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HORIZONS

Disease in freshwater zooplankton: what have we learned and where are we going?

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In the last few decades, zooplankton (especially *Daphnia*) have emerged as a model system for examining the ecological and evolutionary roles of parasites in populations, communities and ecosystems. We build on this foundation, moving towards continued integration of epidemiology and community ecology to understand the distribution and abundance of infectious diseases. Future studies should link processes that occur over multiple time scales: from deep-time phylogenetic patterns that have shaped and been shaped by host–parasite interactions, to the dynamics that play out over decades or within seasons, to the physiological time scales over which parasites operate to infect and kill their hosts. We also consider how the combination of processes across multiple time scales has shaped the biogeography and changing mosaic of host–parasite interactions in time and space. Finally, we consider a future where zooplankton–parasite interactions are influenced by global change. The *Daphnia*–parasite model system offers a powerful tool to link anthropogenic changes to infectious diseases, including zoonotic diseases of significance to human health.

KEYWORDS: *Daphnia*; host; parasite

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INTRODUCTION

Parasites and pathogens can severely depress their host populations, and their ecological impact seems destined to grow as global climate change, species invasions and anthropogenic disturbance intensify (Daszak *et al.*, 2000; Brearley *et al.*, 2012). Freshwater zooplankton (especially *Daphnia*) have increasingly been used to demonstrate connections between ecology, evolution and the distribution and abundance of infectious diseases. Our intent here is not to recreate some excellent recent reviews on these topics (Ebert, 2005, 2008; Lampert, 2011; Miner *et al.*, 2012). Rather we seek to highlight how broad insights gleaned from *Daphnia*–parasite interactions have advanced our understanding of the ecology and evolution of host–parasite interactions. We also point to the frontiers of research using zooplankton systems. We see great opportunities to use plankton to create highly integrative insight into disease. This insight has the potential to move across scales of biology, from within-host physiological and immunological interactions to population and food web dynamics to ecosystem processes (Fig. 1). Work with plankton disease can also facilitate integration of physiological, ecological and evolutionary mechanisms operating across time scales.

WHAT MAKES A MICROBE A PATHOGEN FOR SOME BUT NOT ALL SPECIES OF ZOOPLANKTON?

The evolution of pathogen specificity in infection is a major unanswered question in the infectious disease literature. The dozen or so commonly documented parasites of freshwater zooplankton show a wide spectrum of specificity, ranging from those that infect only certain genotypes of certain species to those infecting a wide range of genotypes and species (Stirnadel and Ebert, 1997; Bittner *et al.*, 2002; Ebert, 2005; Wolinska *et al.*, 2006; Altermatt and Ebert, 2007; Ben-Ami *et al.*, 2008; Duffy *et al.*, 2010; Lampert, 2011). What are the mechanisms underlying this variability? The answer to this question surely depends on traits of both parasite and host. *Daphnia*, like all invertebrates, have an immune system (Mucklow and Ebert,

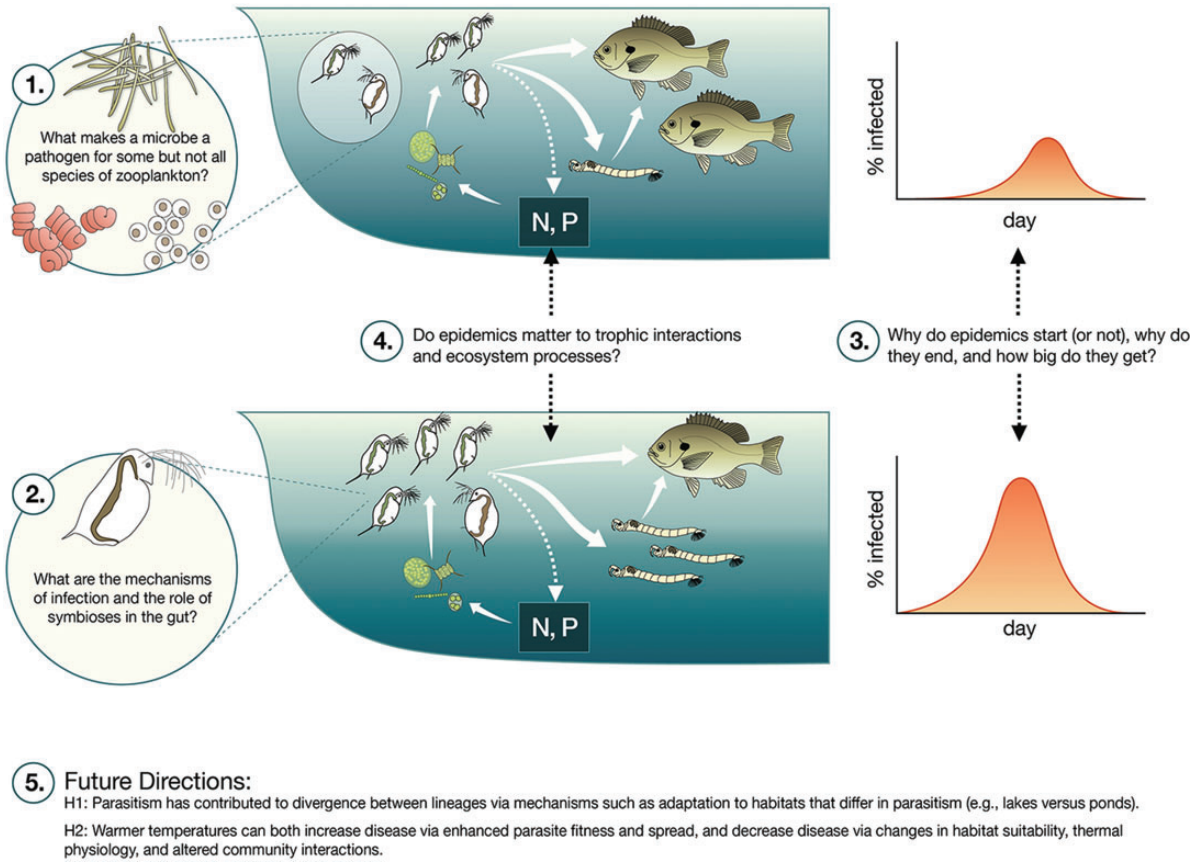

Fig. 1. A conceptual diagram of several of the major concepts described in the text. Numbers correspond to the five major sections of the paper. We list only two hypotheses as examples. The figure depicts two thermally stratified lakes that differ in key habitat features (e.g. strength of stratification) and the relative abundance of key food web players (diluters and predators) that are known to influence the timing and magnitude of epidemics (see also Hall *et al.*, 2010). Figure drawn by John Megahan.

2003; McTaggart *et al.*, 2009; Decaestecker *et al.*, 2011), which in some cases appears ineffective (Auld *et al.*, 2010). What determines whether a particular microbe can evade the immune system of a particular host? Little is known about the links between mechanisms of pathogenicity and host specialization. However, answers to this question are likely to help explain why, in some cases, there is clear evidence for 'local adaptation' (where parasites are most virulent on hosts from the same population; Ebert, 1994; Ebert and Hamilton, 1996; Refardt and Ebert, 2007), whereas, in others, there is no evidence for local adaptation (Duffy and Sivars-Becker, 2007; Searle *et al.* in prep.).

Future research tackling the drivers of host–parasite specificity should focus on the genetic and environmental factors involved in infection and the subsequent evolution of virulence. Flagship work on the *Daphnia magna–Pasteuria ramosa* system has provided some answers at the within-species (genotype) level (Ebert *et al.*, 2004; Mitchell *et al.*, 2005; Jensen *et al.*, 2006; Bieger and Ebert, 2009; Ben-Ami *et al.*, 2011; Hall and Ebert, 2012). Strong genetic specificity of hosts and parasites (Carius *et al.*, 2001;Luijckx *et al.*, 2012) provide an excellent model to uncover mechanisms of resistance to parasitism. However, such specificity is not universal (Duffy and Sivars-Becker, 2007; Auld *et al.*, 2012, Searle *et al.* in prep.). Hence, comparative studies on other zooplankton–parasite systems could provide more insight into within-host mechanisms that govern defense and virulence. It could be particularly interesting to use *Daphnia*–parasite systems that differ in the degree of specificity to address the genetic architecture of parasite susceptibility (see review by Wilfert and Schmid-Hempel, 2008 for how the genetic architecture of susceptibility has been addressed in other systems).

Complementary insight could be gleaned from study of the phylogenetic relationships of Daphniidae and their parasites. Divergent patterns of coevolution, revealed from a deeper time perspective of diversification, might shed light on variation in specificity. We know that evolution of life histories of daphniids depends on multiple selective factors (e.g. predation, resources, competitors) and habitat type (e.g. pond vs. lake) (reviewed in Lampert and Sommer, 2007; Lampert, 2011). Have these various selective factors influenced the evolution and distribution of parasites among daphniid species? Plankton offer great advantages to tackle this problem. Unlike in many other systems, plankton ecologists can readily exploit three key factors, cyclical parthenogenesis, tendency to hybridize and apparent pond-lake divergence into sister species, to identify and disentangle genetic and environmental mechanisms of defense within the context of recent evolutionary divergence by habitat.

However, a (temporary) problem impedes progress on this front. Although many daphniid species have broad ranges, we know little about the biogeography of parasites within different host species. Comparisons within and among clades over broad geographic domains could produce exciting results. To illustrate, consider two important species of pond *Daphnia*. Why are parasites so rare among *D. pulex* in North America yet common in *D. magna* in Europe (Ebert, 2005; Killick *et al.*, 2008; Cáceres *et al.* unpublished data)? Both species live in shallow, often ephemeral water bodies that lack vertebrate predators. Both species have close contact with the sediment and potentially the parasite spores therein (Decaestecker *et al.*, 2002). Does some physiological or ecological adaptation to pond habitat constrain disease emergence in *D. pulex* but not in *D. magna*?

Finally, recent invasions of host species, coupled with 'resurrection' approaches (where it is possible to retrieve the dormant stages from both the host and the parasite over multiple years), can be exploited to study adaptation and possible co-evolution (Decaestecker *et al.*, 2007, 2013). The invasion of *Daphnia lumholtzi* into North America (Havel *et al.*, 2000) and its subsequent infection by *Pasteuria* (M.A. Duffy, unpubl. data) is one such example. Such studies, when coupled with an examination of deep-time evolutionary diversification can help to address questions related to the mechanisms underlying pathogen specificity and virulence.

WHAT ARE THE MECHANISMS OF INFECTION AND THE ROLE OF SYMBIOSES IN THE GUT?

The gut of zooplankton hosts lies at an intersection of resistance, microbiology and physiology. Many pathogens enter the zooplankton host's body via the gut (Ebert, 2005). What defense mechanisms operate in the gut and do they tradeoff with resource acquisition? One type of defense may involve microbes, but we are just beginning to understand the *Daphnia* microbiome (Freese and Schink, 2011). The human microbiome project has indicated that our gut flora can influence disease dynamics within human hosts (Foxman and Goldberg, 2010), and symbionts of other invertebrates can confer resistance to disease (Parker *et al.*, 2013). Can the gut microbiome of *Daphnia* provide critical defense and influence variation in resistance to infection? Theory predicts that the host's symbiont community may facilitate or hinder the evolution of pathogen specialization, yet this theory remains untested for most systems (Antonovics *et al.*, 2013). Furthermore, can changes in microbial gut community influence the seasonal timing of disease outbreaks? Are some pathogens only facultatively pathogenic? If so, which conditions determines their harm or benefit?

The gut may also provide the link between disease, gut physiology and foraging ecology. For instance, gut passage time varies greatly among daphniids (ranging from 5 to >25 min) and this variation reflects differences in body size, gut volume and feeding rate among species and life stages (DeMott *et al.*, 2010). It remains unknown if gut passage time influences susceptibility to pathogens acquired while feeding. Resources can fundamentally alter both host density and key epidemiological traits such as production of infectious propagules (spores) and susceptibility and tolerance to infection (Pulkkinen and Ebert, 2004; Hall *et al.*, 2009a, b, 2010, 2012; Frost *et al.*, 2008a; Civitello *et al.*, 2013). Increased research linking *Daphnia* foraging behavior, physiology and ecology to susceptibility to various species of pathogens is needed to resolve these questions. Such integrative research provides a means of linking mechanisms governing individual host–parasite interactions to population scale dynamics and food web interactions.

WHY DO EPIDEMICS START (OR NOT), WHY DO THEY END, AND HOW BIG DO THEY GET?

There are numerous case studies documenting a repeatable pattern of seasonal increases in prevalence of infection (Lass and Ebert, 2006; Cáceres *et al.*, 2006; Johnson *et al.*, 2009). But what determines when epidemics start, when they end, and how big they get? Epidemiological theory tells us that a parasite will invade its host population and spread when the basic reproductive ratio of the parasite (R_0) exceeds 1. But this invasion success hinges on a variety of factors including climate, physical mixing processes, host behavior, interspecific interactions and levels of host resistance (which may evolve rapidly).

Water movements may trigger the onset of disease in some zooplankton disease systems (e.g. the fungus *Metschnikowia bicuspidata* in *Daphnia dentifera*; Hall *et al.*, 2010). But important questions remain unanswered. Can too much mixing inhibit epidemics by reducing the encounter of host and parasite? Will global change influence disease by altering seasonal mixing patterns? Furthermore, not all diseases seem to require mixing for epidemics to begin. For instance, epidemics of a chytrid (*Polycaryum laeve*) reached peak prevalence in *Daphnia* under the ice (Johnson *et al.*, 2006a).

Habitat selection behavior (both in space and time) is another likely candidate for determining disease transmission. Host aggregation during vertical migration can influence transmission dynamics, as exemplified in the 'Deep Trouble' hypothesis (Decaestecker *et al.*, 2002). *Daphnia* that remain near sediments to avoid visual predators in ponds may increase their encounter rate with parasite spores in sediments. Diapause, both seasonal and prolonged, provides another potentially interesting form of habitat selection by hosts (Hairston and Cáceres, 1996; Cáceres, 1997). Habitat selection theory has largely focused on predation and resource competition and has not fully considered the potential role of parasites (e.g. Leibold, 1990, 1991; Leibold and Tessier, 1991). More generally, how do parasites interact with predators and competitors to determine the spatial and temporal distribution of host and parasite genotypes and species within stratified lakes? How have parasites influenced, or been influenced by host adaptations to the benthic vs. pelagic habitat? One general goal is to understand the net effects of physical processes and host aggregation behavior (which can be influenced by mixing and stratification) in determining encounter and transmission rates.

Interspecific interactions play an important role in determining the outcome of host–parasite interactions. Predators can directly influence disease spread in freshwater zooplankton either by culling infected hosts or by spreading infected propagules while feeding (Duffy *et al.*, 2005; Johnson *et al.*, 2006b; Pulkkinen and Ebert, 2006; Cáceres *et al.*, 2009; Hall *et al.*, 2010). Moreover, both planktivorous fish and *Chaoborus* have well-known indirect effects on their *Daphnia* prey (Tollrian, 1993; Boersma *et al.*, 1998; Reissen, 1999) and these behavioral, morphological and life history changes have the potential to both increase and decrease transmission (Yin *et al.*, 2011; Duffy *et al.*, 2011; Bertram *et al.*, 2013). For a particular host–parasite system, do these direct and indirect effects of predation act in the same direction (thus enhancing the effect of a predator on disease dynamics) or act in opposite directions (making the predator effect more difficult to detect)? Competition may have equally important effects on the distribution and prevalence of disease. Multiple studies have also indicated that the presence of a parasite can reverse competitive rankings among hosts (Wolinska *et al.*, 2006; Bieger and Ebert, 2009; Refardt and Ebert, 2012). Does this interaction between competition and parasitism underlie the temporal habitat selection (seasonal succession) that is so commonly observed in freshwater zooplankton? For example, can a population's seasonal phenology be driven (at least in part) by parasite—mediated selection for the timing to enter or terminate dormancy (Duncan *et al.*, 2006)?

Basin size and shape, which structures trophic interactions, may prohibit disease from spreading in certain habitats (Hall *et al.*, 2010). However, few lakes have been surveyed for the distribution and abundance of parasites in zooplankton. Thus, we still know very little about the relative importance of various mechanisms that shape the biogeography of disease in freshwater zooplankton. Moreover, we still know little about actual dispersal rates

of either host or parasites. Ongoing theoretical developments in 'evolving metacommunity' theory, coupled with other types of network disease models, offer a promising framework in which to integrate ecological and evolutionary mechanisms to study the distribution and abundance of disease (Leibold and Norberg, 2004; Urban and Skelly, 2006; Loeuille and Leibold, 2008; Urban and De Meester, 2009).

DO EPIDEMICS MATTER TO TROPHIC INTERACTIONS AND ECOSYSTEM PROCESSES?

The role that *Daphnia* play in regulating phytoplankton diversity and abundance, nutrient cycling and energy flow is well understood (reviewed in Lampert and Sommer, 2007), but how do parasites alter these interactions? Given that most of these parasites are obligate killers, host densities often decline during epidemics (e.g. Johnson *et al.*, 2006; Hall *et al.*, 2011). Can parasite outbreaks cause or alter a trophic cascade as has been seen in experimental mesocosms (Duffy, 2007)?

If parasite epidemics can have big effects on *Daphnia* populations, can they alter nutrient cycling in lakes? (Frost *et al.*, 2008b) documented significant changes in host stoichiometry as a result of infection by *Pasteuria*. They suggested that infected *Daphnia* may release P at higher rates than their un-infected conspecifics. Could a large enough epidemic influence overall P cycling either through trophic cascades or via altered stoichiometry of host populations? The answer must also consider how infection influences the density and composition of competing grazers, as changes in community structure can influence trophic cascades and nutrient recycling.

Finally, there are a number of unexplored frontiers possible by considering additional parasites or hosts. The role of viruses in freshwater zooplankton is just beginning to be addressed. Natural populations of *Daphnia* harbor circular single-stranded DNA viruses, the prevalence of which can vary throughout the season (Hewson *et al.*, 2013). Will the questions posed above have the same answers for viruses? Will what we have learned from *Daphnia* translate to other species of freshwater zooplankton? Although most studies have focused on *Daphnia* there are also a handful of documented cases of endoparasites of other taxa (e.g. Yan and Larsson, 1988; Thomas *et al.*, 2011). What is needed are more complete natural history studies of parasite ecology and systematics. In many ways we are limited in our ecological and evolutionary studies by a lack of this information. If we are to incorporate parasitism into our understanding of plankton ecology we need more studies on other zooplankton, especially rotifers and copepods.

FUTURE DIRECTIONS

To date, much of the research involving host–parasite interactions has focused either on the ecology of infectious diseases or the evolution of virulence. Given this foundation, the time has come for studies that weave ecology and evolution together, and that integrate processes across levels of biology from physiological defense mechanisms within hosts to life history evolution and clade diversification. The *Daphnia*–parasite system is possibly the best available for studies that will link genome to phenome to understand ecological and evolutionary dynamics of disease. Rapid evolution of both host and parasite is an essential feature of the dynamics of epidemics in *Daphnia* (Duffy and Sivars-Becker, 2007, Wolinska *et al.*, 2008; Wolinska and Spaak, 2009; Duffy *et al.*, 2009; Auld *et al.*, 2012; Duffy *et al.*, 2012). The *P. ramosa*/*Daphnia magna* system is arguably the most intensively studied freshwater zooplankton–parasite system (e.g. Little and Ebert, 1999; Carius *et al.*, 2001; Duncan and Little, 2007; Luijckx *et al.*, 2012). Even here, the genetic structure of natural populations of this parasite remains unknown for most populations, limiting our understanding of the contribution of evolution to these dynamics (Mouton and Ebert, 2008; Andras and Ebert, 2013).

The work of Decaestecker *et al.* (2007, 2013) that takes advantage of the dormant stage of both host and parasite clearly shows that there is evidence of a potential longer-term dynamic. However, one limitation of relying only on what can be reconstructed from the sediments is that it is often impossible to quantify fully both how community structure and seasonal and long-term community dynamics have changed (Jankowski and Straile, 2003). As longer-term data sets accumulate, some of these questions can be resolved. Finally, studies focused on deep time that consider the phylogeographic patterns of both host and parasite are needed. How have those interactions shaped host and parasite life history, both within and among species? How have these phylogenetic differences been modified by adaptation to specific habitats such as lakes versus ponds, or temporal habitat partitioning?

Multi-time scale, joint ecological and evolutionary perspectives are necessary to address a forward looking question: will a warmer world be a sicker world? Mounting evidence indicates that disease prevalence continues to increase among many groups of plant and animal species; furthermore, this increase often ties directly and/or indirectly to global warming (Harvell *et al.*, 1999, 2002; Lafferty *et al.*, 2004; Ward and Lafferty, 2004). Warmer temperatures can both directly enhance parasite fitness and spread by accelerating the thermal physiology of parasites and may also enhance population density, habitat suitability and activity rate (Martens *et al.*, 1999; Harvell

et al., 2002). However, climate change and associated global warming could decrease disease prevalence in some hosts or locations (Hall *et al.*, 2006; Lafferty, 2009; Randolph, 2009). Such outcomes may arise for at least three reasons: changes to habitat suitability (e.g. changes in lake thermal regimes), thermal physiology (host–parasite mis-matches) and changes to the community interactions that influence disease spread. We can start with comparative studies that address these questions in habitats ranging from the tropics to the subtropics to the arctic. What are the latitudinal or other biogeographic patterns of parasitism in freshwater zooplankton?

Zooplankton have long served as model organisms for fundamental research in ecology and evolution. The extensive knowledge of their biology, from genetics to life history and from population to ecosystem dynamics, makes them uniquely valuable in the development and testing of general theory of disease. We suggest that future progress will be made more quickly if emphasis is placed on the integration of processes that govern physiological, ecological and evolutionary aspects of disease.

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