. This omission might be important when immune function of invertebrates can respond successfully to infection (Mucklow and Ebert 2003; Little et al. 2005; Schmid-Hempel 2009). Operation of these systems might incur considerable energetic costs (Kraaijeveld and Godfray 1997; Moret and Schmid-Hempel 2000; Little and Killick 2007), so an immune-explicit DEB-parasite model developed in the future might connect resource traits with immune function (Lazzaro and Little 2009). Additionally, we have not yet challenged these trade-offs with environmental variation. Phenotypic response to variation in resource quantity/quality and predation intensity (Stibor and Lüning 1994; Yampolsky and Ebert 1994) or related genotype-by-environment interactions could change the position of clones along these trade-offs or even obliterate the trade-offs altogether. This issue matters because resources and predation change spatiotemporally. However, if these factors influence host energetics, the DEB model can be modified to make predictions regarding the epidemiological trade-offs discussed here.

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Literature Cited

Agrawal, A. F., and C. M. Lively. 2002. Infection genetics: gene-for-gene versus matching-alleles models, and all points in between. Evolutionary Ecology Research 4:79–90.

Anderson, R. M., and R. M. May. 1991. Infectious diseases of humans: dynamics and control. Oxford University Press, Oxford.

Bolker, B. M. 2008. Ecological models and data in R. Princeton University Press, Princeton, NJ.

Boots, M., and M. Begon. 1993. Trade-offs with resistance to a granulosis virus in the Indian meal moth, examined by a laboratory evolution experiment. Functional Ecology 7:528–534.

Boots, M., and Y. Haraguchi. 1999. The evolution of costly resistance in host-parasite systems. American Naturalist 153:359–370.

Boots, M., A. Best, M. R. Miller, and A. White. 2009. The role of ecological feedbacks in the evolution of host defence: what does theory tell us? Philosophical Transactions of the Royal Society B: Biological Sciences 364:27–36.

Carius, H. J., T. J. Little, and D. Ebert. 2001. Genetic variation in a

host-parasite association: potential for coevolution and frequency dependent selection. Evolution 55:1136–1145.

Decaestecker, E., A. Vergote, D. Ebert, and L. De Meester. 2003. Evidence for strong host clone–parasite species interactions in the *Daphnia* microparasite system. Evolution 57:784–792.

Decaestecker, E., S. Gaba, J. A. M. Raeymaekers, R. Stoks, L. Van Kerckhoven, D. Ebert, and L. De Meester. 2007. Host-parasite "Red Queen" dynamics archived in pond sediment. Nature 450:870–873.

Duffy, M. A., and S. E. Forde. 2009. Ecological feedbacks and the evolution of resistance. Journal of Animal Ecology 78:1106–1112.

Duffy, M. A., and S. R. Hall. 2008. Selective predation and rapid evolution can jointly dampen effects of virulent parasites on *Daphnia* populations. American Naturalist 171:499–510.

Duffy, M. A., and L. Sivars-Becker. 2007. Rapid evolution and ecological host-parasite dynamics. Ecology Letters 10:44–53.

Duffy, M. A., C. E. Brassil, S. R. Hall, A. J. Tessier, C. E. Cáceres, and J. K. Conner. 2008. Parasite-mediated disruptive selection in a natural *Daphnia* population. BMC Evolutionary Biology 8:80.

Duffy, M. A., S. R. Hall, C. E. Cáceres, and A. R. Ives. 2009. Rapid evolution, seasonality, and the termination of epidemics. Ecology 90:1441–1448.

Duncan, A. B., and T. J. Little. 2007. Parasite-driven genetic change in a natural population of *Daphnia*. Evolution 61:796–803.

Ebert, D. 1994. Virulence and local adaptation of a horizontally transmitted parasite. Science 265:1084–1086.

———. 2005. Ecology, epidemiology, and evolution of parasitism in *Daphnia*. National Center for Biotechnology Information, National Library of Medicine, Bethesda, MD. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=Books

Ebert, D., C. D. Zchokke-Rohringer, and H. J. Carius. 2000. Dose effects and density-dependent regulation of two microparasites of *Daphnia magna*. Oecologia (Berlin) 122:200–209.

Elderd, B. D., J. Dushoff, and G. Dwyer. 2008. Host-pathogen interactions, insect outbreaks and natural selection for disease resistance. American Naturalist 172:829–842.

Fenton, A., J. P. Fairbairn, R. Norman, and P. J. Hudson. 2002. Parasite transmission: reconciling theory and reality. Journal of Animal Ecology 71:893–905.

Green, J. 1974. Parasites and epibionts of *Cladocera*. Transactions of the Zoological Society of London 32:417–515.

Grover, J. P. 1997. Resource competition. Chapman & Hall, New York.

Haag, C. R., and D. Ebert. 2004. Parasite-mediated selection in experimental metapopulations of *Daphnia magna*. Proceedings of the Royal Society B: Biological Sciences 271:2149–2155.

Hairston, N. G., Jr., C. L. Holtmeier, W. Lampert, L. J. Weider, D. M. Post, J. M. Fischer, C. E. Cáceres, J. A. Fox, and U. Gaedke. 2001. Natural selection for grazer resistance to toxic cyanobacteria: evolution of phenotypic plasticity? Evolution 55:2203–2214.

Hall, S. R., L. Sivars-Becker, C. Becker, M. A. Duffy, A. J. Tessier, and C. E. Cáceres. 2007*a*. Eating yourself sick: transmission of disease as a function of feeding biology of hosts. Ecology Letters 10:207–218.

Hall, S. R., C. Becker, and C. E. Cáceres. 2007*b*. Parasitic castration: a perspective from a model of dynamic energy budgets. Integrative and Comparative Biology 47:295–309.

Hall, S. R., C. M. Knight, C. R. Becker, M. A. Duffy, A. J. Tessier, and C. E. Cáceres. 2009*a*. Quality matters: food quality and the course of epidemics in a planktonic host-parasite system. Ecology Letters 12:118–128.

Hall, S. R., J. L. Simonis, R. M. Nisbet, A. J. Tessier, and C. E. Cáceres. 2009*b*. Resource ecology of virulence in a planktonic host-parasite system: an explanation using dynamic energy budgets. American Naturalist 174:149–162.

Hoyle, A., R. G. Bowers, A. White, and M. Boots. 2008. The influence of trade-off shape on evolutionary behavior in classical ecological scenarios. Journal of Theoretical Biology 250:498–511.

Kooijman, S. A. L. M. 1993. Dynamic energy budgets in biological systems. Cambridge University Press, Cambridge.

Kraaijeveld, A. R., and H. C. J. Godfray. 1997. Tradeoff between parasitoid resistance and larval competitive ability in *Drosophila melanogaster*. Nature 389:278–280.

Lampert, W., and I. Trubetskova. 1996. Juvenile growth rate as a measure of fitness in *Daphnia*. Functional Ecology 10:631–635.

Lazzaro, B. P., and T. J. Little. 2009. Immunity in a variable world. Philosophical Transactions of the Royal Society B: Biological Sciences 364:15–26.

Little, T. J., and S. C. Killick. 2007. Evidence for a cost of immunity when the crustacean *Daphnia magna* is exposed to the bacterial pathogen *Pasteuria ramosa*. Journal of Animal Ecology 76:1202–1207.

Little, T. J., D. Hultmark, and A. F. Read. 2005. Invertebrate immunity and the limits of mechanistic immunology. Nature Immunology 6:651–654.

May, R. M., and R. M. Anderson. 1983. Epidemiology and genetics in the coevolution of parasites and hosts. Proceedings of the Royal Society B: Biological Sciences 219:281–313.

Miller, M. R., A. White, and M. Boots. 2005. The evolution of host resistance: tolerance and control as distinct strategies. Journal of Theoretical Biology 23:198–207.

Moret, Y., and P. Schmid-Hempel. 2000. Survival for immunity: the price of immune system activation for bumblebee workers. Science 290:1166–1168.

Mucklow, P. T., and D. Ebert. 2003. Physiology of immunity in the water flea *Daphnia magna*: environmental and genetic aspects of phenoloxidase activity. Physiological and Biochemical Zoology 76:836–842.

Read, A. F., P. A. Lynch, and M. B. Thomas. 2008. How to make evolution-proof insectides for malaria control. PLoS Biology 7:e1000058.

Schmid-Hempel, P. 2009. Immune defence, parasite evasion strategies and their relevance for "macroscopic phenomena" such as virulence. Philosophical Transactions of the Royal Society B: Biological Sciences 364:85–98.

Stibor, H., and J. Lüning. 1994. Predator-induced phenotypic variation in the pattern of growth and reproduction in *Daphnia hyalina* (Crustacea: Cladocera). Functional Ecology 8:97–101.

Tessier, A. J., and P. Woodruff. 2002. Trading off the ability to exploit rich versus poor food quality. Ecology Letters 5:685–692.

Wobeser, G. A. 2006. Essentials of disease in wild animals. Blackwell, Oxford.

Yampolsky, L. Y., and D. Ebert. 1994. Variation and plasticity of biomass allocation in *Daphnia*. Functional Ecology 8:435–440.

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