Ecological context influences evolution in host-parasite interactions: insights from the *Daphnia*-parasite model system

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Introduction

"I want to suggest that the struggle against disease, and particularly infectious disease, has been a very important evolutionary agent, and that some of its results have been rather unlike those of the struggle against natural forces, hunger, and predators, or with members of the same species." — JBS Haldane (1949)

Parasites are ubiquitous, and the outcomes of host-parasite interactions can often be measured in terms of life or death. Thus, it is not surprising that in the 70 years since Haldane postulated the importance of parasites as selective agents, studies of host-parasite interactions have provided striking examples of evolution in action (Allison 1954; Boots et al. 2004; Buckling and Rainey 2002; Buckling et al. 1997; Decaestecker et al. 2007; Deom et al. 1986; Dybdahl and Lively 1998; Epstein et al. 2016; Fenner and Fantini 1999; Gibson et al. 2018; Schiebelhut et al. 2018; Schild et al. 1983). Moreover, we now realize that the ecological context—the "natural forces, hunger, and predators" and "members of the same species" to which Haldane referred—modulates the evolutionary outcomes of infectious disease in important and sometimes unexpected ways. Here, we review recent studies that demonstrate that predators, competitors, and the abiotic environment strongly influence the evolutionary dynamics of host-parasite interactions.

Host-parasite interactions are often considered in isolation, but the larger ecological context matters, too. To give just two examples: excluding large vertebrate herbivores increased the prevalence of viruses in plants by increasing the abundance of highly competent hosts (Borer et al. 2009). Similarly, increasing nutrient inputs to ponds elevated levels of disease in frogs by increasing algal abundance which, in turn, increased the abundance of snails, who are

46 intermediate hosts for the parasite (Johnson et al. 2007). These parasites strongly impact their
47 hosts: the plant virus reduces plant longevity, growth, and seed production and the frog parasite
48 causes severe limb deformities. Therefore, it does not require a large leap to imagine that these
49 alterations to ecological context might alter parasite-mediated selection.

50 Human activities are strongly impacting the ecological context in which host-parasite
51 interactions are embedded. Humans are changing abiotic factors in terrestrial and aquatic
52 habitats, including nutrient levels, precipitation regimes, temperature, and pH (Carpenter et al.
53 1998; Field et al. 2012; Weiss et al. 2018). Human activities are also strongly impacting species
54 assemblages via environmental disturbance, climate change, and the introduction and extirpation
55 of different species, including parasites and predators (Britton 2013; Doherty et al. 2016; Prugh
56 et al. 2009; Sala et al. 2000; Urban 2015). Because ecological context influences the prevalence
57 and severity of disease, human-driven changes in abiotic factors and species assemblages can
58 have dramatic consequences for evolution in host-parasite systems.

59 In this review, we highlight some of the ways in which ecological context, including
60 human-driven changes to ecosystems, can influence evolution in host-parasite interactions. We
61 also touch on some ways in which contemporary evolution may change ecological dynamics (i.e.
62 eco-evolutionary feedbacks; Hendry 2016; Strauss et al. 2017). In doing so, we focus in on one
63 particular study system that has yielded key insights: *Daphnia* and their microparasites. *Daphnia*
64 are ecologically important and experimentally tractable, and have emerged as a model system for
65 understanding the ecology and evolution of host-parasite interactions (Cáceres et al. 2014b;
66 Ebert 2005). We first introduce this system, then review studies demonstrating the importance of
67 predators, competitors, and the abiotic environment in altering evolution in host-parasite
68 interactions.

The *Daphnia*-microparasite study system

Ecologists and evolutionary biologists have long studied *Daphnia*, both because of their ecological importance and because of their tractability as a study organism (Ebert 2011; Lampert 2006). *Daphnia* are dominant herbivores in many temperate aquatic ecosystems and serve as important links between primary producers (the phytoplankton they consume from the water column) and consumers (the small fish and predatory invertebrates that feed on *Daphnia*). In addition, their small size and rapid generation time make it possible to work with them in the laboratory and in field studies, allowing scientists to test possible mechanisms underlying patterns observed in nature—an important bridge between the laboratory and the natural world that is not easily crossed in many study systems.

The reproductive system of *Daphnia* also helps explain why they have emerged as an important study system. Most *Daphnia* are cyclical parthenogens, meaning they can reproduce sexually and asexually. Asexual reproduction makes it possible to propagate isofemale (i.e., clonal) lines under standardized laboratory conditions, allowing researchers to differentiate genetic and environmental effects on phenotypic traits. At the same time, the sexually produced offspring are enclosed in long-lived dormant eggs that accumulate in sediments, allowing studies that "resurrect" genotypes from earlier populations so that scientists may understand how populations have changed on scales from decades to centuries (Decaestecker et al. 2007; Frisch et al. 2014; Hairston et al. 1999; Rogalski 2017).

Another advantage of the *Daphnia* system comes from the ability to study multiple replicate lakes or ponds that have well-defined boundaries; this means it is possible to study

multiple populations (essential for evolutionary studies, where population is the unit of replication) and to do so across ecological gradients (e.g., in predation or productivity).

In the past few decades, *Daphnia* and their microparasites have emerged as a model system for understanding infectious diseases (Cáceres et al. 2014b; Ebert 2005; Ebert 2011; Lampert 2011; Little and Ebert 2004). A number of parasites including viruses, bacteria, fungi, oomycetes, microsporidians and protozoa regularly infect *Daphnia* (Ebert 2005; Green 1974; Toenshoff et al. 2018). These parasites have diverse infection dynamics (horizontal vs. vertical transmission, obligate killers vs. continuous transmission) and exert a wide range of effects on their hosts (including early death, castration, and even gigantism; Ebert 2005).

As is true for all organisms, any particular *Daphnia*-parasite interaction is embedded within a much larger, richer ecological context (Miner et al. 2012). When thinking about this ecological context, we need to consider not only the types of interactions that have traditionally been the focus of ecological studies (such as resource levels and predation regimes), but also that pathogens are likely to be infecting multiple members of the food web, and that any one member of the food web is likely to be infected by multiple pathogens.

We begin by reviewing the impact of predation on evolution in host-parasite systems. Next, we consider the potential for species interactions within the same trophic level (especially the presence of multiple host species or multiple parasite species) to alter host-parasite evolution. Finally, we review some ways the abiotic environment can alter evolution of hosts and parasites. In each case, evidence from *Daphnia*-parasite interactions demonstrates that the ecological context impacts the evolution of both the host and the parasite.

Predation alters evolution in host-parasite systems

Predators should alter evolution in host-parasite systems in multiple ways, including by altering the amount of disease in a focal host population. Predation is often thought of as reducing infection prevalence in hosts, especially in cases where predators selectively remove infected hosts (Hudson et al. 1992; Ostfeld and Holt 2004; Packer et al. 2003). However, predators can also increase disease in their host populations via a variety of mechanisms (reviewed in Duffy et al. in press), including by changing prey community composition so that high-quality hosts dominate (Borer et al. 2009), inducing behavioral changes in the prey that increase the risk of infection (Orlofske et al. 2014), or by spreading transmission stages while feeding (Cáceres et al. 2009).

Predators can also alter evolution in host-parasite systems by introducing trade-offs that alter the selective landscape. As one example, hosts may face trade-offs between anti-predator defenses and mounting an effective immune response (Navarro et al. 2004; Rigby and Jokela 2000; Stoks et al. 2006). Predators can also influence parasite evolution via impacts on trade-offs, most notably those related to virulence. Virulence is generally defined as the reduction in host fitness caused by infection, usually due to changes in fecundity or lifespan (Day 2002). Overall, much theory related to the evolution of parasite virulence has focused on the influence of parasites on the host's instantaneous mortality rate (Anderson and May 1982; Day 2002). Under this framework, parasite fitness increases with transmission rate and also with the length of time that a host is infectious; it is generally assumed that higher replication rates of parasites increase transmission but reduce the length of time a host is infectious (e.g., by killing it or triggering an immune response), driving an intermediate optimal virulence (de Roode et al. 2008; Lenski and May 1994). Because of the nature of this trade-off, increases in mortality rates from sources other than infection (including predators) are expected to increase parasite virulence,

since the cost the parasite pays for killing the host quickly is reduced (Lenski and May 1994), though other outcomes are also possible depending on the specifics of the interaction (Choo et al. 2003; Day 2002; Houwenhuyse et al. 2018).

The impacts of predation on host evolution have been the focus of several studies in the *Daphnia dentifera-Metschnikowia bicuspidata* system. In this system, predators influence the overall amount of disease from the common fungal parasite *Metschnikowia*: fish preferentially feed on infected *Daphnia*, strongly reducing infection prevalence (Duffy and Hall 2008; Duffy et al. 2005), whereas invertebrate predators are "predator spreaders" that increase infection prevalence (Cáceres et al. 2009). There are also important trade-offs between predation risk, resistance to disease, and fecundity. Larger bodied *Daphnia* are more susceptible to fish predation (Brooks and Dodson 1965) and to *Metschnikowia* (Hall et al. 2010), but less susceptible to predation by the common, voracious, gape-limited invertebrate predator *Chaoborus* (Pastorok 1981). In addition, there is also a trade-off between resistance to *Metschnikowia* and fecundity, with larger animals being more fecund but less resistant (Hall et al. 2010), though some populations contain animals with high fecundity and high resistance (Auld et al. 2013). These trade-offs—combined with variation among lakes in vertebrate and invertebrate predation rates, resource levels, and host genetic variation—likely explain different evolutionary responses of populations to disease outbreaks, with some populations evolving increased resistance to disease, some evolving increased susceptibility, and some experiencing disruptive selection on resistance (Duffy et al. 2008; Duffy et al. 2012; Duffy and Sivars-Becker 2007).

Work in the *Daphnia dentifera-Metschnikowia bicuspidata* system has focused on evolution of the host but not the parasite because the parasite shows surprisingly little variation

and limited evolutionary potential (Auld et al. 2014; Duffy and Sivars-Becker 2007; Searle et al. 2015). However, predators seem likely to drive evolution in other *Daphnia* parasites, including the common bacterial parasite *Pasteuria*. In an artificial selection experiment using *Daphnia dentifera* hosts and *Pasteuria,* parasites that were selected in an environment that simulated high predation evolved to produce more spores in that environment; however, that came at the cost of reduced performance in low predation environments (Figure 1; Auld et al. 2014). These results suggest that *Pasteuria* collected from lakes with high predation might be more virulent than those from low predation lakes.

Overall, studies on *Daphnia* and their microparasites demonstrate that predators can strongly alter parasite-mediated selection on host populations, trade-offs faced by hosts and by parasites, and selection on parasite traits.

Multihost, multiparasite interactions: influences of competition on evolution in host-parasite systems

Most parasites can infect multiple hosts, and most hosts are infected by multiple parasites (Fenton and Pedersen 2005; Lively et al. 2014). While this is the rule rather than the exception in nature, the majority of research on host-parasite evolution is based around a one-host one-parasite model (Read and Taylor 2001; Rigaud et al. 2010). However, there is an expanding field of research uncovering the complex ways in which interspecific competition can change disease dynamics and evolutionary outcomes.

Multiple Hosts

High biodiversity in hosts can dilute (Johnson et al. 2013; Keesing et al. 2010; Keesing, Holt,

183 and Ostfeld 2006; LoGiudice et al. 2003; Ostfeld and Keesing 2012) or amplify (Randolph and
184 Dobson 2012; Searle et al. 2016; Strauss et al. 2015; Wood et al. 2014) the prevalence of disease.
185 The dilution effect arises when species rich communities contain lower quality (that is, less
186 competent) hosts that slow the spread of the parasite and therefore protect competent focal hosts
187 from infection. While many studies have documented the dilution effect in wild systems
188 (Civitello et al. 2015), there is still vigorous debate about how common dilution is (Randolph
189 and Dobson 2012; Salkeld et al. 2013; Wood et al. 2014).

190 One major shortcoming of dilution effect theory is that it generally ignores competition
191 between diluter and focal hosts, despite coexistence theory showing interspecific host
192 competition has a strong impact on host-parasite dynamics (Bowers and Turner 1997; Greenman
193 and Hudson 2000; Gyllenberg et al. 2012; Saenz and Hethcote 2006). Altering the number of
194 host species changes not only the amount of disease in the system, but also the amount of
195 interspecific competition a focal host experiences, with potentially complex effects on focal host
196 density and disease prevalence (Cáceres et al. 2014a). If adding a host species increases total
197 host density, it could potentially drive an increase in disease in a focal host (amplification), even
198 if the additional host is less competent than the focal host (Searle et al. 2016).

199 Thus, when considering how multiple hosts might alter evolution in host-parasite
200 systems, it is important to recognize that selection will occur both via changes in the amount of
201 disease and via changes in host density, mediated by interspecific competition. A recent study
202 tested the joint influence of infectious disease and competition on eco-evolutionary dynamics in
203 the *Daphnia-Metschnikowia* system (Strauss et al. 2017). The additional host species,
204 *Ceriodaphnia,* is more resistant to *Metschnikowia* than the focal host, *Daphnia dentifera*, but
205 also a competitor for resources. The expectation was that the combination of a virulent parasite

and strong interspecific competition from *Ceriodaphnia* might drive populations of *Daphnia dentifera* to extinction (Strauss et al. 2017). Indeed, in populations where *Daphnia dentifera* had little genetic diversity (and thus low evolutionary potential), the combination of parasitism and interspecific competition resulted in very low densities of the focal host. However, in populations where *Daphnia dentifera* had high diversity (and thus high evolutionary potential), the populations thrived. Surprisingly, this rescue effect arose because hosts evolved increased competitive ability, but not increased resistance. Evolution rescued the focal host from the negative impacts of competition, but also drove larger disease outbreaks (as compared to populations with low evolutionary potential). This demonstrates that introducing a diluter host to curb an epidemic may have unexpected results if we ignore the potential for competition—and rapid evolution—between focal and diluter hosts.

At present, we know that interactions between host species can change transmission dynamics and drive evolution in unexpected ways, but the eco-evolutionary effects of parasitism and competition on a focal host remain difficult to predict. However, by integrating a mechanistic understanding of the types of host-host and host-parasite interactions that occur (Luis et al. 2018; Searle et al. 2016; Strauss et al. 2015), we can better understand how multihost systems can impact host fitness, change parasite transmission dynamics, and ultimately drive rapid evolution in hosts and parasites.

Multiple Parasites

When multiple parasites coexist within a host population, they have the potential to influence each other directly (via competition or facilitation within coinfected hosts) or indirectly (e.g., via altering host lifespan or population density). As a result, the addition of a new parasite has the

potential to alter selection on existing parasites in the system. Coinfections between helminths (including nematodes) and microparasites have been a particular focus of study, in part as a result of influences of helminths on host immune systems (Ezenwa 2016). Work on African buffalo, nematodes, and bovine tuberculosis has demonstrated how coinfecting parasites can influence one another, and also the importance of tests in real world situations. Nematodes suppress the response of the Th1 arm of the immune system in buffalo hosts; Th1 cells protect against microparasites, so the nematode-induced suppression of this part of the immune system should facilitate the invasion of tuberculosis in buffalo (Ezenwa et al. 2010). Those results suggest that removing helminths should decrease microparasite fitness. However, treating African buffalo with anthelminthics actually promoted the spread of bovine tuberculosis: anthelminthic treatment did not influence the likelihood of infection with tuberculosis, but did increase survival after infection, increasing transmission opportunities (Ezenwa and Jolles 2015). Such contrasting impacts of coinfection at the within-host scale vs. the host population scale is not unique to macroparasite-microparasite coinfections. As discussed more below, recent work motivated by the *Daphnia*-microparasite system found that priority effects (where the order of infection determines the impacts parasite species have on each other's fitness) can drive scenarios where parasite competition within a host can actually promote coexistence at the population scale (Clay et al. 2019b).

Host Mortality

One way in which multi-parasite infections may alter the evolution of one or more of the coexisting parasites is by changing the lifespan of the host. As discussed in the predation section, shortening the lifespan of a host generally selects for the evolution of higher virulence,

252 as the optimal virulence of a parasite is thought to reflect a trade-off between transmission rate
253 and host mortality (Bull and Lauring 2014). If a single host individual is coinfected—that is,
254 simultaneously infected by two or more parasite strains or species—that has the potential to alter
255 evolutionary outcomes. In particular, if a coinfecting parasite is virulent (increasing mortality
256 rate on the host), that should select for higher virulence in the other parasite (May and Nowak
257 1995).

258 However, both in theory and in practice, coinfections often yield results that are more
259 complicated than might initially be predicted (as reviewed in Alizon et al. 2013). For example, in
260 a rodent malaria system, immunopathology leads to additional costs associated with parasite
261 virulence, with the potential to drive negative virulence-transmission relationships (Long and
262 Graham 2011). As a result, competition between genotypes coinfecting a single host individual
263 can have major impacts on parasite evolution, increasing or decreasing virulence (Long and
264 Graham 2011; Mideo 2009).

265 Work in the *Daphnia*-parasite system has also demonstrated that interactions between
266 competing parasites can sometimes drive initially counterintuitive results. In an experiment using
267 *Daphnia magna* and the gut microsporidian *Glugoides intestinalis*, treatments with *low* host
268 mortality rates resulted in the evolution of *higher* virulence (Ebert and Mangin 1997). This
269 pattern arose due to competition between coinfecting strains of the parasite; lower host mortality
270 rates increased the amount of time parasites spent competing amongst themselves within hosts,
271 driving the evolution of faster parasite growth and therefore higher virulence (Gandon et al.
272 2001). This underscores the need to understand the mechanisms of within-host interactions in
273 order to predict parasite evolution.
274

Order of Infection

While much theory on the evolution of virulence focuses on the impacts of changes in host mortality rate, other factors can also influence virulence evolution. Increasingly, scientists are recognizing that the order in which parasites arrive in a host can influence both host and parasite fitness and that those impacts can vary between genotypes (Al-Naimi et al. 2005; de Roode et al. 2005; Marchetto and Power 2018; Pollitt et al. 2015).

In the *Daphnia-Pasteuria* system, a study found that virulence was influenced not only by infections consisting of multiple strains of a parasite, but also by the order of infection (Ben-Ami et al. 2008). In simultaneous coinfections or sequential infections where a more virulent parasite strain arrived first, virulence (host mortality rate) and parasite fitness (spore production) matched that of the more virulent strain. However, when the less virulent parasite infected first, virulence resembled an average between single infections of the two strains. Additionally, both parasites suffered lower fitness, likely due to interactions akin to scramble competition. Surprisingly, these mixed-strain infections also led to higher host fecundity than did single infections (*Pasteuria* has dramatic effects on fecundity; Ebert 2005), suggesting coinfections may be less harmful to hosts than single infections in the short term. Overall, the authors concluded that high rates of coinfection would select for virulent parasites, which outcompete less-virulent strains (Ben-Ami et al. 2008).

Studies of *Daphnia* infected with multiple parasite species (rather than multiple strains of the same species) also have found that the order of infection is important to host and parasite fitness. A study of *Daphnia galeata,* the fungus *Metschnikowia*, and the ichthyosporean *Caullerya mesnili* found that simultaneous coinfections were significantly more virulent (in terms of host lifespan and fecundity) than were single infections or sequential coinfections (Lohr

et al. 2010). They found that *Caullerya* had higher fitness when it arrived first in sequential coinfections, whereas *Metschnikowia* had higher fitness if it arrived second. A new study on *Daphnia dentifera*, *Pasteuria*, and *Metschnikowia* also found *Metschnikowia* benefitted from second arrival (Clay et al. 2019b). However, in this case, *Pasteuria* fitness was highest in single infections and low in coinfections, regardless of whether it arrived first or second, likely due to the shortened host lifespan of coinfected hosts. Overall, priority effects can influence parasite prevalence and coexistence, changing pathogen community structure (Clay et al. 2019a; Clay et al. 2019b), which underscores the importance of linking within- and between-host processes to understand host-multiparasite dynamics.

In the case of the interactions between *Pasteuria* and *Metschnikowia*, it is interesting to note that the dominant driver of low fitness for *Pasteuria* in coinfections seems to be shortened host lifespans driven by *Metschnikowia* (Clay et al. 2019b). *Pasteuria* is a parasitic castrator, with a relatively slow life history compared to *Metschnikowia* (Auld et al. 2014). However, as discussed above in the predation section, experimental evolution studies have demonstrated that *Pasteuria* can evolve to increase its fitness in high mortality environments (Auld et al. 2014). In the future, it would be interesting to use experimental evolution to explore the potential of *Pasteuria* to evolve to better compete with *Metschnikowia* and other coinfecting parasites.

The influence of the abiotic environment on evolution in host-parasite systems

Humans are dramatically altering the abiotic environment in which host-parasite interactions take place. Perhaps most obviously, climate change is altering mean environmental temperature, as well as the duration and variation of temperature extremes (Field et al. 2012), which can strongly influence the outcome of host-parasite interactions (Lafferty 2009). However, climate

change also alters precipitation regimes, with consequences for water clarity in aquatic systems (Williamson et al. 2015). Human activities also drastically alter nutrient levels in natural ecosystems (which drives changes in primary producer communities) and add pesticides and other novel chemicals to environments (Carpenter 2008; Stokstad and Grullón 2013). Our understanding of evolution in action developed from the *Daphnia*-parasite system makes it clear that these anthropogenic alterations to the abiotic environment should influence evolutionary dynamics of hosts and parasites (Figure 2).

Temperature

Climate change is altering mean temperatures as well as variability in temperature in ecosystems worldwide (Coumou and Rahmstorf 2012; Field et al. 2012). Temperature can influence the likelihood of a host encountering and/or being infected by a pathogen (e.g., Elderd and Reilly 2014; Hall et al. 2006), parasite development rates and transmission stage production (e.g., Poulin 2006), host thermal stress (with impacts on things such as immune function; Dittmar et al. 2014), and the fitness impacts of infection on hosts (e.g., Vale et al. 2008). Thus, temperature should strongly influence evolution in host-parasite systems.

Research on the *Daphnia*-parasite system has helped us understand how altered temperatures might influence the amount of disease and how hosts evolve in response to disease outbreaks. Recent research on the *Daphnia-Metschnikowia* system suggests that a warmer world will be a sicker world (Shocket et al. 2018). A mesocosm experiment showed that warmer temperatures resulted in larger epidemics, primarily because of temperature dependence in transmission rates. Temperature-dependent transmission arose because the host encounters

343 fungal spores while foraging, and foraging rate (and, therefore, parasite exposure rate) increased
344 with temperature.

345 An experimental study of the *Daphnia-Pasteuria* system shows that these alterations in
346 disease levels can alter evolutionary outcomes (Auld and Brand 2017b). The timing and
347 magnitude of disease outbreaks depended on mean temperature and temperature variability, as
348 did parasite-driven evolution of the host populations. An increase of 3°C drove much larger
349 disease outbreaks that were associated with strong parasite-driven selection and associated
350 reductions in host diversity. Interestingly, this study also looked at a second aspect of
351 environmental variation—the impact of spatial structure on host-parasite populations. The study
352 used physical mixing to homogenize populations, while no mixing allowed populations to form
353 and retain spatial structure. As with temperature, the size of the epidemic and the tempo and
354 mode of evolution were influenced by the mixing treatment. Furthermore, a follow up study
355 found that mixing influenced patterns of adaptation and (co)evolution in the host and parasite
356 (Auld and Brand 2017a). This has interesting potential links with climate change as well, as
357 increasing severity of storms might change mixing regimes in aquatic habitats.

358

359 *Water clarity*

360 An underappreciated component of climate change is that increases in heavy precipitation bring
361 more dissolved organic matter into aquatic systems, making surface waters darker and increasing
362 turbidity and cloudiness in the water column (Williamson et al. 2017; Williamson et al. 2015).
363 This means that climate change is leading to reduced light penetration in surface waters. This can
364 reduce prey visibility, which will change the rate of predation and its impact on host-parasite
365 dynamics. Notably, one study found that selective predation on infected *Daphnia* was eliminated

366 in high dissolved organic matter conditions (Johnson et al. 2006), so the ability of fish predators
367 to reduce disease in *Daphnia* hosts might be eliminated in darker waters.
368 Darker surface waters may also reduce the likelihood that waterborne parasites will be
369 killed by sunlight. For example, *Metschnikowia* is highly sensitive to light, and darker lakes
370 generally have smaller disease outbreaks (Overholt et al. 2012). Thus, changes in lake light
371 environments should alter the size of disease outbreaks and the parasite-mediated selection
372 associated with them. Moveover, it might drive selection on the parasite, if parasite genotypes
373 vary in their sensitivity to light. An exciting potential avenue for future research would be to take
374 advantage of spore banks (Decaestecker et al. 2007; Decaestecker et al. 2004) to look for
375 evolutionary change over time in the parasite's ability to tolerate light associated with changes in
376 light penetration.
377
378 *Nutrient levels and primary production*
379 Humans strongly alter nutrient levels, greatly increasing the amount of bioavailable nitrogen and
380 phosphorus in the environment. This increases primary productivity, which can increase the
381 amount of disease a focal host experiences, especially due to increases in host density (Johnson
382 et al. 2007).
383 Work on several different *Daphnia*-parasite systems has explored links between nutrient
384 levels, disease, and host fitness or evolution. In the *Daphnia*-*Metschnikowia* system, more
385 productive lakes had larger disease outbreaks during which hosts evolved greater resistance to
386 infection, whereas lakes with lower productivity had smaller disease outbreaks during which
387 hosts evolved greater susceptibility to infection (Duffy et al. 2012). In the *Daphnia*-White Fat
388 Cell Disease system, nutrient enrichment increased infection prevalence and intensity

389 (Decaestecker et al. 2015) but also led to less efficient nutrient assimilation in *Daphnia*, resulting
390 in lower disease tolerance (Reyserhove et al. 2017). A study on a natural lake population of
391 *Daphnia longispina* found that the seasonal influx of environmental nutrients increased algal
392 food quality, driving higher prevalence of two gut endoparasites; however, this also drove a
393 decrease in the prevalence of an epibiont and overall parasite species richness (Aalto et al. 2014).
394 These contradictory effects are likely due to species-specific stoichiometric demands of parasites
395 and hosts (Aalto et al. 2014). Finally, a laboratory study using the *Daphnia-Pasteuria* system
396 demonstrated that the nutrient content (C:P ratio) of the food a host consumes influences parasite
397 virulence (Frost et al. 2008).
398 Increased nutrient levels can also strongly influence the community of primary
399 producers; in lakes, high nutrient levels are typically associated with dominance by
400 cyanobacteria. Work on *Daphnia* and their parasites suggests that cyanobacteria alter host
401 susceptibility, though the specific effects vary across parasites (Coopman et al. 2014; Sanchez et
402 al. in press; Tellenbach et al. 2016). An interesting avenue for future research will be
403 understanding how human-driven changes in phytoplankton communities alter parasite-driven
404 evolution of *Daphnia* populations.
405
406 *Pesticides*
407 Pesticides are widely used human-made chemicals, trailing only fertilizers in terms of the extent
408 and amount of use (Stokstad and Grullón 2013). Work on other systems shows that pesticide use
409 can strongly influence host-parasite interactions. Sub-lethal pesticide exposure has been shown
410 to increase susceptibility of the European honeybee *Apis mellifera* to a gut pathogen, the fungus
411 *Nosema spp*. (Pettis et al. 2013; Wu et al. 2012), increase the within-host density of the fungus

412 (Pettis et al. 2012), and even increase the mortality rate of bees already infected with the
413 pathogen (Vidau et al. 2011).

414 Research on *Daphnia* also shows that pesticides can alter the virulence of their parasites.
415 The virulence of *Pasteuria* on *Daphnia magna* increased with increasing concentrations of the
416 pesticide carbaryl, including higher levels of early mortality and earlier castration of infected
417 hosts (Coors et al. 2008), even with just short term exposure (Coors and De Meester 2011).
418 Notably, increased virulence was also seen with a second parasite, the microsporidian
419 *Flabelliforma magnivora* (Coors et al. 2008). Thus, the presence of pesticides in lakes and ponds
420 could alter the virulence of parasites, which should alter the nature of the transmission-mortality
421 trade-off (and, thus, the evolution of virulence), as well as alter selection on *Daphnia*
422 populations. In future research, it would also be interesting to focus on the impact of other
423 anthropogenic pollutants, including road salts (Cañedo-Argüelles et al. 2019), on *Daphnia*-
424 parasite interactions.

425

426 **Conclusions**

427 In the 70 years since Haldane (1949) suggested that parasites might be especially important
428 drivers of evolution, it has become abundantly clear that parasitism is, indeed, a major selective
429 force. Haldane contrasted the impacts of parasites with those of other "natural forces, hunger,
430 and predators, or with members of the same species". However, we now know that populations
431 are not influenced by parasites *or* by other food web members—rather, they all interact. Thus,
432 when studying evolution in host-parasite interactions, we need to consider that the amount of
433 disease and the nature and tempo of evolution will be modulated by the biotic and abiotic context
434 in which the host-parasite interaction is embedded.

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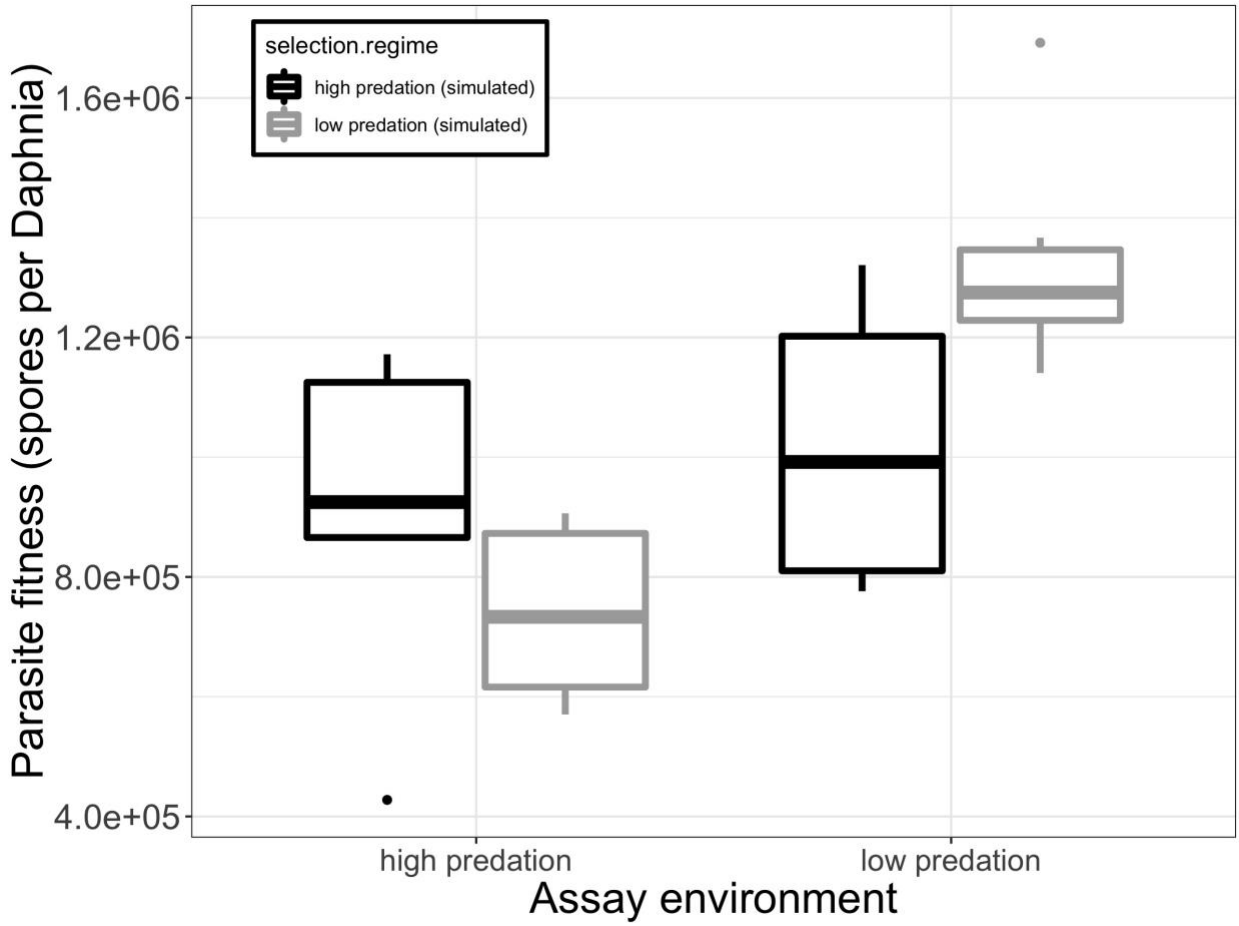

Figure 1. The bacterial parasite *Pasteuria ramosa* evolved higher fitness in high predation environments, but this came at the cost of lower fitness is low predation environments. *Pasteuria* was selected in environments that simulated high predation (shorter host life span; shown with black bars) or environments that simulated low predation (longer host life span; shown with gray bars). Parasite fitness was then assayed in two environments, one simulating high predation (shorter host lifespan) and one simulating low predation (longer host life span). High predation selection lines produced significantly more spores in high predation assay environments than did low predation selection lines when assayed in high predation environments (compare the gray

779 and black bars on the left; planned contrast: z = -3.07, p = 0.0021). When assayed in low
780 predation environments, however, low predation selection lines produced more spores (compare
781 the gray and black bars on the right; planned contrast: z = 2.70, p = 0.0070). Data are replotted
782 from Auld et al. (2014).
783

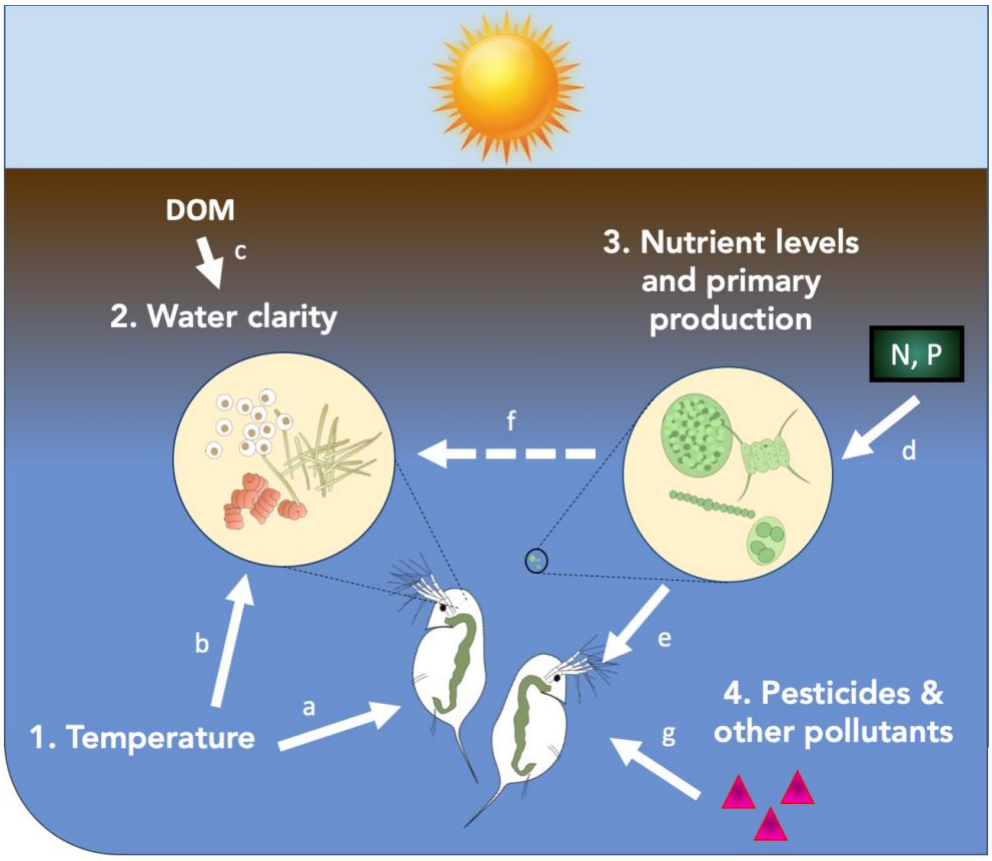

Figure 2. Humans are dramatically altering the abiotic environment, with consequences for evolution of hosts and parasites. 1) Human activities are increasing average temperatures as well as the duration of temperature extremes; (a) this has direct effects on *Daphnia* (by impacting their feeding rate), and (b) parasites (by impacting their development rates). 2) Human activities are also altering precipitation regimes, which increases the amount of dissolved organic matter (DOM) arriving in lakes, making water darker and (c) potentially reducing degradation of parasites by sunlight. 3) Humans are also altering nutrient levels and therefore (d) primary production, which (e) changes *Daphnia* feeding rates (and therefore growth and infection rates). (f) The prevalence of primary producers indirectly affects parasites through changes to host feeding rates, plus the nutritional and medicinal quality of different phytoplankton mediate host

796 resistance and tolerance. Finally, 4) agricultural practices and other human activities are adding
797 pesticides and other novel chemicals to the environment, which (g) can impact the wellbeing of
798 hosts by reducing their tolerance to pathogens. All of those changes should have impacts on host-
799 parasite interactions, as discussed in the main text.
800