

REVIEW

Ecological feedbacks and the evolution of resistanceMeghan A. Duffy^{1*} and Samantha E. Forde²¹*School of Biology, Georgia Institute of Technology, Atlanta, GA 30332-0230, USA; and* ²*Ecology and Evolutionary Biology Department, University of California, Santa Cruz, California 95064, USA***Summary**

1. The idea that parasites can affect host diversity is pervasive, and the possibility that parasites can increase host diversity is of particular interest. In this review, we focus on diversity in the resistance of hosts to their parasites, and on the different ways in which parasites can increase or decrease this resistance diversity.
2. Theoretically, parasites can exert many different types of selection on host populations, which each have consequences for host diversity. Specifically, theory predicts that parasites can exert negative frequency-dependent selection (NFDS) and disruptive selection on resistance, both of which increase host diversity, as well as directional selection and stabilizing selection on resistance, both of which decrease host diversity.
3. Despite these theoretical predictions, most biologists think of only NFDS or directional selection for increased resistance in response to parasitism. Here, we present empirical support for all of these types of selection occurring in natural populations. Interestingly, several recent studies demonstrate that there is spatiotemporal variation in the type of selection that occurs (and, therefore, in the effects of parasitism on host diversity).
4. A key question that remains, then, is: What determines the type of parasite-mediated selection that occurs? Theory demonstrates that the answer to this question lies, at least in part, with trade-offs associated with resistance. Specifically, the type of evolution that occurs depends critically on the strength and shape of these trade-offs. This, combined with empirical evidence for a strong effect of environment on the shape and strength of trade-offs, may explain the observed spatiotemporal variation in parasite-mediated selection.
5. We conclude that spatiotemporal variation in parasite-driven evolution is likely to be common, and that this variation may be driven by ecological factors. We suggest that the feedback between ecological and evolutionary dynamics in host–parasite interactions is likely to be a productive area of research. In particular, studies addressing the role of ecological factors (e.g. productivity and predation regimes) in driving the outcome of parasite-mediated selection on host populations are warranted. Such studies are necessary if we are to understand the mechanisms underlying the observed variation in the effects of parasites on host diversity.

Key-words: adaptive dynamics, co-evolution, evolutionary ecology, host–parasite interactions, Red Queen.

Introduction

Ecologists and evolutionary biologists are intensely interested in the factors driving diversity in natural populations. Parasitism has received particular attention as a possible driver of host diversity (Summers *et al.* 2003). In 1949, Haldane suggested that parasites are important selective forces on their host populations, and that they have the potential to promote host diversity (reprinted in Haldane 1992). Haldane

first suggested the possibility of Red Queen dynamics (although that term was not introduced until the 1970s; Van Valen 1973), stating that ‘the most that the average species can achieve is to dodge its minute enemies by constantly producing new genotypes’. Since then, this idea has been of particular interest to ecologists and evolutionary biologists because of its implications for the evolution of sex (Hamilton 1980; Hamilton, Axelrod & Tanese 1990; Summers *et al.* 2003; also see references that follow).

In the intervening years, a great deal of theoretical and empirical work has been done on parasite-driven evolution

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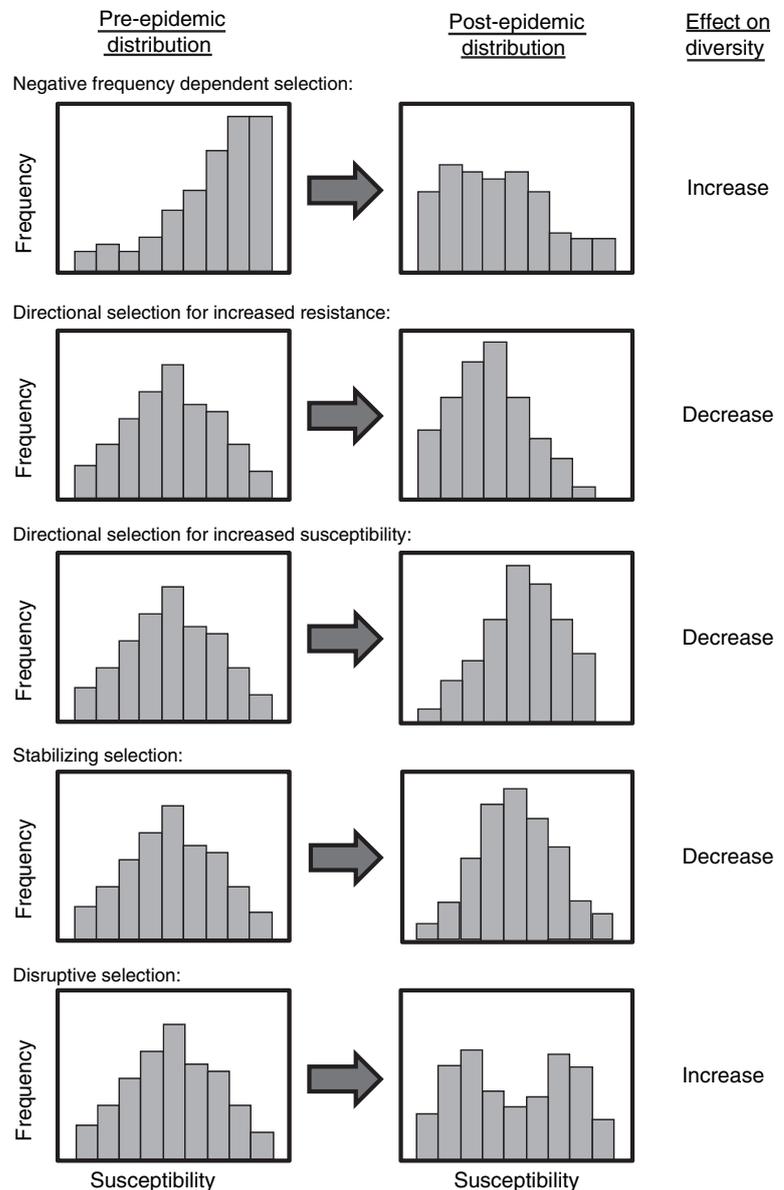


Fig. 1. Effects of different types of parasite-mediated selection on the distributions of susceptibilities in a host population. The panels on the left show the distributions in the population prior to an epidemic, while the panels on the right show the distributions after the epidemic. For each scenario, the effect of parasite-mediated selection on host diversity is stated. For directional, stabilizing and disruptive selection, we assume (for simplicity) that the population begins with an approximately normal distribution of susceptibilities. However, with negative frequency-dependent selection, the most common genotypes should also be the most susceptible, so a normal pre-epidemic distribution would not be expected; rather, the distribution should be skewed so that highly susceptible genotypes are the most common.

of host populations, including the influences of parasites on host diversity. Based on this research, it is clear that parasites can exert many different types of selection on their host populations, some of which will increase host diversity, and some of which will decrease it (Fig. 1). We review the theoretical predictions regarding parasite-driven evolution of host populations, discuss the implications for host diversity and provide empirical examples of these different types of selection. We find that, in some systems, the type of selection that occurs varies between studies, sites or years. Theory suggests that this variation is due to changes in the strength and shape of trade-offs associated with resistance, and recent empirical evidence suggests that these trade-offs are likely to be influenced by ecological factors. Thus, we propose that spatiotemporal variation in parasite-driven evolution is likely to be common, and that a productive area for future research will link studies of the ecological factors that influence trade-offs with studies documenting parasite-mediated selection.

Types of selection

We start by focusing on negative frequency-dependent selection (NFDS), which increases host diversity, as this is a form of parasite-mediated selection with which many people are familiar. Next, we move on to the other types of selection that are possible: directional selection for increased resistance, directional selection for increased susceptibility, stabilizing selection and disruptive selection. While both types of directional selection and stabilizing selection result in decreased host diversity, disruptive selection increases it, making it a second means by which parasites can promote host diversity (in addition to NFDS; see Fig. 1; also see Appendix S1).

With NFDS, parasites 'track' the common host genotypes, reducing their fitness and favouring rare genotypes (Woolhouse *et al.* 2002). This means that the fitness of a genotype declines with increasing frequency, because the parasites that are best at infecting that genotype become common. This

tracking is driven by genetic matching between host and parasite, and forms the basis for most of the theory constructed to understand the effects of host–parasite co-evolution on sex and recombination – most notably, the Red Queen hypothesis (e.g. Hamilton *et al.* 1990). The Red Queen hypothesis states that selection will favour rare host genotypes in the face of co-evolving parasites, because obligate parasites will be under strong selection to infect the most common host genotypes (Jaenike 1978; Hamilton 1980; Bell 1982). NFDS helps in maintaining the diversity of host genotypes through time.

Theoretical studies on host–parasite co-evolution have used several different approaches, including, most commonly, ‘gene-for-gene’ and ‘matching alleles’ models (Agrawal & Lively 2002; Woolhouse *et al.* 2002). Gene-for-gene models assume that one parasite genotype is universally virulent. These models are generally used for plant systems, in part because of support for gene-for-gene dynamics in crop systems (Agrawal & Lively 2002; Hancock 2005). With matching alleles models, no parasite genotype is universally virulent; rather, infection depends on a specific match between the host and parasite genotypes. These models are more typical of literature on animal host–parasite interactions, in part because they are based on the invertebrate immune system (Agrawal & Lively 2002). In reality, there can be a continuum between gene-for-gene and matching alleles models of infection, and even small departures from a strict gene-for-gene model (where one parasite genotype has universal virulence) can lead to NFDS (Agrawal & Lively 2002). Theory predicts that, with NFDS, parasite-driven changes in the host population may be lagged in time (Seger 1988; Dybdahl & Lively 1998; Woolhouse *et al.* 2002).

The first empirical evidence for Red Queen dynamics in natural populations was found in a snail–trematode (*Potamopyrgus antipodarum*–*Microphallus* sp.) system (Dybdahl & Lively 1998; Table 1). Common host clones were tracked by parasites in a time-lagged fashion, and recently common host clones were more infectable than rare ones; these results were consistent with a co-evolutionary model of this system (Dybdahl & Lively 1998). Further support for time-lagged Red Queen dynamics in this system comes from an experimental study in which the infection frequencies of host genotypes that were previously common were compared with those that were previously rare, with results supporting NFDS (Koskella & Lively 2007).

Evidence for NFDS and Red Queen dynamics have also been found in studies of *Daphnia magna* and the bacterium *Pasteuria ramosa*. In this system, there are strong host clone–parasite isolate interactions; no single host clone is resistant to all parasite isolates and no parasite isolate is highly infective to all host clones (Carius, Little & Ebert 2001). This genotype specificity suggests the possibility of co-evolution via NFDS. A recent study took advantage of the accumulation of dormant stages of the host and parasite in lake sediments to reconstruct rapid co-evolutionary dynamics (Decaestecker *et al.* 2007). The susceptibility of *Daphnia* was higher when they were exposed to contemporary parasites, and lower when exposed to parasites from earlier or later time periods, which matched the dynamics generated by a matching alleles model parameterized for this system.

Parasites can also exert other types of selection on resistance in their host populations, leading to changes in host diversity. Theoretical studies on the evolution of resistance to parasitism suggest that, when costs to resistance are present

Table 1. Summary of possible types of parasite-mediated selection and the empirical examples discussed in this review

Form of selection	Empirical examples	References	Notes
Negative frequency-dependent	<i>Potamopyrgus antipodarum</i> – <i>Microphallus</i> sp.	Dybdahl & Lively 1998; Koskella & Lively 2007	Red Queen dynamics
	<i>Daphnia magna</i> – <i>Pasteuria ramosa</i>	Carius <i>et al.</i> 2001; Decaestecker <i>et al.</i> 2007	Red Queen dynamics and strong host–parasite genotype specificity
Directional selection for increased resistance	<i>Oryctolagus cuniculus</i> – <i>Myxoma</i>	Dwyer <i>et al.</i> 1990; Fenner & Fantini 1999	Host–parasite co-evolution
	<i>Myzus persicae</i> – <i>Aphidius colemani</i>	Herzog <i>et al.</i> 2007	
	<i>Paramecium caudatum</i> – <i>Holospira undulata</i>	Lohse <i>et al.</i> 2006	Cost of resistance
	Bacteria–bacteriophage	Chao <i>et al.</i> 1977; Buckling & Rainey 2002; Brockhurst <i>et al.</i> 2003	Selective sweeps
Directional selection for increased susceptibility	<i>Amphicarpaea bracteata</i> – <i>Synchytrium decipiens</i>	Parker 1991	Cost of resistance
Stabilizing	<i>Eurosta solidagininis</i> –parasitoid	Weis <i>et al.</i> 1992	Trade-off between susceptibility to predation and parasitism
Disruptive	<i>Columba livia</i> –feather lice (<i>Columbicola</i> spp.)	Clayton <i>et al.</i> 2005	Cost of resistance
	<i>Daphnia dentifera</i> – <i>Metschnikowia bicuspidata</i>	Duffy <i>et al.</i> 2008	Evolution of bimodal distribution of susceptibility; trade-offs
	<i>Plodia interpunctella</i> –virus	Mealor & Boots 2006	Bimodal distribution of susceptibility; trade-offs
	<i>Pseudomonas aeruginosa</i> –PP7	Brockhurst <i>et al.</i> 2005	Diversity increased after phage addition; costs of resistance

(as is generally thought to be the case), several different types of selection are possible, including directional selection for increased resistance or increased susceptibility, stabilizing selection (in which an intermediate level of resistance is favoured) and disruptive selection (in which highly resistant and highly susceptible genotypes are favoured; Frank 1994; Boots & Bowers 1999; Boots & Haraguchi 1999; Kopp & Gavrillets 2006; Hoyle *et al.* 2008). Directional and stabilizing selection should both decrease host diversity, while disruptive selection should increase host diversity (Endler 1986). This makes parasite-driven disruptive selection particularly interesting, as it provides another means by which parasites can increase host diversity (in addition to the more commonly thought of NFDS discussed before).

In general, directional selection for increased resistance should be favoured in cases where costs of resistance are low (or absent), or when rates of parasitism are very high (Bowers, Boots & Begon 1994; Frank 1994). On the other hand, when costs of resistance are very high, or when rates of parasitism are low, directional selection for increased susceptibility can occur (Bowers *et al.* 1994; Frank 1994). A classic example of directional selection is the evolution of resistance of rabbits (*Oryctolagus cuniculus*) to Myxoma virus in Australia (Dwyer, Levin & Buttel 1990; Fenner & Fantini 1999). Myxoma virus was introduced to Australia in 1950 in an attempt to control invasive European rabbits (Fenner & Fantini 1999). Over the next few decades, rabbits evolved resistance (and the virus evolved reduced virulence), reducing the effectiveness of the virus as a biocontrol agent (Fenner & Fantini 1999).

A number of other studies have also demonstrated the evolution of increased resistance in host populations exposed to parasites. For example, in a study in which peach-potato aphids, *Myzus persicae*, were allowed to evolve for several generations with or without a parasitoid wasp, *Aphidius colemani*, treatments with *A. colemani* evolved to contain only a single, highly resistant clone, whereas the control treatments retained a diverse suite of clones (Herzog, Müller & Vorburger 2007). In another example, *Paramecium caudatum* that were exposed to the bacterial parasite *Holospora undulata* evolved resistance (as compared with naive hosts; Lohse, Gutierrez & Kaltz 2006). This evolution of resistance occurred even in the presence of both significant host–parasite genotype interactions and a cost of resistance (as resistant genotypes had lower division rates).

At least one study has found the opposite pattern – the evolution of increased susceptibility in a host population exposed to parasites. In this study, genotypes of the plant *Amphicarpaea bracteata* that were resistant to the pathogen *Synchytrium decipiens* decreased in frequency over a 2-year period during which the pathogen was common (Parker 1991). This result was attributed to observed trade-offs between resistance and life-history traits, including the number of seeds produced per plant.

Cases where directional selection results in the fixation of advantageous mutations (such as those conferring resistance)

are referred to as selective sweeps. In these cases, polymorphisms are transient; while fixation is usually thought of as occurring rapidly, this is not necessarily the case (Woolhouse *et al.* 2002). A number of empirical examples of host–parasite interactions characterized by selective sweeps come from experiments with bacteria and bacteriophage (Chao, Levin & Stewart 1977; Buckling & Rainey 2002; Brockhurst *et al.* 2003; Poullain *et al.* 2008). These studies have documented increased resistance and infectivity over time, reflecting repeated sweeps of adaptive mutations in both host and parasite.

Gandon *et al.* (2008) formulated two simple models that illustrate the difference between directional selection via selective sweeps (i.e. arms race dynamics of co-evolution between hosts and parasites) and NFDS. This study focuses on changes in parasite infectivity, although could be applied to host resistance as well. Under arms race dynamics, one expects there to be a monotonic increase in fitness with time, as a larger shift will allow the parasite (or host) to have accumulated more beneficial mutations. In contrast, under NFDS, the fitness of a given parasite (or host) genotype will fluctuate when exposed to hosts (or parasites) from different times, so, in general, there should not be monotonic increases in fitness over time. An exception occurs at short time-scales, when you can see monotonic increases in fitness over time; given that many ecological studies occur over relatively short time-scales, this is an important caveat. However, with NFDS over longer time-scales, hosts can be more susceptible to contemporary parasites than to ancestral or future parasites, as was seen in the study of Decaestecker *et al.* (2007) discussed before. Testing these predictions requires the ability to measure the performance of the parasite against contemporary hosts, as well as on those from the past and future. In systems where such studies are not possible, evaluating mean fitness across space can be used as an alternative, assuming co-evolution between host and parasite is not synchronized across communities. In these cases, the dynamics over space may be very similar to those over time (Frank 1994; Woolhouse *et al.* 2002; Gandon *et al.* 2008).

Parasites can also impose stabilizing selection on host populations. Specifically, if the trade-off curve between resistance and another trait (such as fecundity) is strongly accelerating (Fig. 2), i.e. if resistance is increasingly costly, then stabilizing selection for an intermediate resistance level is expected (Boots & Haraguchi 1999; Hoyle *et al.* 2008). Support for parasite-mediated stabilizing selection comes from several systems with trade-offs associated with parasite resistance. Susceptibility to parasitoid attack in the insect *Eurosta* is positively correlated with gall size, while susceptibility to predation is negatively correlated with gall size (Weis, Abrahamson & Andersen 1992). Together, this leads to stabilizing selection on gall size (and, hence, susceptibility). Similarly, susceptibility to lice in rock pigeons (*Columba livia*) decreases with increasing beak overhang, but beaks with larger overhangs are more

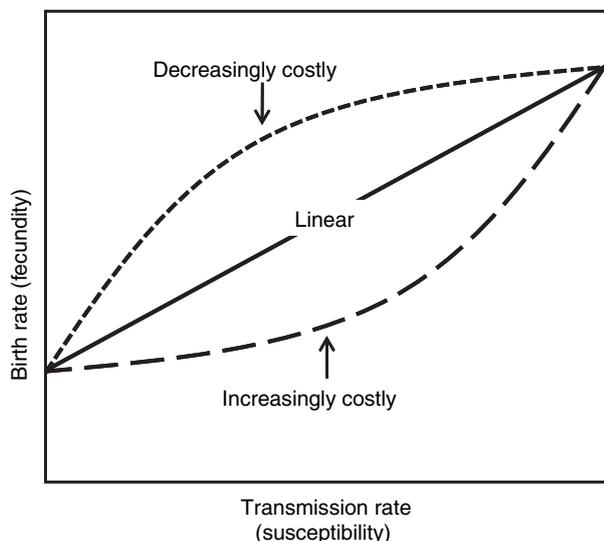


Fig. 2. Three possible shapes for trade-off curves between transmission and birth rates. The shape and strength of trade-offs associated with resistance critically influence the type of parasite-mediated selection that occurs during epidemics.

susceptible to breakage (Clayton *et al.* 2005). This leads to stabilizing selection on beak morphology (and, again, susceptibility).

Finally, for a number of different trade-off shapes and strengths, theory predicts disruptive selection on resistance (Frank 1994; Boots & Haraguchi 1999; Kopp & Gavrilets 2006; Hoyle *et al.* 2008). This result is analogous to findings for other exploiter–victim relationships, including plant–herbivore interactions, where plants can invest heavily in defenses or, alternatively, can ‘outgrow’ their enemies (Berenbaum 2001). Disruptive selection is most likely with decelerating trade-offs, but can also occur in some cases with weakly accelerating and linear trade-offs (Fig. 2; Hoyle *et al.* 2008).

Several studies provide empirical evidence for parasite-mediated disruptive selection. A population of *Daphnia dentifera* showed a normal distribution of susceptibilities prior to an epidemic of the yeast *Metschnikowia bicuspidata* and a bimodal distribution after, which is expected with disruptive selection (see Fig. 1; Duffy *et al.* 2008); recent evidence suggests trade-offs between resistance and fecundity (S.R. Hall, M.A. Duffy, C.R. Becker & C.E. Cáceres, unpublished data). A population of the Indian meal moth, *Plodia interpunctella*, had a bimodal distribution of susceptibility to a viral parasite (Mealor & Boots 2006); combined with previous evidence for trade-offs associated with resistance (Boots & Begon 1993), this suggests previous disruptive selection on this population. Finally, a study on *Pseudomonas aeruginosa* and the bacteriophage PP7 found increased diversity of *P. aeruginosa* after introduction of the phage, although this effect was transient (Brockhurst, Buckling & Rainey 2005); resistant phenotypes were less fit in the absence of the phage than the sensitive phenotypes, indicating a cost of resistance.

Spatiotemporal variation in the form of parasite-mediated selection

One universal feature of theoretical studies on parasite-driven evolution of host populations is that the nature of the trade-offs associated with resistance is crucial. This is particularly interesting given that environmental context should influence both the strength (Coley 1986; Bohannan *et al.* 2002; Koricheva 2002; Lopez-Pascua & Buckling 2008) and shape (Jessup & Bohannan 2008) of trade-offs. Therefore, for a single host–parasite interaction, there may be spatiotemporal variation in the type of selection exerted by the parasites.

Indeed, there is empirical evidence for varying outcomes of host–parasite interactions. Two examples are provided by interactions between *Daphnia* and their microparasites. First, as discussed before, the bacterium *Pas. ramosa* has been shown to drive NFDS on populations of *D. magna* (Decaestecker *et al.* 2007). In a different *D. magna* population, however, a different *Pasteuria* epidemic resulted in directional selection (Duncan, Mitchell & Little 2006; Duncan & Little 2007). Second, the yeast *M. bicuspidata* has driven both directional selection and disruptive selection on populations of *D. dentifera* (Duffy & Sivars-Becker 2007; Duffy *et al.* 2008). Further evidence for variation in the outcome of host–parasite interactions come from the seed parasitic moth *Greya politella* and its host plant *Heuchera grossulariifolia*, where parasite-mediated selection varied across years and populations (Nuismér & Ridenhour 2008). Finally, there is also evidence of varying outcomes of host–parasite interactions from studies of *Escherichia coli* and bacteriophage. A study of *E. coli* and phage found differences between continuous (chemostat) and serial cultures. Chemostats were more spatially complex, and also had significantly more sensitive bacteria (Schrag & Mittler 1996). In addition, a study of *E. coli* and the bacteriophage T7 suggested that the form of selection likely differed among resource environments; the diversity of hosts increased over time in low resource environments but decreased in high resource environments (Forde *et al.* 2008). Overall, these results suggest that the effects of parasites on host populations may show considerable variation in space and time (see also Thompson 2005), and that this variation may be explained by ecological factors.

Suggestions for future studies

As summarized before, there is theoretical and empirical support for many different types of parasite-mediated selection. Yet, in our experience, most empiricists still consider only NFDS and directional selection. A key motivation for this review was to urge empiricists to consider all possible types of selection when conducting their studies. Additionally, we must acknowledge that there is likely to be spatiotemporal variation in the outcome of host–parasite interactions. Therefore, studies should be replicated across populations and/or years to determine the range of outcomes that occur in a particular system.

Finally, we must move beyond simply documenting the effects of parasites on their host populations. To start, we must begin to disentangle the mechanisms driving different types of parasite-mediated selection. Future studies should consider how the ecological context in which host–parasite interactions are embedded influences trade-offs associated with resistance, and determine whether this corresponds with changes in the type of parasite-mediated selection that occurs. At the same time, we must begin to understand the ecological consequences of these different types of selection. For example, directional selection for increased susceptibility might terminate epidemics (Duffy & Sivars-Becker 2007; Duffy & Hall 2008; Duffy *et al.* 2009), but disruptive selection or directional selection for increased susceptibility might favour longer-term persistence of the parasite. Studies disentangling these eco-evolutionary dynamics would greatly improve our understanding of how and why parasites influence host diversity.

Conclusions

Parasites can exert a number of different types of selection on their host populations, all of which have consequences for host diversity. Specifically, parasite-mediated selection can decrease host diversity when parasites exert directional selection for increased susceptibility or increased resistance, or stabilizing selection for an intermediate level of resistance. Conversely, parasites can increase host diversity when they drive NFDS (due to host–parasite genotype interactions) or disruptive selection (in which highly susceptible and highly resistant genotypes are favoured). All of these types of selection have empirical support.

A universal feature of the theoretical literature on parasite-driven evolution of host populations is that the type of selection that occurs depends critically on the nature of trade-offs associated with resistance. This is important because the strength and shape of trade-offs can be strongly influenced by environmental context. Taken together, these findings suggest that substantial spatial and temporal variation in the type of parasite-mediated selection on host populations – and the subsequent effects on host diversity – may be the norm. While this provides an added challenge for empirical studies, recognizing this potential variation, and designing studies to explicitly address this variation, is likely to be essential in understanding the effects of parasitism on diversity in natural populations.

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Supporting Information

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

Appendix S1. Parasite-mediated selection and its effects on host diversity.

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