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ECOLOGICAL IMMUNOLOGY

Disease ecology meets ecological immunology: understanding the links between organismal immunity and infection dynamics in natural populations

Dana M. Hawley*[,1] and Sonia M. Altizer[2]

[1]*Department of Biology, Virginia Tech, Blacksburg, Virginia 24061, USA; and* [2]*Odum School of Ecology, University of Georgia, Athens, Georgia 30602, USA*

Summary

1. Ecological immunology and disease ecology are two relatively young disciplines that apply ecological approaches and principles to traditionally non-ecological fields. In both cases, an ecological perspective has allowed new insights to emerge by focusing attention on variation over space and time, and by emphasizing the role of the environment in shaping individual responses and the outcome of host-pathogen interactions. Here we review the growing conceptual interface between these two rapidly evolving fields.

2. Areas of synergy between ecological immunology and disease ecology aim to translate variation in within-host processes (e.g. immunity) into between-host dynamics (e.g. parasite transmission). Emerging areas of synergy include potential immune mechanisms that underlie host heterogeneity in disease susceptibility, teasing apart the effects of environmental factors such as seasonality and climate on host susceptibility and pathogen dynamics, and predicting the outcome of co-infection by functionally distinct groups of parasites that elicit different immune responses.

3. In some cases, practical limitations have constrained the merging of ideas in ecological immunology and disease ecology. We discuss several logistical challenges, including dissecting the relative roles of host exposure and susceptibility, establishing links between measures of immunity and pathogen resistance in wild populations, and incorporating relevant immune variation into prevailing disease ecology modeling frameworks.

4. Future work at the interface of these two fields should advance understanding of life-history theory, host-pathogen dynamics, and physiological ecology, and will also contribute to targeted approaches for wildlife health and zoonotic disease prevention.

Key-words: coinfection, immune defense, sickness behaviour, superspreader, seasonality, within-host dynamics

Introduction

Ecological immunology and disease ecology are two relatively young disciplines that apply ecological approaches and principles to traditionally non-ecological fields. In particular, ecological immunology examines the underlying causes of variation in immune function between individuals or populations (e.g. Norris & Evans 2000; Schulenburg *et al*. 2009), and disease ecology examines mechanisms that determine how parasites spread through and influence populations and communities (e.g. Hudson *et al*. 2002; Collinge & Ray 2006). In both cases, an ecological perspective has allowed new insights to emerge by focusing attention on variation in host-parasite interactions over space and time, and by seeking to identify general processes and principles that transcend taxonomic boundaries. Perhaps most importantly, an ecological approach emphasizes the role of the environment in shaping individual responses and the outcome of host-pathogen interactions, and integrates processes across multiple scales of biological organization. Finally, both fields recognize the key interplay between ecological interactions and evolutionary changes in hosts and parasites (Altizer, Harvell & Friedle 2003).

*Correspondence author. E-mail: hawleyd@vt.edu

I made a mistake: this ref was meant to be Anderson and May 1979. The Anderson and May 1978 ref should be deleted from the references section and replaced with: Anderson, R.M. and May, R. M. 1979. Population biology of infectious diseases: Part I. Nature. 280: 361-367.

The majority of [illegible] focused on pathog[illegible]e host populations, st[illegible]a son and May in the late 1970s (Anderson & May 1978; May & Anderson 1978). This historical focus has transitioned more recently to understanding how multiple sources of heterogeneity, including individual variation in host susceptibility, can influence host-parasite interactions (Dwyer, Elkinton & Buonaccorsi 1997; Boots *et al.* 2009; Yates, Antia & Regoes 2009). For example, individual variation in infectiousness is commonly observed for many pathogens, with superspreaders contributing disproportionately to disease spread for both macro- and microparasites (Lloyd-Smith *et al.* 2005). Identifying immune mechanisms that underlie superspreading could help build a predictive understanding of disease spread through variable populations, and represents a key area of synergy between ecological immunology and disease ecology. There is also growing awareness that co-infections by multiple parasite species can affect a host's response to any single infection; recent studies have begun to uncover general rules regarding the role of host immunity in determining the outcome of such heterogeneous infections (Graham 2008) and their effects on dynamics in the field (Jolles *et al.* 2008). Thus, examining immune-mediated interactions between parasite species is another area of synergy between these two developing fields.

The field of ecological immunology emerged from the study of vertebrate life-histories and physiological trade-offs within and among species (e.g. Sheldon & Verhulst 1996). The major assumption that immune responses, and resistance to parasites more broadly, are costly, forms the basis of an ecological immunology approach. Mechanisms underlying these costs have been hotly debated (e.g. Lochmiller & Deerenberg 2000; Sandland & Minchella 2003), but the simple idea remains that individuals are not equally and maximally resistant to all potential parasites and pathogens they encounter. Instead, resistance constitutes a costly investment that must be traded off with other traits such as reproduction, sexual ornamentation, and dispersal (e.g. Lochmiller & Deerenberg 2000). In addition, evidence from field and laboratory studies suggests links between environmental conditions such as food availability and temperature and the ability of animals to better understanding of temporal and spatial variation in resistance to parasites and pathogens, the historical purview of disease ecologists.

In this review, we discuss the growing conceptual and empirical interface of the fields of disease ecology and ecological immunology (Fig. 1; Table 1). We identify several areas of synergy between the two fields, including the role of superspreaders and key hosts in the dynamics of infectious disease, the influence of environmental factors such as climate and seasonality on infection and immunity, sickness behaviour as an immune component directly linking within- and between- host processes, and the consequences of and immune mechanisms mediating co-infection. We also discuss the major challenges inherent in merging these two fields, and the broader implications for future work at the interface of ecological immunology and disease ecology.

Outstanding areas of synergy between disease ecology and ecological immunology

THE IMMUNOLOGY OF SUPERSPREADING AND KEY HOSTS

Superspreaders are individuals who contribute disproportionately to disease transmission (Lloyd-Smith *et al.* 2005). Historically, the best-known superspreader was Mary Mallon, also known as Typhoid Mary, a cook and asymptomatic carrier of *Salmonella enterica* Typhi who infected at least 54 individuals during her lifetime (Soper 1939). Closely related to the concept of superspreading is the 20/80 rule, which holds that 20% of individuals in a population are responsible for 80% of the disease transmission (Woolhouse *et al.* 1997). This phenomenon is widespread among macroparasites, for which intensity patterns tend to follow a negative binomial distribution in wild populations (e.g. Shaw & Dobson 1995), and also applies to directly-transmitted human diseases including measles, smallpox and pneumonic plague (Lloyd-Smith *et al.* 2005). For example, superspreaders were implicated in the early dynamics of the severe acute respiratory

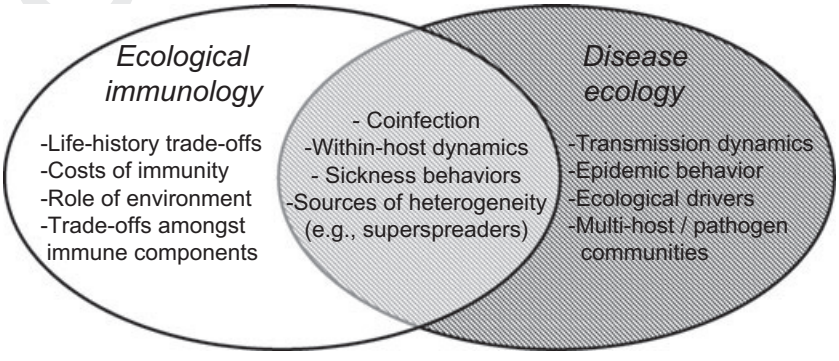

Fig. 1. Active and proposed areas of synergy between the fields of ecological immunology and disease ecology.

Table 1. Examples of studies to date that have attempted to integrate measures of immune function with resistance to ecologically relevant parasites in natural systems. These selected studies are not intended as an exhaustive list, and the strength of the relationships between immune function and infection processes depends on the host species examined

Host-pathogen system	Topic	Relevance of immune findings to infection/disease	Representative publications
African buffalo – *Mycobacterium bovis*	Coinfection; immune trade-offs	Worm-infected buffalo more susceptible to TB infection; coinfection increases host mortality and alters disease dynamics; hematologic values vary with animal age and sex, season, and herd affiliation	Jolles *et al*. 2008; Beechler, Jolles & Ezenwa 2009
Sea fan – *Aspergillus; Montastraea* coral and yellow band disease	Role of sea temperature, climate change	Warmer temperatures increase two metrics of cellular immunity and melanization, but also increase pathogen growth rates and virulence	Ward, Kim & Harvell 2006; Harvell *et al*. 2007; Mydlarz *et al*. 2008
Rabbit-nematode (*Graphidium strigosum* and *Trichostrongilus retortaeformis*)	Immune-mediated ntensity f unity climate change	Seasonal reproduction lowers female immunity and triggers peak shift in age-intensity curves; variation in acquired immunity to helminths determines which nematode species show increased burdens in warmer years	Cattadori *et al*. 2005; Cattadori, Boag & Hudson 2008; Cornell *et al*. 2008
Bumblebees – *Crithidia bombi, Nosemi bombi*	Life-history and immunity; trade-offs priming; Social roles and immunity	Foraging workers have lower immunity, immunity highest in most productive colonies, trade-offs between generalized versus specific immune defense (defense against dominant parasite strains compromises general encapsulation ability)	Doums & Schmid-Hempel 2000; Sadd *et al*. 2005; Baer & Schmid-Hempel 2006; Moret & Schmid-Hempel 2009; Otti & Schmid-Hempel 2008
Damselflies, gregarine gut parasites and water mites	Sexual selection and immunity; coinfection; costs of immunity	Darker males have greater immunity and parasite resistance; infection by water mites increases susceptibility to other parasites; immune challenge increases male dispersal propensity	Rantala *et al*. 2000; Honkavaara, Rantala & Suhonen 2009; Suhonen, Honkavaara & Rantala 2010
Crickets – nematodes/ parasitoid flies	Sex differences in immunity; the role of immunity in sexual selection and signal honesty	Females respond most strongly to songs of males corresponding to those mounting a high immune response as measured by encapsulation ability; Selection for elimination of male calling signal in parasitized population	Fedorka, Zuk & Mousseau 2005; Tregenza *et al*. 2006; Zuk, Rotenberry & Tinghitella 2006; Fedorka & Mousseau 2007
Grouse-nematode	Immunity and infection in males	Testosterone effects on immunosuppression are driven by hormonal changes; link with higher transmission during breeding season and individual variation in parasite infection	Mougeot *et al*. 2004, 2005a,b; Seivwright *et al*. 2005; Mougeot, Redpath & Piertney 2006
House Finches – *Mycoplasma gallisepticum*	Effects of social behaviour, flock size	Social status influences immune responses and resistance to *Mycoplasma* infection; intraspecific competition causes immunosuppression; higher group sizes are co er disease prevalence; Average group sizes declined following *Mycoplasma* epidemic	Hawley, Lindström & Wikelski 2006; Hawley, Davis & Dhondt 2007; Altizer, Hochachka & Dhondt 2004; Hochachka & Dhondt 2006

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lower case 'a'

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syndrome (SARS) epidemic in southeast Asia, where some individuals accounted for 40 or more secondary cases (Li *et al*. 2004). Because hosts that are responsible for a large number of cases represent obvious targets for infectious disease control measures, the mechanisms that underlie this phenomenon are of great public health interest (Woolhouse *et al*. 1997).

Superspreaders can be characterized by higher infectiousness or pathogen shedding, sometimes in the absence of visible disease symptoms, or they can have more frequent or numerous contacts with susceptible hosts (e.g. Lloyd-Smith *et al*. 2005; Temime *et al*. 2009). Most studies to date have focused on behavioural correlates of superspreading, especially in the context of social network analyses. Thus, the extent to which immune mechanisms contribute to higher infectiousness or asymptomatic carrier status represents a key area for future work. Other outstanding questions include (i) do physiological host characteristics such as pathogen tolerance (e.g. the maintenance of host fitness in the presence of a pathogen load; Read, Graham & Räberg 2009) commonly characterize superspreaders? And (ii) do host immune characteristics relevant to superspreading also relate to host life-history, sex, or infection by other pathogens?

In wildlife disease systems, multiple studies point to large, sexually mature males as 'key hosts' that contribute disproportionately to parasite transmission (e.g. Moore & Wilson 2002; Perkins *et al*. 2003; Clay *et al*. 2009). For example, one study of helminths infecting yellow-necked mice

(*Apodemus flavicollis*) showed that population-level transmission declined significantly when males, but not females, were treated to remove parasites (Ferrari *et al.* 2004). More generally, patterns of sex-biased infection have prompted a growing interest in immunological mechanisms that drive heterogeneity in susceptibility and transmission (e.g. Rolff 2002; Nunn *et al.* 2009), including the role of reproductive hormones (Folstad & Karter 1992). An elegant experiment by Mougeot *et al.* (2005a) directly measured the influence of testosterone on host immunity vs. behaviour by implanting male red grouse (*Lagopus scoticus scoticus*) with testosterone while simultaneously blocking the aromatase enzyme key to the production of aggressive behavioural responses, thereby elevating circulating testosterone while eliminating its effects on behaviour. Enhanced susceptibility of testosterone-implanted males to parasites was still detected, suggesting an immunological cause for sex differences in infection. Although Mougeot *et al.* (2005a) demonstrated that sex differences in infection in red grouse persisted in the absence of testosterone-mediated behavioural changes, it is still possible for behavioural and immunological effects of testosterone to interact in some vertebrate systems: indeed, testosterone has been demonstrated to have important effects on transmission-relevant behaviours such as contact rate (e.g. Grear, Perkins & Hudson 2009), aggressiveness, and territory density (e.g. Mougeot *et al.* 2005b). If immunological and behavioural effects co-occur and interact additively or synergistically, testosterone may serve as a common driver of superspreading phenomena, broadly linking within- and among-host processes across vertebrate host taxa. While the relevance of these findings for other types of hosts and pathogens remain unknown, understanding the immunological and life-history determinants of superspreaders and key hosts is an area ripe for investigation at the interface of disease ecology and ecological immunology.

RESPONSE TO SEASONALITY AND CLIMATE

The seasonality of immunity and seasonal infectious disease dynamics often go hand in hand, although direct linkages between the two have rarely been investigated. Many vertebrate pathogens show seasonal changes in incidence (reviewed in Altizer *et al.* 2006). In humans, influenza displays some of the strongest seasonal dynamics recorded to date, with distinct winter epidemics in temperate regions, and far less seasonality in the tropics (Reichert *et al.* 2004; Viboud, Alonso & Simonsen 2006). Several explanations have been forwarded to explain the seasonality of human influenza, including the idea that host susceptibility increases during the winter months. In humans, vitamin D deficiency caused by limited exposure to sunlight has been linked with a higher incidence of respiratory infections and lower expression of antimicrobial peptides (Cannell *et al.* 2006). For example, one study of pneumococcal disease in humans showed that the strongest predictor of new cases was extended periods of low UV radiation (White *et al.* 2009), which the authors attributed to either direct effects on pathogen survival or altered vitamin D metabolism. Experimental work also showed that vitamin D increased human T-cell receptor signalling and the activation of T-cells (von Essen *et al.* 2010) As with many infectious disease systems, however, the question remains open as to whether the most important drivers of seasonal human influenza epidemics are changes in host immunity, direct environmental impacts on the pathogen, or seasonal changes in host contact rates (Lipsitch & Viboud 2009). Nevertheless, a clearer understanding of the mechanistic links between environmental factors and immunity might help predict the timing and duration of outbreaks, and could promote alternative intervention strategies, such a nutritional supplementation during winter months.

More generally, there is growing awareness that hosts can exhibit intra-annual rhythms in immune function (reviewed in Dowell 2001; Nelson & Demas 1996; Nelson *et al.* 2002), which could drive changes in infection and recovery following host exposure. In wildlife, seasonal changes in immunity could arise from (i) changes in disease threats over time (which can further influence the relative benefits of investment in immunity at different times of the year); and (ii) trade-offs between immunity and other seasonally varying investments, such as costly reproduction (Box 1; reviewed in Nelson *et al.* 2002; Martin, Weil & Nelson 2008). For example, seasonal changes in physiological demands such as molting, pre-migratory fattening or winter thermoregulation are expected to cause reduced immunity (Sheldon & Verhulst 1996; Norris & Evans 2000) but only a handful of studies have examined these patterns in the wild.

Long-distance migration in birds is one of the best-studied seasonal activities that may mediate both immune changes and pathogen dynamics in host populations. Owen & Moore (2006) explored seasonal variation in immunity in three species of thrushes and documented that migrating birds were significantly immunocompromised relative to conspecifics measured outside of the migratory season. When they examined a single species further in captivity (Swainson's thrush; *Catharus ustulatus*), they found that detectable immunosuppression occurred solely with the onset of migratory restlessness (Owen & Moore 2008a), suggesting a seasonal immune rhthym that occurs regardless of the energetic costs associated with long-distance flight. However, the energetic costs of migration also appear to exacerbate seasonal immune rhthyms in this system: thrushes that arrived at stopover sites in poorest condition showed the lowest counts of lymphocytes and leukocytes (Owen & Moore 2008b). Together, these results suggest a potential role for seasonal events like migration in the dynamics of zoonotic pathogens such as West Nile Virus (Owen *et al.* 2006) and avian influenza (Weber & Stilianakis 2007). Such a potential role has thus far only been examined for the zoonotic lyme disease (Gylfe *et al.* 2000), and consistent with the immune results detected above, migratory restlessness alone reactivated latent *Borrelia* infections in captive redwing thrushes. However, it is important to note that not all pathogens will pose greatest disease risk in winter, and between seasonal immune

changes likely vary by species. A study of seasonal immunity in captive red knots, for example, showed no declines in costly immune defenses during the annual periods of mass gain (Buehler *et al*. 2008); however, this could be explained by constant access to high quality food in captive animals. Interestingly, this same study showed a down-regulation of the most costly defenses during the summer period, when birds would be widely dispersed on breeding territories. The authors therefore proposed that animals down-regulate defenses during times of year when host contact rates (and presumably disease risk) is low, and invest more in defenses during winter months. Overall, untangling the likely complex causative relationships between seasonal changes in infection dynamics and immune function will require monitoring immunological changes in the context of ecologically-relevant pathogens.

Box 1. Reproduction, immunity and parasite infection in mammals

In females, pregnancy, lactation, and offspring care can account for reduced immunity and periods of high parasite transmission (Festa-Bianchet 1989). In gestating placental mammals, for example, one important phenomenon is called the periparturient rise, whereby females lower their own immunity to prevent harming their fetuses (Lloyd 1983). It is important to note that an alternative explanation for reduced immunity during gestation is that resource based trade-offs drive immune suppression (reviewed in Martin, Weil & Nelson 2008). As one example that illustrates how female reproduction and immunity can affect parasite transmission, European rabbits (*Oryctolgaus cuniculus)* undergo seasonal shifts in immunity leading to peaks in the transmission of the gastrointestinal nematode, *Trichostrongylus retortaeformis*. As rabbits age from juveniles to adults, they acquire strong immunity to this parasite following previous exposure, leading to a convex-shaped age-intensity curve (Cattadori *et al*. 2005). When females become pregnant, their acquired immunity is reduced, such that the age intensity curve no longer declines in older animals during the breeding season (Cattadori *et al*. 2006). In terms of host-parasite population dynamics, this results in females shedding high numbers of infective stages just before their young begin foraging, thus generating seasonal increases in transmission during the spring and summer months. As a result, a 'peak-shift' occurs (Woolhouse 1998), in which the maximum intensity of infection increases and the age at peak infection simultaneously declines. This is an excellent example of how changes in immune response driven by host reproduction can drive temporal changes in transmission dynamics and shifts in age-intensity curves for macroparasites. An important challenge, however, is reconciling which immune processes most strongly mediate resistance to parasite infections, and how these depend on exposure levels in the field.

Beyond seasonality, disease risk and host defenses can vary with climate more generally. One interesting idea proposed recently is that climate variability can increase amphibian susceptibility to disease, an effect supported by a regional analysis of short-term climate fluctuations and chytrid-mediated frog declines in the tropics (Rohr & Raffel 2010). This mechanism could arise if changes in immune responses lag behind short-term increases and decreases in temperature, as suggested by previous studies (e.g. Maniero & Carey 1997; Raffel *et al*. 2006). In red-spotted newts, for example, short-term temperature fluctuations reduced some circulating leukocyte numbers, suggesting that these animals could be more susceptible to infectious diseases during times of climatic instability (Raffel *et al*. 2006). These issues are important for predicting how well amphibians and other ectotherms can mount an immune response against infectious agents outside of their typical climate envelope, and the role of climate variability, in addition to average changes in temperature, on host susceptibility to emerging infectious diseases (Fisher 2007).

Temperature stress can also impact immune defenses in invertebrate host species, with consequences for disease spread. For example, in the marine blue mussel *Mytilus edulis,* elevated temperatures (in the presence of low-level copper contamination) reduced hemocyte function, important for phagocytosis, and limited the hosts' ability to clear infection by a bacterial *Vibrio* pathogen (Parry & Pipe 2004). Similarly, for Pacific oysters *Crassostrea gigas*, warm temperature stress caused high mortality in the presence of *Vibrio* infections (Sindermann 1990). In other systems, warmer temperatures can increase immune activity, but this effect might be overcome by positive effects of temperature on parasite replication and development. In gorgonian corals, for example, immune enzymes and cellular immunity are activated by warmer sea temperatures (Ward, Kim & Harvell 2006; Mydlarz *et al*. 2008). However, opportunistic coral pathogens also grow faster and become more virulent at warmer temperatures, an effect that probably underlies recent disease outbreaks in the Caribbean following rising ocean temperatures (Harvell *et al*. 2007). Similar effects of temperature on the development of parasites in arthropod vectors could override positive associations between insect immunity and environmental temperature (Box 2). Nevertheless, epidemiological implications of temperature-mediated changes in host immunity remain to be explored for the vast majority of infectious agents, and could have great importance for predicting how disease dynamics will respond to both short-term temperature anomalies and long-term climate change.

Box 2. Ecological immunology of vectors

Disease vectors such as mosquitoes can mount immune responses against the pathogens they carry, but how does the strength of these immune responses vary with vector life-history trade-offs or environmental factors such as temperature? Because the transmission of vector-borne pathogens should be driven equally by immune events

occurring in the vector and the comparatively well-studied vertebrate host, vector defenses could affect the spatio-temporal dynamics of vector-borne diseases and public health strategies seeking to manage these pathogens. However, despite extensive work on vector competence and dissemination barriers for vector-borne pathogens of human interest, significantly less is known regarding the cost of infection for vectors, potential mechanisms of vector immunity, and the variation in immunity in natural vector populations. A recent review by Tripet, Aboagye-Antwi & Hurd (2008) highlights potential contributions of ecological immunology to mosquito-malaria interactions, including the following:

- Parasite-mediated costs to vectors
- Immunity-mediated costs
- Effects of genetic and environmental factors on mosquito fitness and infection
- Maintenance of resistance and susceptibility in natural populations

While the above questions address evolutionary and genetic mechanisms of resistance, vectors are also excellent models for ecological factors that mediate resistance over space and time. For example, warmer temperatures can increase the rate of melanization of foreign bodies and the phenoloxidase response to infection in mosquitoes (Suwanchaichinda & Paskewitz 1998), thus potentially increasing mosquito immune defense against malaria and other vector-borne diseases, However, warmer temperatures up to 27 °C also increase parasite development within vectors (although extremely hot temperatures can reduce *Plasmodium* survival; Noden, Ken & Beier 1995). Moreover, because warmer temperatures also speed up mosquito development, parasite development, female biting rates and oviposition (reviewed in Pascual *et al*. 2006; Martens *et al*. 1995), it is possible that the net effects on vector and parasite development will override indirect effects of environmental temperature on vector immunity.

Studies of immune variation in mosquito vectors have the powerful ability to combine state-of-the-art mechanistic tools (genomic, transcriptomic, and proteomic) to quantify immune mechanisms and costs, laboratory experiments that can manipulate vector and parasite genetics as well as environmental variables, and access to natural populations of vectors with varying levels of exposure to key pathogens. As such, mosquito vectors and their pathogens offer exciting opportunities for merging the fields of ecological immunology and disease ecology in novel and significant ways. Recent studies of *Plasmodium* resistance in mosquitoes illustrate the power of experimental approaches (that capitalize on multiple selected lines) to identify fitness costs of resistance and tolerance to malaria (e.g. Voordouw, Koella & Hurd 2008; Voordouw, Anholt & Hurd 2009). These studies underscore the strong limitations on selection for increased resistance in the wild, which could present a major hurdle for malaria control via manipulation of vector immunity.

COINFECTION BETWEEN PARASITE SPECIES

Trade-offs among arms of the immune system and their ability to impact pathogen dynamics are of recent interest to immunologists and disease ecologists alike (e.g. Graham *et al*. 2007; Pedersen & Fenton 2007; Graham 2008). An area of focus in both fields is the classical trade-off between T-helper 1 (Th1) and T-helper 2 (Th2) responses in the vertebrate adaptive immune response. Although each cell type performs multiple and diverse functions, the former of these two lymphocyte types (Th1) broadly regulates responses to most intracellular parasites (e.g. viruses) whereas Th2 cells respond primarily to extracellular parasites such as helminths. Jolles *et al*. (2008) recently provided one of the first demonstrations that within-host immune dynamics can have significant effects on disease dynamics at the population level: in African buffalo, worm infections are negatively associated with the probability of tuberculosis infection (TB; caused by *Mycobacterium bovis*) at both the individual and herd level. Furthermore, co-infection with worms and TB was associated with striking declines in host body condition. The authors used a dynamic model to show that immunological trade-offs combined with high mortality of co-infected hosts qualitatively capture the observed patterns of disease in free-ranging buffalo populations.

In some cases, the dynamics of confection, and specifically the Th1/Th2 trade-off, can be quantified by circulating levels of key signalling molecules like cytokines (reviewed in Graham 2008). In vertebrates, a subset of cytokines are responsible for simultaneously enhancing one response while suppressing the other. For example, Jolles *et al*. (2008) examined levels of IFNγ in buffalo to test for immunological trade-offs underlying coinfection with TB and macroparasitic worms. This cytokine promotes a Th1 response targeting intracellular infection (such as caused by TB bacteria), while down-regulating cytokines such as IL-10 which stimulate immune responses to macroparasites. Jolles *et al*. (2008) found evidence for a direct trade-off between circulating levels of IFNγ1 (Th1 response) and eosinophil counts, their measure of a Th2-type response, in buffalo. Because of their critical role in mediating immune trade-offs and coinfection outcomes, cytokines were recently highlighted by Graham *et al*. (2007) as linking within-host immune processes to among-host transmission outcomes, allowing predictions to be formulated for how a current infection affects the establishment of an incoming one. In addition to the practical advantages of measuring cytokine levels at single time points (as opposed to performing experimental pathogen or immune challenges), the roles of cytokines tend to be conserved across different host-pathogen interactions (Kourlilsky & Truffa-

Bachi 2001), making them a useful tool for future studies at the interface of ecological immunology and disease ecology (Bradley & Jackson 2008; Jolles *et al*. 2008). Studies in humans have used cytokine profiles to predict parasite infection patterns; e.g. Jackson *et al*. (2004) identified a significant positive correlation between IL-10 levels and specific nematode infections. Extending cross-sectional studies of cytokine profiles to wildlife populations could help researchers examine how chronic immune activation by a group of functionally similar parasites (e.g. extracellular macroparasites) affects the invasion of other pathogens, and how immune tradeoffs further depend on host life-history characteristics or environmental factors (Bradley & Jackson 2008).

In humans, it is well known that that the immunosuppressive effects of HIV/AIDS facilitate infection by other pathogens, leading to the development of devastating disease. But how important is co-infection as a mechanism of immune suppression and a driver of disease-induced mortality more broadly? The answer will depend on the parasites/pathogens involved, and the extent to which they compete for host resources and limit host defenses (Pedersen & Fenton 2008; Graham 2008). Anthropogenic stressors or extreme climate events could also exacerbate the immunosuppressive consequences of co-infection in natural populations. For example, Munson *et al*. (2008) noted that canine distemper virus (CDV) caused high mortality in Serengeti lions (*Panthera leo*) in some years but not others, and found that high-mortality epidemics seemed to result from the interactive effects of CDV and the tick-borne *Babesia* parasite. While neither pathogen alone causes notable mortality in lions, the immunosuppressive effects of CDV were associated with unusually high *Babesia* parasitemias and high mortality (approaching 70% in co-infected lion prides). As tick-borne *Babesia* infections were at highest prevalence during and just following an extreme drought, the authors suggest that co-infection of lions and resulting mortality could be exacerbated by extreme weather events associated with global climate change (Munson *et al*. 2008).

The role of immunity in mediating interactions between parasites is also relevant for human health and infectious disease control. In some parts of the world where helminths are prevalent in humans, HIV, TB and malaria are more common, and there is more rapid progression to AIDS following infection (e.g. Bundy, Sher & Michael 2000). Studies have shown that humans infected with parasitic worms show a pattern of immune dysfunctions, including decreased secretion of certain cyctokines and inhibition of T-cell proliferation (Maizels & Yazdanbakhsh 2003). One clinical study of human AIDS patients in Ethiopia showed that individuals with higher helminth egg loads also presented with higher HIV-1 viral titres; after treating patients to reduce worm loads, those patients who had many worms to start with showed declines in the HIV virus load 6 months after helminth removal (Wolday *et al*. 2002), supporting the idea that chronic helminth infection can enhance the progression of HIV infection. It is important to note that other field trials have found that helminth removal did not significantly reduce HIV-1 viral titres (Modjarrad *et al*. 2005); or that removal of *Ascaris* nematodes, but not other helminths, increased CD4+ cell counts and reduced viral loads (Walson *et al*. 2008). Although the mechanistic relationship between helminth infection and HIV/AIDS remains under debate, collectively, these studies suggest that helminth infection patterns and associated immunological changes could underlie large-scale variation in the transmission and impacts of microparasitic diseases.

SICKNESS BEHAVIOUR: LINKING WITHIN- AND BETWEEN-HOST PROCESSES?

Animal behaviour forms a critical link between within-host immunity and among-host transmission, and therefore represents a key area of integration for ecological immunology and disease ecology. In some host-parasite systems, healthy animals actively avoid infected conspecifics (Kiesecker *et al*. 1999; Behringer, Butler & Shields 2006), presumably to reduce their own risk of infection. These avoidance behaviours could covary with other resistance mechanisms: in one of the few studies to date to explicitly examine genetic covariation between host susceptibility and exposure, sheep from lines that were resistant to gastrointestinal helminths (as produced by a selective breeding program) also avoided foraging in parasite-rich areas of habitat more effectively (Hutchings *et al*. 2007). Infected animals can also behave in diverse ways that alter the potential for pathogen transmission, including alterations of foraging behaviour, activity levels, and investment in sexual reproduction (reviewed in Moore 2002). In some cases, these behaviours represent adaptive manipulations by parasites to increase the probability that transmission stages will reach susceptible individuals. In other cases, changes in host behaviour can arise from effects of pathology (e.g. Hawley, Davis & Dhondt 2007) or acute phase responses to infection (Johnson 2002). The extent to which these behavioural-induced changes influence disease dynamics in natural populations remains largely unknown.

An area of growing interest in ecological immunology is the suite of vertebrate behavioural changes termed 'sickness behaviours' which are induced early on by many infections as part of a broader set of acute phase responses (Adelman & Martin 2009). Sickness behaviours, which include lethargy, anorexia, decreased libido and postures that reduce heat loss, are thought to adaptively conserve energy for immune defense (Hart 1988). In turn, these adaptive behaviours are subject to life-history trade-offs that vary in species examined to date with factors such as ambient temperature (Aubert *et al*. 1997), daylength (Owen-Ashley *et al*. 2006), social status (Cohn & Sa-Rocha 2006), and the timing of infection in relation to reproduction (Owen-Ashley & Wingfield 2006). The extent to which individuals or species vary in sickness behaviour can be measured using standardized injections with non-pathogenic antigens such as lipopolysaccharide (LPS), which mimics a generalized bacterial infection (Adelman & Martin 2009). This technique can be applied to free-living

populations to address whether infection-induced behavioural changes vary with latitude (Adelman *et al.* 2010), season, or host life history characteristics, and how these behaviours affect contact rates and the potential for pathogen transmission. Field experiments might also reveal whether individuals that suppress sickness behaviours could act as superspreaders of infection, and whether sickness behaviours are associated with recovery from infection. Importantly, sickness behaviours are mediated by changes in corticosterone levels (Johnson, Propes & Shavit 1996) and the expression of pro-inflammatory cytokines produced by activated leukocytes (Kent *et al.* 1992). Thus, the involvement of cytokines serves to link sickness behaviour, an arguably among-host process, directly to the vertebrate immune response. Interestingly, if links can be demonstrated between peripheral cytokine levels and expressed behaviours, the mechanisms that underlie variation in sickness behaviours over space and time in free-living vertebrate populations may be measurable via circulating cytokine levels alone.

Because transmission is often the limiting factor in the initiation and maintenance of pathogen epidemics (Swinton *et al.* 2002), infection-induced changes such as sickness behaviour can influence broad-scale disease dynamics (Lloyd-Smith, Getz & Westerhoff 2004; Funk *et al.* 2009). In laboratory rats, treatment with the bacterial mimic LPS resulted in significant avoidance of injected animals' bedding by healthy conspecifics (Arakawa, Arakawa & Deak 2010). This fascinating result indicates that olfactory changes in individuals injected with a bacterial mimic are sufficient to alter contact rates between healthy and susceptible individuals in rats and potentially other vertebrate species that utilize olfactory cues. In birds, which are thought to rely less heavily on olfactory cues than mammals, behavioural changes involved in the sickness response may directly impact contact rates. In male house finches, for example, sickness behaviour, including reduced aggression, resulting from infection with the bacterium *Mycoplasma gallisepticum* was shown to attract healthy conspecifics seeking to avoid behavioural aggression at feeders (Bouwman & Hawley 2010). These changes will likely increase encounters between healthy and infected animals, and hence facilitate the transmission and maintenance of *M. gallisepticum* in wild populations. In damselflies, on the other hand, immune challenge (implantation of a nylon fibre) to mimic parasitoid or macroparasite attack caused high dispersal rates away from home territories, which might serve to limit further parasite exposure if affected animals seek to avoid the source habitat where 'infection' occurred (Suhonen, Honkavaara & Rantala 2010). In systems strongly influenced by kin selection, infected animals may isolate themselves to avoid infecting conspecifics; for example, worker ants (*Temnothorax unifasciatus*) experimentally infected with a pathogenic fungus were shown to leave their nests permanently well before death (Heinze & Walter 2010), an outcome that could effectively shut down pathogen transmission.

Examples of sickness behaviours discussed here capture extremes of the potential influence of behaviour on transmission, but generalizations across taxa are likely to emerge with further study. For example, infections in closely-related kin societies may be more likely to result in the apparently altruistic self-isolation of infected individuals, whereas infections among unrelated group members could cause behavioural changes that inadvertently augment transmission, as in the house finch example. Regardless of whether behavioural changes increase or decrease transmission, they are seldom included in mathematical disease models because so little is known as to whether and how hosts alter their behaviour once infected, or in response to infected conspecifics. Incorporating behavioural changes into mathematical models of disease dynamics is a critical, and arguably more feasible, way in which to estimate the impact of these changes on disease dynamics more broadly (Funk *et al.* 2009). Overall, the potential for synergy at this intersection of animal behaviour, ecological immunology, and disease ecology is particularly exciting given that animal behaviour forms a crucial link between within- and among-host processes.

Practical considerations in merging ecological immunology and disease ecology

SAMPLING AND INTERPRETATION

Both ecological immunology and wildlife disease ecology have faced criticism arising from the use and interpretation of immune assays in field studies (e.g. Adamo 2004; Kennedy & Nager 2006; Wobeser 2006). Results of single immune assays such as wing web swelling in response to phytohemagglutinin (PHA) injection in vertebrates have been criticized for being overly and/or inappropriately interpreted (Kennedy & Nager 2006) in part owing to challenges in linking immune measures to resistance or recovery from specific pathogens, and also because of an almost-universal lack of correlation among immune assays within single individuals or species (Blount *et al.* 2003; Matson *et al.* 2006). In recent years, eco-immune investigators are moving away from single measures of immunocompetence (Viney, Riley & Buchanan 2005) toward a diverse toolbox of new techniques that better account for different selective pressures operating on each component of the immune system (e.g. Buehler *et al.* 2008). However, questions in interpretation remain: for example, do higher antibody titers indicate a stronger immune system, and does a strong immune response represent active current infection or the enhanced ability to ward off future infections?

Disease ecologists also face significant practical challenges in the measurement and interpretation of infection status. Biases in the detection of disease abound for almost all free-living systems (Wobeser 2006), especially for studies where non-destructive sampling is required. Assays of pathogen or antibody presence have sensitivities and/or specificities as low as 42%, even for well-studied human infections such as HIV (e.g. Guy *et al.* 2009). Furthermore, the interpretation of disease exposure history or antibody prevalence can vary, especially because some antibody-positive individuals could be actively infected whereas others might have recovered from infection and potentially, but not necessarily, acquired

immunity to re-infection. Experimental infections to measure host resistance in a standardized way might be unethical or impractical to perform for many vertebrate animals or for species of conservation concern. Furthermore, when such challenge experiments are completed, outward signs of disease can reflect immunopathology rather than direct effects of pathogen infection (e.g. Graham 2002). Finally, a 'competent' immune system may employ tolerance strategies, making immune 'competence' difficult to assess via infection outcome alone.

The fitness consequences of immune investment and pathogen burdens provide a critical context for understanding observed outcomes, but are often overlooked in both disease ecology and ecoimmunological studies (Baucom & DeRoode 2010; Graham, Shuker & Little 2010). For example, hosts that invest in costly defenses in the absence of exposure to disease-causing agents could be making a flawed investment that will ultimately lead to lower fitness, but such hosts might readily be deemed 'immune competent' by traditional ecoimmune assays (e.g. immune cell recruitment, parasite agglutination and/or lysis, and antibody production). The evolutionary costs of immune deployment in the absence of infection have been particularly well documented in plants (e.g. Walters *et al*. 2009) and insects (e.g. McKean *et al*. 2009; Voordouw, Anholt & Hurd 2009; and are crucial for understanding the evolution of resistance, or lack thereof, in natural populations. Recent work in *Drosophila melanogaster* indicates that defense against an opportunistic pathogen can evolve in only 10 generations in the laboratory, but these immune defenses resulted in reduced longevity and larval viability (Ye, Chenoweth & McGraw 2009). Perhaps most interestingly, the authors simultaneously measured gene expression changes in selected *Drosophila* lines, and found what appeared to be pleiotropic changes in processes related to the detected costs of resistance: as cellular immunity was enhanced, developmental processes were disrupted. The ever-increasing feasibility of next-generation sequencing will facilitate the generation of transcriptomes and microarrays for non-model organisms, allowing researchers to measure the expression of many genes simultaneously during immune activation and pathogen infection. These technologies are certain to form the basis of many exciting new lines of research on the mechanisms underlying evolutionary costs of immunity, and could reveal how different types of costs (such as those that affect growth and development vs. reproductive investment) influence the evolution of resistance to pathogens in natural host populations.

UNDERSTANDING LINKS BETWEEN IMMUNE MEASURES AND INFECTION STATUS

The issues surrounding sampling and interpretation described above represent only a subset of challenges inherent in linking variation in immune competence with variation in infection status, including pathogen loads and the development of disease. Because disease measures such as pathogen load are typically influenced by diverse aspects of the immune system, using one or two immune assays to directly predict host responses to a given pathogen may be unrealistic (Keil, Luebke & Pruett 2001). On the other hand, immune assays and parasite load can show similar responses to ecological variables (e.g. if immune response assays decrease during long-distance migration, parasite load increases), and should in theory represent manifestations of the same underlying phenomena. A recent meta-analysis by Knowles, Nakagawa & Sheldon (2009) compared the effects of clutch size manipulations in birds on immune assay responses and blood parasitaemia; their results highlight one of the strengths of using standardized immune assays in the field. Specifically, clutch manipulations had invariably greater effect sizes on immune assays than on parasi insert space after (2009) gawa & Sheldon (2009)suggest that the lower statistical effect of clutch sizes on parasitemia may result from variation in exposure, which can affect parasitaemia levels as much as variation in immunity. These differences in effect size suggest that, in many cases, immune assays can offer statistically more powerful response variables for a given biological factor of interest (in this case, the cost of reproduction). Furthermore, immune assays are potentially informative for a broad range of parasites and pathogens, arguably offering more 'bang for buck' than pathogen challenge assays which are likely to be system-specific. On the other hand, the interpretation of immune assay results will be constrained by a lack of knowledge of ecologically relevant parasites and pathogens and their associated spatiotemporal dynamics.

Attempts to link host susceptibility to pathogens with responses to non-pathogenic immune assays must also consider the role of the pathogen during the infection process (Sadd & Schmid-Hempel 2009). Although immune assays typically measure responses to static, non-replicating entities, parasites and pathogens practice diverse forms of immune evasion and/or manipulation that remain unaccounted for by the majority of ecological immunology studies to date (Sadd & Schmid-Hempel 2009). Characteristics of host immunity that clear infection in the presence of actively replicating parasites or rapidly changing parasite epitopes likely differ significantly from those that successfully clear a static insult, but how so requires further exploration. Finally, it is important, where possible, to directly address genetic heterogeneities in hosts and parasites, often regarded as 'noise' in ecological field studies. These genotype-level interactions can crucially determine infection outcomes in natural host-parasite systems (e.g. Lazarro & Little 2009; DeRoode & Altizer 2010). For example, one recent study highlighted genotype-specific determinants of the immune response mounted by bumblebees to trypanosome parasites (Riddell *et al*. 2009), thus underscoring the need to examine immune defense in the context of naturally-occurring host-parasite variation.

THE ROLE OF EXPOSURE: LINKING WITHIN- AND AMONG- HOST PROCESSES

A final key challenge in the merger of ecoimmunology and disease ecology is that exposure will vary alongside immune

responses, and in some cases, the two may covary if susceptible individuals are also most likely to be exposed (Hutchings *et al*. 2007). Knowledge of pathogen exposure is therefore critical to ask whether variation in infection outcomes results from underlying immune variation, behavioural processes that control transmission, or both. The study of key signalling molecules such as hormones or cytokines, both of which are known to have dual effects on exposure and susceptibility, might offer progress in field and experimental studies of susceptibility and exposure. As highlighted above, testosterone is known to increase transmission-relevant behaviours such as contact rate, and has also been implicated in immunosuppression across a range of taxa. Similarly, inflammatory cytokines and corticosterone released during the innate immune response influence both within-host processes (e.g. immune cell recruitment, effector mechanisms) and, for the majority of mammals and birds studied to date, among-host processes (e.g. sickness behaviour). Their functional conservation across diverse vertebrate taxa make hormones and cytokines even more compelling mediators for considering mechanistic associations between within-and among-host processes.

Finally, knowledge of pathogen exposure in the context of immune variation is needed to build mechanistic models of pathogen transmission, with the ultimate goal of applying insights from ecological immunology to a broader understanding of infectious disease dynamics. Immunological processes not only impact susceptibility to initial pathogen invasion but can also affect among-host processes such as pathogen shedding from infected hosts and host recovery rates (hence extending the duration of the infectious period). The dynamical importance of host response to infection is likely vastly underestimated in disease ecology precisely because it is intimately tied to transmission. In other words, because host immunity is considered part of the transmission process in disease studies, and because most focus on heterogeneity in transmission concerns differential host contact rates, the distinct role of immune variation is rarely considered outside of impacts on recovery rates and immunity to re-exposure. Because the equilibrium conditions and dynamical behaviour of infectious disease models are sensitive to processes that affect transmission vs. recovery (e.g. Anderson & May 1981, 1986), there is a pressing need to identify which epidemiological parameters are most strongly affected by changes in individual immune systems, and how this is best incorporated into a modeling framework. Ecological immunology approaches could therefore help disease ecologists to tease apart the relative importance of differential exposure to infection vs. differential susceptibility in mediating variation in disease over space and time.

Conclusions and broader implications

Ecological immunology and disease ecology are young fields with intersecting growth trajectories: ecological immunology is developing stronger links to infection outcomes and pathogen resistance, and disease ecology is moving from a primarily population-level historical approach toward a more mechanistic understanding of within-host dynamics and heterogeneity in host susceptibility. This intersection sets the stage for a suite of exciting work at the interface of these two disciplines. At present, the conceptual interface of the two fields is arguably growing more quickly than the methodological interface, where significant challenges remain. In addition to the challenges in interpretation detailed above, the methodological merger of these two growing fields has been sorely limited by the lack of reagents appropriate for sophisticated immunological assays in non-model organisms (e.g. Bradley & Jackson 2008). However, the increasing ease of transcriptome generation should allow for the rapid development of qPCR-based approaches to measure immune gene expression in non-model organisms. In other cases, immune assays can readily be modified from closely related model systems (Jackson *et al*. 2009). Overall, the increasing availability of novel, and potentially more targeted, immunological methods for non-model species sets the stage for an exciting generation of studies linking immune variation and disease dynamics in free-living systems.

The merger of ecological immunology and disease ecology should ideally harness the strengths of both fields: from ecological immunology, a proximate and ultimate understanding of spatiotemporal variation in immune responses within and among species, and from disease ecology, a detailed understanding of the ecological context, including transmission dynamics and coinfection with other parasites, in which these immune responses are expressed. The fitness consequences of individual immune phenotypes and their consequences for pathogen dynamics can only be understood when both perspectives are effectively combined. We expect that a successful merger of these two fields will lead to a broader understanding of outstanding questions in life-history evolution, behavioural ecology, sexual selection, and host-pathogen ecology and evolution. Studies at the interface of these two fields, by seeking common conceptual and mechanistic ground, are particularly likely to identify principles that span taxa and ecological scales, thereby increasing their broader relevance. From an applied perspective, identifying the key anthropogenic and non-anthropogenic factors that regulate host susceptibility and disease dynamics in natural populations could allow for the development of novel disease intervention measures for humans and wildlife alike. For example, knowledge of the times of year or external conditions under which host defenses are likely to be lowest could inform focused monitoring and treatment of at-risk populations. As noted earlier, growing understanding of how different pathogen species interact via the host immune system could facilitate treatments to improve host health by removing competing immune demands. In the face of anthropogenic factors such as global climate change and deteriorating environmental quality that are simultaneously impacting a wide range of taxa, unifying principles regarding host immunity and disease dynamics are sorely needed.

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