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Variation in costs of parasite resistance among natural host populations

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Abstract

Organisms that can resist parasitic infection often have lower fitness in the absence of parasites. These costs of resistance can mediate host evolution during parasite epidemics. For example, large epidemics will select for increased host resistance. In contrast, small epidemics (or no disease) can select for increased host susceptibility when costly resistance allows more susceptible hosts to outcompete their resistant counterparts. Despite their importance for evolution in host populations, costs of resistance (which are also known as resistance trade-offs) have mainly been examined in laboratory-based host–parasite systems. Very few examples come from field-collected hosts. Furthermore, little is known about how resistance trade-offs vary across natural populations. We addressed these gaps using the freshwater crustacean *Daphnia dentifera* and its natural yeast parasite, *Metschnikowia bicuspidata*. We found a cost of resistance in two of the five populations we studied – those with the most genetic variation in resistance and the smallest epidemics in the previous year. However, yeast epidemics in the current year did not alter slopes of these trade-offs before and after epidemics. In contrast, the no-cost populations showed little variation in resistance, possibly because large yeast epidemics eroded that variation in the previous year. Consequently, our results demonstrate variation in costs of resistance in wild host populations. This variation has important implications for host evolution during epidemics in nature.

Introduction

Parasites are a potent selective force that can drive evolution of increased resistance in populations of their hosts (Ibrahim & Barrett, 1991; Buckling & Rainey, 2002; Laine, 2006; Duncan & Little, 2007; Duffy *et al.*, 2012). Nevertheless, susceptible hosts persist (Henter & Via, 1995; Kraaijeveld *et al.*, 1998). Costs of resistance provide a likely explanation for this persistence because resistant hosts have lower fitness in the absence of the parasite (Biere & Antonovics, 1996; Sheldon & Verhulst, 1996; Kraaijeveld & Godfray, 1997; Duncan *et al.*, 2011). Such trade-offs between resistance and other fitness traits can maintain diversity for resistance in natural populations (Gillespie, 1975; Antonovics & Thrall, 1994). Furthermore, these trade-offs can drive divergence between populations that vary in exposure to parasites (Hasu *et al.*, 2009; Duncan *et al.*, 2011).

Our insights into costs of resistance largely stem from artificial selection on laboratory populations of hosts; examples from wild-collected hosts are rare (especially in animals, though see Biere & Antonovics, 1996 and Gibson *et al.*, 2013 for plant examples). In these laboratory-based selection studies, replicated host lines are either selected for increased parasite resistance or stay

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under relaxed selection. Fitness-related traits are then compared between the selected and nonselected lines in the absence of parasites (Kraaijeveld & Godfray, 1997; Luong & Polak, 2007; Boots, 2011; Duncan *et al.*, 2011). Although this approach produces valuable insight, it cannot tell us whether these costs are common in nature or whether they vary across multiple populations within a given host–parasite system. This gap merits attention because resistance trade-offs may differ between populations, especially if those populations vary in the severity of parasite epidemics that they experience. Furthermore, costs of resistance may vary because resistance trade-offs can themselves evolve. Indeed, differential selection between populations could reduce variation in one or both traits, thus altering the trade-offs seen among populations (Lande, 1982; Via & Lande, 1985; Roff *et al.*, 2002).

There are, however, challenges associated with comparing resistance trade-offs across multiple populations. Host resistance often depends on either the genotype of the parasite or the specific combination of host genotype and parasite isolate (termed genetic specificity: see Carius *et al.*, 2001; Salvaudon *et al.*, 2007; de Roode & Altizer, 2010; Auld *et al.*, 2012). Genetic specificity seriously complicates experiments that primarily focus on host traits. We avoided this obstacle using the freshwater crustacean, *Daphnia dentifera,* and its virulent yeast parasite, *Metschnikowia bicuspidata*. The likelihood of a particular *Daphnia* genotype suffering infection from *Metschnikowia* (hereafter: yeast) does not depend on the yeast isolate to which it is exposed (that is, there is no genetic specificity; Duffy & Sivars-Becker, 2007). Therefore, we can assay the resistance of hosts from multiple populations using a single yeast isolate. A second obstacle is that for a given host genotype, one must measure both resistance to parasitism and fitness when unexposed to the parasite. Fortunately, *Daphnia* are cyclically parthenogenetic. For our host, this means they typically reproduce asexually in the laboratory (and also throughout most of the epidemic season: Duffy *et al.*, 2008). Therefore, using clonal lines, we can obtain a 'genetic snapshot' of wild host populations and then measure both parasite resistance and birth rate in the absence of the parasite for each individual genotype.

Prior empirical and theoretical work predicts that resistance-fecundity trade-offs should be common in *Daphnia*. The mechanism underpinning this trade-off hinges upon host's feeding rate. When all else is equal, high feeding rate enables high host fecundity (Hall *et al.*, 2010), provided food quality is also good (Hall *et al.*, 2012). However, high feeding rate also elevates host exposure to the transmission stages of the yeast parasite (free-living spores distributed in the host's environment: Ebert, 2005) because rapid feeders contact more yeast spores per unit time (Hall *et al.*, 2007, 2010). Consequently, genetic variation in host's feeding rate can drive a resistance-fecundity trade-off, assuming little genetic variation in susceptibility of hosts for a given contact (exposure) rate with spores.

We see signatures of these resistance trade-offs in the evolutionary responses of *Daphnia* populations to yeast epidemics. Yeast epidemics occur regularly in the wild (Duffy *et al.*, 2010), driving declines in the density of host populations (Hall *et al.*, 2011) and rapid evolution of hosts. Comparisons of host resistance at the start vs. the waning end of epidemics have revealed three major outcomes of parasite-mediated selection: directional selection for increased resistance of hosts (Duffy & Sivars-Becker, 2007; Duffy & Hall, 2008; Duffy *et al.*, 2009, 2012); parasite-mediated disruptive selection, where a yeast epidemic simultaneously favoured both increased and decreased resistance (Duffy *et al.*, 2008); and directional selection for decreased resistance of hosts (Duffy *et al.*, 2012). These latter two forms of selection hint at costs of resistance in populations of hosts in nature. When parasite epidemics are either small or absent, selection can favour low-resistance hosts, provided there is a fitness cost of resistance (Boots & Haraguchi, 1999; Boots *et al.*, 2009). In these scenarios, more susceptible hosts outcompete their highly resistant counterparts.

We looked for costs of resistance in five natural lake populations using a total of 144 *Daphnia* isofemale lines collected in 2010. There was a cost of resistance in two of the five populations. This cost manifested as a positive association between the risk of infection from the yeast (measured as parasite transmission rate, the inverse of resistance) and host fecundity in the absence of the parasite (measured as instantaneous birth rate). Further, hosts collected as epidemics waned were generally more resistant to infection than those collected before. However, the slope of the resistance-fecundity trade-off did not vary between the two collections. This result means that current epidemics (during 2010) selected for increased resistance overall, but not alter the trade-offs themselves. Populations with no detectable trade-off (three of five) showed substantially lower mean and variance in infection risk than did populations with trade-offs. Large epidemics in the previous year (2009: Duffy *et al.*, 2012) may have eroded genetic variation for resistance, thus reducing detectability of the trade-offs in those populations.

Materials and methods

Study system

We sampled 144 *Daphnia* clonal isofemale lines (henceforth lines) from five lakes in Greene and Sullivan Counties, IN, USA. These lakes were Beaver Dam (36 lines), Canvasback (27 lines), Downing (26 lines), Island (25 lines) and Midland (30 lines). We aimed to sample the standing genetic variation of the host population before and after the parasite epidemic. Thus,

in each of these lakes, approximately half of the lines were collected prior to a yeast (*M. bicuspidata*) epidemic. The other half was collected as the epidemic waned (similar to the design in Duffy *et al.*, 2008, 2012). We did not genotype these lines. However, it seems likely that they were unique genotypes: *D. dentifera* populations are refounded each year from sexually produced diapausing eggs (Càceres, 1998); this annual recolonization maintains substantial diversity in the water column. Each of the sampled populations also suffered a yeast epidemic in the previous year (2009), although these epidemics varied in size (see Duffy *et al.*, 2012). Epidemic size in 2009 was determined by calculating the area under the curves of prevalence over time for each lake, estimated from visual diagnosis of hosts from weekly samples. This measure is referred to as the integrated prevalence (Duffy *et al.*, 2012).

The yeast isolate was collected from multiple infected hosts from Baker Lake, Michigan, and has been propagated in a single susceptible *D. dentifera* clone (referred to as the Standard genotype) in the laboratory since 2003. The fact that the parasite isolate was collected hundreds of miles away from the host population (and 7 years previously) minimized the likelihood of it exhibiting local adaptation to particular study populations. All hosts were asexually propagated in beakers containing 100 mL mixed media (50% Artificial *Daphnia* Medium (Kluttgen *et al.*, 1994): 50% filtered lake water from Lake Lanier, Buford, GA, USA) and fed ample food (20 000 *Ankistrodesmus falcatus* algal cells mL^{-1} day^{-1}).

Resistance assay

Infection assays were blocked according to host population, and methods were similar to those used in Duffy & Sivars-Becker (2007) and Duffy *et al.* (2012). For each line, 80 *Daphnia* aged between 1 and 3 days were reared in 100-mL beakers (eight beakers; 10 *Daphnia* per beaker). After 6 days, a subset of these animals was randomly distributed across eight experimental beakers to minimize variation due to maternal effects. However, as we did not maintain separate replicate sublines for each isofemale line, it is possible that maternal effects or other environmental effects have influenced some of our estimates. There were 25–36 lines per block, eight replicates per line and six host individuals per replicate. Experimental beakers were then exposed to the yeast. In addition, each block contained eight replicates of the Standard line (also with six host individuals per replicate) to enable comparison across blocks. On the day of parasite exposure, each replicate beaker was exposed to 20 000 yeast spores (200 spores mL^{-1}) and fed low food (10 000 mL^{-1} algal cells) for 24 h to promote increased spore uptake. Twenty-four hours later, hosts were transferred into fresh media and fed standard amounts of food (20 000 cells mL^{-1} per day). *Daphnia* were moved to clean media again 5 days later. Ten days after parasite exposure, all hosts were scored for infection based on visible growth of yeast spores in the body cavity using a dissecting microscope (50×). Throughout the experiment, replicates were maintained at 20 °C on a 16:8 hour light/dark cycle.

Fecundity assay (in hosts not exposed to the parasite)

Using the same host lines (including the Standard line), we examined host fecundity and survival in the absence of the parasite with a life table design. Methods were similar to the infection assay, except there were 8–10 replicates of each line for each lake and only a single 1-day-old host per replicate. However, these hosts were not exposed to the parasite. Hosts were kept under standard conditions and moved to clean media every other day. The timing of reproduction and the number of offspring per clutch were recorded for clutches 1–4, and the offspring were removed. We also recorded the day of death when mortality occurred before the release of the fourth clutch of offspring.

Analyses

Analyses were performed using R (Ihaka & Gentleman, 1996; R, 2005) and MATLAB (MathWorks, 1999). All data used for these analyses are archived at Dryad (data files: b and Beta data for multiple Daphnia lines from five natural populations).

First, we calculated the two components of the resistance trade-off outlined by Boots & Haraguchi (1999): host resistance and host fecundity when uninfected. Using data from the resistance assay, we calculated infection risk (an inverse measure of resistance) for each host line by estimating the parasite transmission rate, β. If we assume that susceptible hosts (S) decline in number due to infection after contact with spores (Z) (i.e. $dS/dt = -\beta SZ$), we can predict prevalence of infection, P, as: $P = [S(t)/S(0)] = \exp(-\beta Zt)$, where $S(t)$ is the remaining number of susceptible hosts after exposure time t and $S(0)$ is the initial number of hosts. Best fitting values of β were found using maximum likelihood with the binomial distribution as the likelihood function (see Hall *et al.*, 2007; Civitello *et al.*, 2012 for more details). Using data from the fecundity assay, we calculated each host line's instantaneous birth rate in the absence of the parasite (b). This was calculated in two steps (described in more detail in Civitello *et al.*, 2013): first, we estimated instantaneous population growth rate of each line, r, using the Euler–Lotka equation; then, we estimated instantaneous death rate, d, by fitting an exponential survival model (McCallum *et al.*, 2002; Civitello *et al.*, 2013). As, by definition, $r = b - d$, we estimated birth instantaneous

rate as $b = r + d$. Expression of the trade-offs using these traits, scaled instantaneously, is most relevant to models of host evolution during epidemics (see Boots & Haraguchi, 1999; Boots *et al.*, 2009).

Next, we evaluated among-block consistency by comparing the resistance and fecundity of the Standard line across blocks. There was no significant variation across blocks in the proportion of infected hosts (for the infection assays) and total offspring production per *Daphnia* (for the life history assays) of the Standard line (see Fig. S1, in the supporting information). This result justifies simultaneous analysis of data from all lakes below.

Then, we examined how the relationship between parasite transmission rate (β) and fecundity (b) varied both spatially (across populations) and temporally (before and after the epidemic). This was done by fitting a generalized least squares (GLS) model to the transmission rate data. In this model, b, lake population and epidemic status (whether the genotypes were collected pre- or post-epidemic) were fitted as fixed effects (along with all interactions). We used the GLS framework because it could account for unequal variances across factor levels; this was important because variance in β differed considerably across populations (see below). A stepwise model reduction procedure helped to determine significance of explanatory variables (Crawley, 2007). For the within-population analyses, we characterized trade-offs between parasite transmission rate (β) and fecundity (b) using standard major axis regression (SMA) using the *lmodel2* package in R. The SMA method accounts for error in both b and β and therefore better predicts the slope of trade-offs (Legendre & Legendre, 1998). Within-population analysis of the effect of epidemic status on β was carried out using Welch's t-tests. Next, we examined whether the population means for β and b depended on whether or not the population exhibited a resistance trade-off (type II ANOVAS, with population nested within trade-off status (trade-off present/trade-off absent) and a White correction for unequal variances; see Cribari-Neto, 2004). Finally, we examined whether the variance differed across populations for both β and b (Bartlett tests), and whether variance in these traits depended on the presence/absence of a resistance trade-off (F-tests).

Results

Populations varied in the relationship between parasite transmission rate (β) and host birth rate (b) as evidenced by a significant statistical interaction between b and population (Table 1, Fig. 1). Within-population analysis revealed, there was a significant positive relationship between β and b in Beaver Dam ($r = 0.41$, $P < 0.01$; this correlation remains significant when the very low birth rate point is omitted from the analysis) and Canvasback ($r = 0.47$, $P < 0.0001$; Fig. 1). The other three populations did not show a significant relationship between β and b (Downing: $r = 0.11$, $P = 0.33$; Island: $r = 0.19$, $P = 0.20$; Midland: $r = -0.23$, $P = 0.11$; Fig. 1).

Table 1 Summary of the fit of the generalized least squares model that accounted for unequal variances across populations. The model tests the effects of instantaneous host birth rate in the absence of infection (b), host population or host epidemic status (pre- or post-epidemic) on parasite transmission rate (β); P-values < 0.05 are indicated in bold.

	Reduced model			Full model
	d.f.	F	P	d.f.
Instantaneous pop birth rate (b)	1	0.05	0.82	1
Population (Pop)	4	12.82	**<0.0001**	4
Epidemic status (Epi)	1	13.61	**0.0003**	1
b × Pop	4	3.18	**0.0156**	4
b × Epi	–	–	NS	1
Pop × Epi	–	–	NS	4
b × Pop × Epi	–	–	NS	4
Error	133			124

Overall, hosts collected as epidemics waned were more resistant to infection (i.e. had lower mean β) than those collected prior to epidemics. This result manifested as a statistically significant effect of 'epidemic status' (Table 1; see also Fig. 2). When analysed individually, not all lake populations exhibited significant increases in resistance following the epidemic (Fig. 2). However, the absence of a statistical interaction between 'epidemic status' and 'population' meant that the general pattern of parasite-mediated selection did not differ among populations.

The five populations differed in both their mean and variance for parasite transmission rate (mean β: see GLS results in Table 1; variance in β: Bartlett's $K^2 = 67.28$, d.f. = 4, $P < 0.0001$). Those populations that paid a cost for resistance (i.e. showed a resistance-fecundity trade-off: Beaver Dam and Canvasback; filled symbols) had significantly higher transmission rates than those three lakes that did not show significant trade-offs (open symbols; effect of trade-off status: $F_{1,139} = 25.14$, $P < 0.0001$; effect of population (trade-off status): $F_{3,139} = 5.60$, $P < 0.001$). The populations that paid a cost for resistance also had the lowest variance in transmission rate ($F_{62,80} = 4.05$, $P < 0.0001$; Figs 2 and 3a). Lakes that suffered the largest epidemics in the previous year (measured as integrated prevalence) did not exhibit trade-offs, (Fig. 3a; data based on Duffy *et al.*, 2012). However, the Downing population suffered a relatively small epidemic and yet also did not exhibit a cost of resistance (Fig. 3a).

The five populations also differed in their mean and variance for instantaneous population birth rate. Those populations that paid a cost of resistance had significantly lower mean instantaneous birth rate (effect of

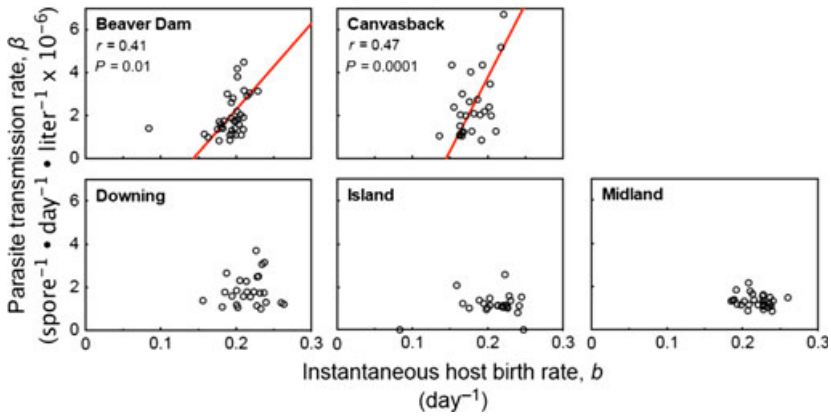

Fig. 1 Associations between parasite transmission rate (β) and instantaneous host birth rate in the absence of the parasite (b) across five natural host populations. Significant relationships were found in two populations: Beaver Dam and Canvasback (top row).

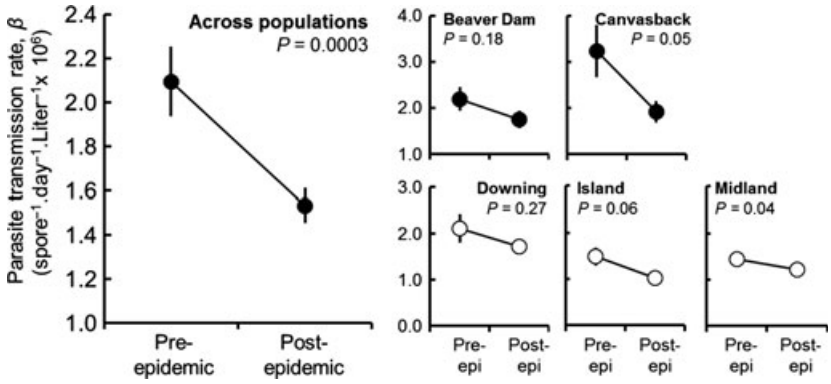

Fig. 2 The effect of epidemics on infection risk to the parasite, that is, transmission rate (β), across populations (large panel) and within each population (small insets). Filled circles denote populations with significant trade-offs between resistance and fecundity (Fig. 1); open symbols represent populations without trade-offs. (Error bars are standard errors.)

trade-off status: $F_{1,139} = 62.44$, $P < 0.0001$; effect of population (trade-off status): $F_{3,139} = 2.25$, $P = 0.085$). Although there were significant differences in the variance of birth rate between populations (Bartlett's $K^2 = 11.96$, d.f. = 4, $P = 0.02$), these differences did not depend on trade-off status ($F_{62,80} = 0.77$, $P = 0.29$; Figs 2 and 3b).

Discussion

Costs of resistance are central to the evolution of host and parasite populations (Chao *et al.*, 1977; Bergelson, 1994; Henter & Via, 1995; Kraaijeveld & Godfray, 1997; Rigby *et al.*, 2002). They occur when investment in traits associated with resistance to parasitism leads to a correlated decrease in another fitness trait of hosts; hence, they are also referred to as resistance trade-offs. We tested for costs of resistance in five natural populations of the crustacean *D. dentifera* to its yeast parasite, *M. bicuspidata*. Costs of resistance manifested as a positive association between infection risk, that is, parasite transmission rate (β), and instantaneous birth rate of hosts in the absence of the parasite (b) (Fig. 1). We found significant costs in two of the five populations (Beaver Dam and Canvasback).

Why are there costs of resistance in some populations but not others? One possibility involves the erosion of genetic variance in resistance (parasite transmission rate, β) by large epidemics during the previous year. Two of the cost-free populations (Island and Midland) had very large epidemics during 2009 that elicited parasite-mediated directional selection towards increased resistance (Duffy *et al.*, 2012). These populations also exhibited very low variance for resistance during the following season in 2010. Thus, strong, directional, parasite-mediated selection for increased resistance during the previous year (2009) may have reduced genetic variance in these populations (Fig. 3). Such an effect matters because reduced variance in one or both traits in a trade-off can alter the shape and strength of the trade-off, potentially making it difficult to detect (Lande, 1982; Via & Lande, 1985; Roff *et al.*, 2002).

This reasoning alone cannot sufficiently explain the lack of trade-off in some lakes in 2010, however. First, the Downing population suffered a relatively small epidemic in 2009 and yet exhibited no cost of resistance. Second, if selection reduced variation in transmission rate, it should also have reduced variation in birth rate – that is, assuming that feeding rate positively correlated with both infection risk and birth rate (Hall *et al.*,

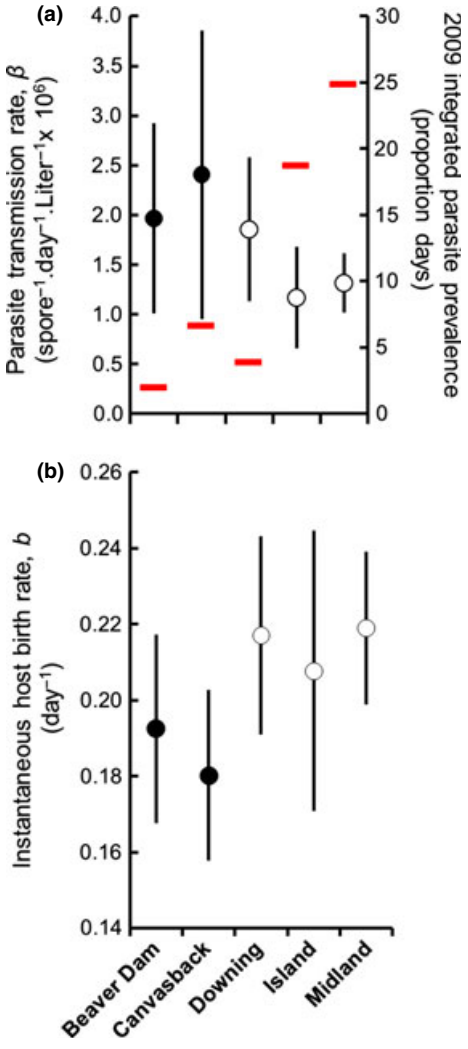

Fig. 3 (a) Variation among host populations in transmission rate of the parasite (β; left axis, dot and vertical error bars), an inverse index of host resistance and the previous year's (2009) epidemic size (right axis, horizontal bars; measured as integrated parasite prevalence, from Duffy *et al.*, 2012). (b) Instantaneous birth rate of hosts in the absence of the parasite (b), grouped by host population. Filled circles denote populations with significant resistance trade-offs (Fig. 1); open symbols represent populations without trade-offs. (Error bars denote standard deviations.)

2010). Instead, no-cost populations had very low infection risk yet had a high mean and similar variation in birth rate relative to populations that exhibited a cost of resistance (Figs 1 and 3). Why is this?

One possibility challenges the feeding-based model for the trade-off. Remember that infection risk depends on the product of exposure to parasites (feeding rate) and per-spore susceptibility to parasites consumed (Hall *et al.*, 2007, 2010). Mean infection risk could be low in no-cost populations if mean exposure was low (due to low feeding rate), mean per-spore susceptibility was low, and/or if per-spore susceptibility and feeding rate negatively covary (see Appendix S2). If resistance stemmed from reduced feeding rate alone, mean and variance of fecundity should also have dropped following parasite-mediated selection (because low feeding rate correlates with low birth rate). This prediction received no support (Fig. 1). Thus, we suspect that per-spore susceptibility played an important role in driving the observed patterns and that its contribution to overall host susceptibility varied across populations.

We also evaluated whether yeast epidemics in 2010 affected expression of fecundity-resistance trade-offs in 2010. This within-season effect would have arisen as a statistical interaction on infection risk involving instantaneous host birth rate, epidemic status and lake population. We found no such interaction (Table 1). Instead, we found a simpler overall pattern: host resistance increased (i.e. infection risk dropped) across all populations following parasite epidemics in 2010 (Table 1). Although this pattern was not statistically significant in all populations when each was analysed individually, the overall analysis indicated the same general pattern across all populations. Thus, we found no evidence for decreased resistance as in the previous year (Duffy *et al.*, 2012).

Costs of resistance to infection matter because they shape the evolution of host populations and can promote maintenance of diversity in host resistance (Gillespie, 1975; Antonovics & Thrall, 1994). However, most of our understanding of fitness-resistance trade-offs stems from laboratory-based selection experiments. Eventually, the search for these trade-offs must move to natural populations. Here, we found trade-offs in two of five lake populations. In the three others, we saw low variation in the resistance trait. In two of those three lakes, the low variance in resistance followed large epidemics during the previous year (2009). Thus, our results suggest that natural populations vary in costs of resistance, perhaps due to past epidemics. These differences may potentially govern the evolutionary response of host populations to epidemics both within and among years (Boots & Haraguchi, 1999).

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Figure S1 Parasite transmission rate and early host fecundity in the standard isofemale line across the five population blocks.

Appendix S1 Use of standard genotypes to compare blocks.

Appendix S2 Variance and covariance in resistance and birth rate.

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