Symposium

Interesting Open Questions in Disease Ecology and Evolution*

Curtis M. Lively,1,† Jacobus C. de Roode,2 Meghan A. Duffy,3 Andrea L. Graham,4 and Britt Koskella5

1. Department of Biology, Indiana University, Bloomington, Indiana 47405; 2. Department of Biology, Emory University, Atlanta, Georgia 30322; 3. Department of Ecology and Evolutionary Biology, University of Michigan, Ann Arbor, Michigan 48109; 4. Department of Ecology and Evolutionary Biology, Princeton University, Princeton, New Jersey 18544; 5. Biosciences, University of Exeter, Penryn Campus, Tremough, Cornwall TR10 9EZ, United Kingdom

Introduction

Studies on the ecology and evolution of infectious diseases have expanded at an increasing rate over the last several decades (fig. 1). This interest seems to have originally stemmed from models suggesting that host-parasite interactions might explain previously anomalous features of the natural world, such as sexual reproduction (Hamilton 1980), female mate choice (Hamilton and Zuk 1982), the maintenance of genetic diversity (Haldane 1949), and the regulation of host populations (Anderson and May 1979; May and Anderson 1979). The interest was further increased by early theory on the evolution of parasite virulence (May and Anderson 1983) as well as by concerns regarding the emergence of infectious diseases. Here we present a short list of interesting open questions for future research. The questions are based on an American Society of Naturalists Symposium in 2013 entitled, "Disease Ecology, Evolution, and Coevolution." Our list is not meant to be exhaustive, as many important questions remain, but we hope that it will encourage additional work in these areas.

Question 1: What Is the Effect of Host Genetic Diversity on the Spread of Infectious Disease?

This is not a new question (see Read et al. 1995), but it remains an open one. Some theoretical work suggests that host genetic diversity by itself should not affect disease spread (Springbett et al. 2003; Yates et al. 2006; Nath et al. 2008), but it could reduce the severity of epidemics if they occur (Springbett et al. 2003). Another model suggests, in contrast, that $R_0$ should be inversely proportional to the genetic variation for resistance in the host population (Lively 2010). The difference in results comes from different assumptions regarding the nature of the variation in the host and parasite populations. It would seem, at present, that genetic variation in susceptibility (where all hosts are susceptible to some degree) does not have a large effect on $R_0$ (Springbett et al. 2003; Yates et al. 2006; Nath et al. 2008), while genetic variation among hosts for their self/nonself recognition systems could reduce $R_0$, provided different parasite strains infect different host genotypes (Lively 2010).

Hence, whether or not host genetic diversity reduces the risk of infection will depend heavily on the answer to a related question: what is the genetic basis for disease resistance? Highly polymorphic genetic systems that require some kind of phenotypic match (or molecular mimicry) by the parasite for successful infection would be the most likely to reduce $R_0$. Much remains to be discovered, but recent data suggest that such polymorphic systems do exist, even for organisms that do not have the sophisticated immune responses of vertebrate animals (e.g., Tian et al. 2002; Mitta et al. 2012; Thrall et al. 2012; Drayman et al. 2013; Barribeau et al. 2014). Detailed information from a broader array of organisms would be highly valued.

There is also a need for more field and laboratory studies that experimentally examine the notion that genetic diversity can reduce disease prevalence and $R_0$. The idea has support from agricultural systems (Zhu et al. 2000; Mundt 2001), but experiments involving natural populations are rare (reviewed in King and Lively 2012). Some exceptional work in support of the idea has been published on the diseases of *Daphnia* (Altermatt and Ebert 2008; Ganz and Ebert 2010) and bees (Schmid-Hempel 1998), but more experimental studies on a greater variety of natural systems is needed.
Figure 1: Number of publications per year, as revealed by a PubMed advanced search with the term “disease” and with either the term “ecolog*” or “evolution*,” where the asterisks indicate the inclusion of any alternate endings to the words.

Question 2: How Is Host/Parasite Genetic Diversity Maintained?

This is one of the longest-standing questions in the ecology and evolution of infectious disease, but much still remains to be discovered regarding the generality and the relative importance of various evolutionary mechanisms. Perhaps Haldane (1949) was correct to think that the advantage of possessing rare resistance genotypes leads naturally to the maintenance of genetic diversity, but the evidence from natural populations is restricted to just a few study systems (e.g., Antonovics and Ellstrand 1984; Koskella and Lively 2009; Wolinska and Spaak 2009; Thrall et al. 2012). Moreover, if parasite-mediated selection can favor rare host genotypes, can it also favor cross-fertilization over self-fertilization and parthenogenesis, as originally suggested by Hamilton (1980), Levin (1975), and Jaenike (1978), and as studied by Vergara et al. (2014) in this symposium issue?

Recent work in ecoimmunology has proposed an additional (but not mutually exclusive) explanation for the maintenance of genetic diversity in hosts. These relate specifically to trade-offs in host immunity (Sheldon and Verhulst 1996; Demas and Nelson 2012). For example, given experimental evidence that resistance against parasites can deplete the host’s energetic reserves (e.g., Martin et al. 2007) and cause collateral damage to the host’s own tissues (e.g., Clatworthy et al. 2007), costs of immunity have the potential to reduce survival or fecundity of resistant hosts in nature. When the risk of exposure is low, costs of imm-

Question 3: What Are the Effects of External Biotic and Abiotic Factors on Virulence and the Risk of Infection?

Most of our current understanding of host-parasite dynamics stems from variations on classical susceptible-infected (SI) models (Kermack and McKendrick 1927; Anderson and May 1982, 1991; Hudson et al. 2002). These models generally view the host-parasite interaction as a two-way interaction and assume that virulence, parasite transmission, and host resistance/tolerance are fully controlled by host and parasite (reviewed in Restif and Koella 2003). However, environmental variables, both abiotic and biotic, can dramatically alter these traits. For example, variables such as temperature and diet have been shown to strongly alter parasite growth, transmission, and virulence (Agniewski and Koella 1999; Brown et al. 2000; Thomas and Blanford 2003; Mitchell et al. 2005; Wolinska and King 2009; Lefèvre et al. 2013; Howick and Lazzaro 2014). In addition, virulence, as measured under laboratory or greenhouse conditions, may vastly underestimate the fit-
ness effects of infection in the wild, especially when virulence increases with increasing host density (i.e., when virulence is density dependent; Lively 2006; Donnelly et al. 2012). At present there are only a few studies that experimentally examine this possibility under natural conditions (e.g., Lively et al. 1995; Bell et al. 2006). Finally, as discussed below, hosts and parasites are members of larger communities of interacting species, which creates additional challenges for measuring parasite fitness and virulence in the wild. Meeting these challenges, however, seems essential to fully understand the evolution of host-parasite interactions.

Community effects on host-parasite dynamics can occur through both density- and trait-mediated effects. Many studies to date have shown that a third species can have density-mediated indirect effects by changing the absolute or relative abundance of host species and thereby altering disease prevalence and severity (Mitchell et al. 2002; LoGiudice et al. 2003; Keeling et al. 2006; Johnson et al. 2008, 2013; Borer et al. 2009). Trait-mediated indirect effects are also becoming increasingly apparent (Raffel et al. 2008; 2010). For example, studies have shown that predatory midges can enhance parasite transmission by tearing apart parasite-filled water fleas (Cáceres et al. 2009; Auld et al. 2014), that predators can suppress the immunity of a herbivorous beetle to its parasites (Ramirez and Snyder 2009), and that aphids can increase the virulence of monarch butterfly parasites by reducing the defensive chemistry of shared food plants (de Roode et al. 2011). Trait-mediated indirect effects are especially pervasive in tritrophic interactions between plants, herbivorous animals and their parasites, where virulence, transmission, and host defenses are regularly altered by plant defensive chemistry and nutrition (Cory and Hoover 2006).

Environmental and community effects on host-parasite interactions are not necessarily passive effects. Indeed, it is becoming increasingly clear that hosts may employ specific behaviors to increase their protection against parasites, thereby reducing parasite virulence and transmission. Such behaviors may focus on abiotic factors such as temperature, as demonstrated by infected locusts that seek out higher temperatures to reduce fungal pathogen growth (Elliot et al. 2002), or they may focus on natural products or living species. For example, wood ants and bees incorporate conifer resin into their nests, which reduces microbial growth (Chapuisat et al. 2007; Simone et al. 2009). Moreover, a wide variety of animal species, from apes to woolly bear caterpillars, specifically consume antiparasite plants in response to active infection or risk of disease (Huffman 2001; Singer et al. 2009; de Roode et al. 2013). However, it is once again important to recognize that the host-parasite interaction is embedded in a larger food web and that, in some cases, strategies used to reduce the risk of attack by one natural enemy might increase vulnerability to another (e.g., Ramirez and Snyder 2009; Duffy et al. 2011).

The fact that abiotic and biotic factors can alter host-parasite interactions—and that animals may specifically use these factors to reduce infection and virulence—may have important consequences for disease ecology and evolution. Although some insights have been gained, especially with regard to the relationship between relative host abundance and parasite infection and virulence (Johnson et al. 2013), many other questions remain. For example, environmental conditions—whether abiotic or biotic—generally vary strongly across host habitat. Thus, hosts across a population will rarely all experience the same environment. Instead, host populations may be better viewed as inhabiting an environmental mosaic in which environmental conditions and ecological communities vary (Thompson 1994). Such environmental heterogeneity may contribute to the maintenance of genetic variation in hosts and parasites (Wolinska and King 2009) and is likely to influence the severity of disease outbreaks (e.g., Duffy et al. 2012). Environmental heterogeneity may also affect the evolution of virulence. As shown in this issue, the passaging of parasites through immune-suppressed hosts can lead to the evolution of more virulent parasites strains (Barclay et al. 2014). Hence, a geographic mosaic that contains pockets of immune-suppressed individuals could lead to the evolution and spread of more virulent forms of disease.

Environmental and community effects may also be crucial to our understanding of host and/or parasite local adaptation. Natural selection is generally expected to lead to parasite populations that are more infective to their local host populations (Gandon and Michalakis 2002). However, many studies have looked for, but not found, such adaptation (reviewed in Greischar and Koskella 2007; Hoeksema and Forde 2008). One potential reason for the lack of local adaptation is that many of these studies are based on lab experiments in which hosts and parasites from multiple populations are exposed to each other under laboratory conditions. These studies would capture any specific genetic adaptations but would miss any effects of the local environment or ecological community (e.g., Sternberg et al. 2013). Therefore, adaptations that rely on interactions with the environment, or other interacting species, would be detected only when replicating those factors (Cory and Myers 2004; Lazzaro et al. 2008; Sternberg and Thomas 2014). Finally, depending on the study system, allowing hosts to display their natural behavior in the wild could be crucial, as hosts may evolve resistance through behaviors such as medication (Choisy and de Roode 2014). Laboratory studies of local adaptation can nonetheless generate valuable information, and they can
be used to more precisely dissect the rates of evolutionary change, as shown by two articles in this symposium issue (Koskella 2014; Morran et al. 2014).

Question 4: Are Lessons Learned from Single Host-Parasite Pairings Generalizable to the Multihost-Multiparasite Networks That Dominate in Nature?

Most hosts are infected by multiple parasite species, and most parasites can infect multiple host species. However, while such multihost-multiparasite interactions are the norm in nature, they have received relatively little empirical study (Fenton and Pedersen 2005; Rigaud et al. 2010). In the most simplistic (and unrealistic) scenario, a system would be composed of a single parasite genotype and a single host genotype. In reality, communities are composed of many host and parasite species, each of which contains many genotypes. What fundamental differences emerge when this complexity is added? The addition of diversity within species is likely to be important, as discussed in question 1 above. Here, we focus on the addition of interspecific diversity. Can the outcomes of multihost-multiparasite interaction networks be predicted by studies of the individual components?

In some cases, the presence of multiple species will fundamentally alter the outcomes of host-parasite interactions. For example, because of impacts on the immune system (e.g., mutual inhibition among the T cell subsets required to clear “worms” versus those that clear “germs”; Zhu and Paul 2010; van den Ham et al. 2013), multiparasite dynamics might differ from those predicted from studies of single host and parasite species (Lello et al. 2004; Ezenwa et al. 2010). In this case, adding species may be fundamentally different from adding additional genotypes of the same species. Either way, within-host community ecology can be conceptualized as a tritrophic system in which parasites must compete for resources and evade predation by the immune system (Pedersen and Fenton 2007). Such a framework has proven predictive of the outcome of multispecies infections in both lab (Graham 2008) and field (Pedersen and Antonovics 2013). Indeed, trait-mediated indirect effects due to within-host tritrophic interactions may be as pervasive as those due to external tritrophic interactions (highlighted under question 3, above). Furthermore, theoretical studies of evolution of multihost parasites suggest that the presence of multiple host species can lead to initially unexpected outcomes, such as decreased parasite virulence with increased host mortality in certain scenarios (Gandon 2004; Rigaud et al. 2010).

In other cases, lessons learned from studies of intra-specific diversity might be instructive for studies of networks of species. For example, negative frequency-dependent selection by parasites can drive cycling among host genotypes (Jokela et al. 2009; Thrall et al. 2012). For multihost parasites, in many cases, we expect parasites to specialize on different host species (Gandon 2004). In these cases, can negative frequency-dependent selection by parasites drive cycling of host species? This idea has been explored in some depth within microbial communities, where bacteriophages are known to alter apparent competition among their hosts (reviewed in Fuhrman and Schwabach 2003; Koskella and Brockhurst 2014), but is rarely addressed in eukaryotic systems.

Question 5: What Is the Role of Host Microbiota in Shaping Disease Ecology and Evolution?

Recent interest in the influence of host microbiota (communities of microorganisms living in and on eukaryotic hosts) on organismal fitness has uncovered a key role of these commensals in mediating susceptibility to disease. For example, the gut microbiota of bumblebees was shown to have a stronger effect on susceptibility to the parasite *Crithidia bombi* than did the host genotype (Koch and Schmid-Hempel 2012). Similarly, the gut microbiota of humans and mice are known to influence susceptibility to intestinal pathogens (reviewed in Buffie and Pamer 2013), there is evidence suggesting human vaginal microbiota confer protection against HIV infection (Petrova et al. 2013), and skin-associated microbial communities are known to act as a first line of defense against pathogen colonization and infection (Harris et al. 2009; Gallo and Nakatsuji 2011; Naik et al. 2012). Given the known competitive, cooperative, and even spiteful interactions among microbial organisms, any disease protection mediated by the microbiota could be conferred either directly via microbe-microbe interactions or indirectly via the host immune system (Kamada et al. 2013). Unlocking this complexity will be central to predicting when and how immunity is conferred.

Although it is now clear that host microbiota can alter susceptibility to disease, it remains an open question as to how important this might be relative to host genetics and environment, and how generalizable the current evidence will prove to be. After all, there are clear cases where particular loci in the host genome are known to be directly involved in disease resistance (Mackey et al. 2002), but it is unknown whether and how the microbiota might interact with host genetics to influence disease. In relation to question 1 above, there is also a good possibility that the variation among hosts with regard to the microbiota they harbor will increase the effective host diversity in a population. For example, even when two hosts share the same suite of alleles conferring resistance, the outcome of infection may well differ depending on the composition
of the microbial communities they harbor. On the other hand, host genotype could play a key role in shaping the microbiota, which could in turn affect disease resistance (Spor et al. 2011; Olivares et al. 2013). Disentangling the complex interactions between host genetics, environmental factors, and microbiota on shaping disease susceptibility is likely to be a large feat, requiring a multidisciplinary approach.

Microbial communities, including those living in or on eukaryotic hosts, are highly dynamic over time, and we might therefore expect variation in disease susceptibility over the course of a host’s lifetime. Drivers of change in microbial communities over time include colonization and evolution, for example, in response to bacteriophage viruses. The human gut microbiota are known to host a high prevalence of phages (Stern et al. 2012), and the leaves of horse-chestnut trees harbor phages that are remarkably well adapted to their local bacterial hosts (Koskella 2014). When such shifts in the microbiota lead to dysbiosis, the results can be both harmful and difficult to reverse. For example, alterations to the gut microbiota can render human hosts more likely to develop high densities of pathogenic Clostridium difficile in their gut. Treatment with traditional antibiotic therapy often fails, but treatments that alter the gut microbiota via fecal transplants have been remarkably successful (Taur and Pamer 2014). However, there is also new evidence that a mismatch between host genotype and the gut microbiota can contribute to the development of cancer (Kodaman et al. 2014) showing that there is still much to be learned about interactions between hosts (including humans) and their microbiomes. It will be of great interest moving forward to monitor the success of “cross-fostering” treatments (such as fecal transplants), as they will no doubt uncover the importance of host genetics in shaping the taxonomic composition and host protective effect of the microbial community. Furthermore, it will be important to determine how coevolution between the host and the microbiota influences any protection provided (Bäckhed et al. 2005). Finally, a better understanding of which microbial organisms are the key players in shaping disease susceptibility is required before we can make predictions regarding disease spread in a population or further the development of any specific “probiotic” treatments for alleviating or preventing disease.

Conclusions

The surge of interest in the ecology and evolution of host-parasite interactions (fig. 1) has led to some important findings but also to new questions and new ways to conceptualize older questions. One of the major themes running through questions considered here is that the development of new study systems would be very valuable, especially where natural populations can be used in laboratory experiments and/or where experimental studies can be conducted in the wild. One of the difficulties for the future may stem from the great variety of ways in which host and parasites interact in nature and the context in which the interaction takes place. While this variety of systems may prevent sweeping generalizations (at least in the short term), it also seems essential to understand in order to make headway on both basic and applied questions in disease biology (e.g., Rudge et al. 2013). Taken together, it seems likely that this emerging field of study will continue to expand.

Acknowledgments

We thank the American Society of Naturalist for sponsoring our symposium, “Disease Ecology, Evolution, and Coevolution,” held in Snowbird, Utah, in 2013. We also thank the University of Chicago Press for printing this special symposium issue without charge to the ASN. Finally, we thank P. Morse for her guidance on the production of this volume and A. Gibson for comments on the final draft.

Literature Cited


Barclay, V. C., D. Kennedy, V. C. Weaver, D. Sim, J. O. Lloyd-Smith, and A. F. Read. 2014. The effect of immunodeficiency on the evolution of virulence: an experimental test with the rodent ma-
Buffie, C. G., and E. G. Pamer. 2013. Microbiota-mediated coloni-
Bell, T., R. P. Freckleton, and O. T. Lewis. 2006. Plant pathogens
Ca´ceres, C. E., C. J. Knight, and S. R. Hall. 2009. Predator-spreaders:
Drayman, N., Y. Glick, O. Ben-nun-shaul, H. Zer, A. Zlotnick, D.
Duffy, M. A., J. H. Ochs, R. M. Penczykowski, D. J. Civitello, C. A.
Ezenwa, V. O., R. S. Etienne, G. Luikart, A. Beja-Pereira, and A. E.
Froud-Williams, R. J. 2011. Unhealthy herds: indirect effects of predators
Gandon, S., and Y. Michalakis. 2002. Local adaptation, evolutionary
Haldane, J. B. S. 1949. Disease and evolution. La Ricerca Scientifica
Hamilton, W. D. 1980. Sex versus non-sex versus parasite. Oikos 35:
Hamilton, W. D., and M. Zuk. 1982. Heritable true fitness and bright
Harris, R. N., R. M. Brucker, J. B. Walke, M. H. Becker, C. R. Schwantes,
Howick, V. M., and B. P. Lazzaro. 2014. Genotype and diet shape
Hudson, P. J., A. Rizzoli, B. T. Grenfell, H. Heesterbeek, and A. P.

laria Plasmodium chabaudi. American Naturalist 184(suppl.):S47–
Bell, T., R. P. Freckleton, and O. T. Lewis. 2006. Plant pathogens
drive density-dependent seedling mortality in a tropical tree. Ecol-
Consumers indirectly increase infection risk in grassland food webs.
dependent expression of virulence in a trypanosome infecting
resistance against intestinal pathogens. Nature Reviews Im-
Chapuisat, M., A. Opliger, P. Magliano, and P. Christie. 2007. Woa-
ant use resin to protect themselves against pathogens. Proceedings of
Choisy, M., and J. C. de Roode. 2014. The ecology and evolution of
animal medication: genetically fixed response versus phenotypi-
plasticity. American Naturalist 184(suppl.):S31–S46.
Clatworthy, M. R., L. Willcocks, B. Urban, J. Langhorne, T. N. Wil-
2007. Systemic lupus erythematosus–associated defects in the
inhibitory receptor FcgammaRIIb reduce susceptibility to malaria.
Proceedings of the National Academy of Sciences of the USA 104:
de Roode, J. C., T. Lefe`vre, and M. D. Hunter. 2013. Self-medication
Choisy, M., and J. C. de Roode. 2014. The ecology and evolution of
animal medication: genetically fixed response versus phenotypi-
plasticity. American Naturalist 184(suppl.):S31–S46.
Clatworthy, M. R., L. Willcocks, B. Urban, J. Langhorne, T. N. Wil-
2007. Systemic lupus erythematosus–associated defects in the
inhibitory receptor FcgammaRIIb reduce susceptibility to malaria.
Proceedings of the National Academy of Sciences of the USA 104:
7169–7174.
Cory, J. S., and K. Hoover. 2006. Plant-mediated effects in insect-
de Roode, J. C., T. Lefe`vre, and M. D. Hunter. 2013. Self-medication
de Roode, J. C., R. M. Rarick, A. J. Mongue, N. M. Gerardo, and
M. D. Hunter. 2011. Aphids indirectly increase virulence and trans-
mission potential of a monarch butterfly parasite by reducing de-
461.
versity Press, Oxford.
Donnelly, R., A. Best, A. White, and M. Boots. 2012. Seasonality
selects for more acutely virulent parasites when virulence is density
Gallo, R. L., and T. Nakatsuji. 2011. Microbial symbiosis with the
innate immune defense system of the skin. Journal of Investigative
Gandon, S., and Y. Michalakis. 2002. Local adaptation, evolutionary
potential and host–parasite coevolution: interactions between mi-
utation, migration, population size and generation time. Journal of
for resistance to infection depend on parasite diversity. Ecology 91:
1263–1268.
Graham, A. L. 2008. Ecological rules governing helmhinth-micropar-
asite co-infection. Proceedings of the National Academy of Sci-
ences of the USA 105:566–570.
Pemberton, and D. H. Nusseuy. 2010. Fitness correlates of heritable
variation in antibody responsiveness in a wild mammal. Science 330:
662–665.
Haldane, J. B. S. 1949. Disease and evolution. La Ricerca Scientifica
19(suppl.):68–76.
Hamilton, W. D. 1980. Sex versus non-sex versus parasite. Oikos 35:
282–290.
Hamilton, W. D., and M. Zuk. 1982. Heritable true fitness and bright
Harris, R. N., R. M. Brucker, J. B. Walke, M. H. Becker, C. R. Schwantes,
D. C. Flaherty, B. A. Lam, et al. 2009. Skin microbes on frogs
prevent morbidity and mortality caused by a lethal skin fungus.
Hayward, A. D., R. Garnier, K. A. Watt, J. G. Pilkington, B. T. Grenfell,
2014. Heritable, heterogeneous and costly resistance of sheep
against nematodes and potential feedbacks to epidemiological dy-
namics. American Naturalist 184(suppl.):S58–S76.
affecting local adaptation between interacting species. American
Howick, V. M., and B. P. Lazzaro. 2014. Genotype and diet shape
resistance and tolerance across distinct phases of bacterial infec-
tion. BMC Evolutionary Biology 14:56.


Petrova, M. I., M. den Broek, J. Balzarini, J. Vanderleyden, and S.


Editor: Troy Day