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SYMPOSIUM

From Host Immunity to Pathogen Invasion: The Effects of Helminth Coinfection on the Dynamics of Microparasites

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Synopsis Concurrent infections with multiple parasites are ubiquitous in nature. Coinfecting parasites can interact with one another in a variety of ways, including through the host's immune system via mechanisms such as immune trade-offs and immunosuppression. These within-host immune processes mediating interactions among parasites have been described in detail, but how they scale up to determine disease dynamic patterns at the population level is only beginning to be explored. In this review, we use helminth–microparasite coinfection as a model for examining how within-host immunological effects may influence the ecological outcome of microparasitic diseases, with a specific focus on disease invasion. The current literature on coinfection between helminths and major microparasitic diseases includes many studies documenting the effects of helminths on individual host responses to microparasites. In many cases, the observed host responses map directly onto parameters relevant for quantifying disease dynamics; however, there have been few attempts at integrating data on individual-level effects into theoretical models to extrapolate from the individual to the population level. Moreover, there is considerable variability in the particular combination of disease parameters affected by helminths across different microparasite systems. We develop a conceptual framework identifying some potential sources of such variability: Pathogen persistence and severity, and resource availability to hosts. We also generate testable hypotheses regarding diseases and the environmental contexts when the effects of helminths on microparasite dynamics should be most pronounced. Finally, we use a case study of helminth and mycobacterial coinfection in the African buffalo to illustrate both progress and challenges in understanding the population-level consequences of within-host immunological interactions, and conclude with suggestions for future research that will help improve our understanding of the effects of coinfection on dynamics of infectious diseases.

Introduction

Over the past few decades, research on the ecology of infectious diseases has contributed unique insights into host–parasite interactions in nature (Tompkins et al. 2011). More recently, and in response to a global rise in emerging infectious diseases (EIDs) in humans and wildlife, a series of novel theoretical and conceptual models have expanded the way we view EIDs and the factors underlying the emergence of infectious diseases (May et al. 2001; Wolfe et al. 2007; Keesing et al. 2010). While research on EIDs has typically focused on how factors external to the host, such as climate, habitat, or changes in host densities, and social interactions influence the dynamics of transmission, processes internal to the host are now being incorporated into these studies (Lloyd-Smith et al. 2005). In particular, the blending of concepts from immunology with theory from disease ecology is changing the way ecologists approach a number of central questions (Graham et al. 2007; Bradley and Jackson 2008; Hawley and Altizer 2011). For example, a significant body of research on infectious diseases in humans shows that coinfection can play a critical role in the infection process via effects on the host immune response (Karp and Auwaerter 2007; van Riet et al. 2007; Supali et al. 2010), and a smaller number of studies link the interactions

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between coinfecting parasites and pathogens to epidemiological patterns of human disease (Bruce et al. 2000; Abu-Raddad et al. 2006; Wearing and Rohani 2006). These studies highlight the fact that incorporating processes occurring within the host may be central to understanding the dynamics of infectious diseases, especially with respect to the invasion and emergence of disease (Lloyd-Smith et al. 2008).

Coinfection is particularly relevant for studies of natural populations because the overwhelming diversity of parasites, coupled with the widespread nature of parasitism, creates an immense opportunity for concurrent infection. Indeed, most individual hosts, from humans to wild animals, are simultaneously infected with multiple species of parasites (Petney and Andrews 1998), and parasites co-occurring within a single host can interact in a variety of ways that may influence the abundance, distribution, and dynamics of one another (Pedersen and Fenton 2007). Consequently, prior infection with one parasite may strongly determine a host's response to subsequent infection by other parasites. Variation among hosts in the likelihood of acquiring and/or transmitting a parasitic infection is a central feature of many infectious diseases (Cattadori et al. 2007), and the magnitude of this heterogeneity among hosts can be a crucial determinant of the probability of invasion and persistence of a disease in a host population (Lloyd-Smith et al. 2005). Thus, given the ubiquity of coinfection in nature, and the effects coinfecting parasites are likely to have on one another, interactions among parasites may be a major force generating variation in the transmission of disease and in shaping infectious disease dynamics.

Parasites that co-occur within a single host can interact in several different ways, and the mechanisms whereby such interactions take place have been discussed in detail (Graham et al. 2007; Pedersen and Fenton 2007; Graham 2008). Immune-mediated mechanisms underlying interactions between helminth parasites and intracellular microparasites (i.e., pathogens such as viruses, some bacteria, and protozoa) within hosts are particularly well-characterized in human and laboratory animal systems (Brown et al. 2006a; Hartgers and Yazdanbaksh 2006; Kamal and Khalifa 2006; Secor 2006; Moreau and Chauvin 2010), but the relevance of these interactions for patterns of disease at the population level are still poorly understood. In particular, although it is becoming increasingly clear that coinfection may at least partially account for patterns of disease prevalence observed in humans and wildlife (Abu-Raddad et al. 2006; Jolles et al. 2008; Telfer et al. 2010), there is still a significant gap in our understanding of the context in which interactions among parasites are most likely to contribute significantly to disease dynamics. In this article, we use coinfection between helminths and microparasites as a model to explore how within-host immunological effects may scale up to the population level, with a specific focus on the effects helminths may have on microparasite invasion ability. To begin, we discuss how coinfection can alter disease transmission parameters relevant for quantifying the probability of microparasite invasion. We also briefly review the literature on helminth–microparasite coinfection to evaluate the body of evidence for effects of coinfection on these different parameters. Next, we develop a simple conceptual framework to explore the consequences of helminth coinfection for the dynamics of infectious diseases when all transmission-relevant parameters are considered simultaneously and in different contexts. We then review data from African buffalo (*Syncerus caffer*), a case study in which ongoing work is examining cross-scale linkages between immune-mediated within-host effects and disease dynamics. Finally, we conclude with some key directions for future research.

Linking immune mechanisms to disease transmission parameters

In the context of immune-mediated interactions among parasites, coinfections involving helminths and microparasites are of particular interest because helminth infections are ubiquitous in human and animal hosts (Petney and Andrews 1998), and helminths should have strong effects on the transmission and persistence of secondary microparasitic infections (Graham et al. 2007). Effects of helminths on microparasite infections are expected to result from at least two distinct immune mechanisms. First, helminths typically induce a T-helper cell type 2 (Th2) immune response, involving cytokines such as interleukin (IL)-4, IL-5 and IL-13, which promote effector mechanisms suitable for combating large extracellular invaders (Else and Finkelman 1998). However, Th2 cytokines simultaneously down-regulate T-helper cell type 1 (Th1) cytokines such as interferon (IFN)-γ, IL-12 and tumor necrosis factor (TNF)-α, which promote effector mechanisms involved in fighting intracellular microparasites (Mosmann and Sad 1996). Second, many helminths protect themselves from host immunity by exploiting host immunoregulatory pathways that enhance the activity of regulatory T cells (T_{reg}), which stimulate the release of regulatory cytokines-like transforming growth factor (TGF)-β and IL-10

(Maizels et al. 2004). This immunomodulation by helminths ultimately leads to suppression of both Th1 and Th2 immune responses. Helminth infections can thus reduce immune responsiveness in general, and responses protecting against microparasites in particular. As a result, prior infection by helminths can facilitate many microparasite infections at the individual level, and potentially alter their dynamics at the population level.

To assess the potential for helminths to affect the dynamics of microparasite infections, it is necessary to consider all the parameters relevant to disease dynamics that might simultaneously be altered by helminth coinfection. Classic Susceptible-Infected-Recovered (SIR) compartment models provide a simple framework for visualizing these effects (Fig. 1). Entry to the infected class occurs via disease transmission to susceptible (S) individuals, while hosts exit the infected class either via mortality or recovery (R) from infection. Helminth infection may increase the rate of disease transmission (β) by enhancing host susceptibility and infectiousness, and/or alter the duration of infectiousness by influencing disease-related mortality (α) and recovery (γ) rates. The pathogen basic reproductive number, R_0, provides an easily interpreted measure integrating these potential effects of helminths on microparasite disease dynamics. R_0 is the number of secondary infections a single index case is expected to generate in a naïve host population, and can be calculated as the rate at which new infections arise (β), multiplied by the infectious period: $1/(\mu + a + \gamma)$, where μ represents the background mortality rate. R_0 can be interpreted as an index of pathogen invasion ability, with invasion only possible if $R_0 > 1$, and disease spread more rapid with increasing R_0. Previous assessments of the role of helminths in the dynamics of microparasites have focused on the effects of helminths on host susceptibility and infectiousness, i.e., the numerator of R_0 (Graham et al. 2007), or on its denominator, via mortality associated with the macroparasite (Fenton 2008). However, helminths may simultaneously affect the R_0 of microparasites via both numerator and denominator—transmission rate and infectious period. Interestingly, while helminth effects on the transmission rate will typically increase microparasite R_0 (due to release from control by the immune system), effects on the infectious period can take either direction. Effects which decrease recovery from disease will tend to increase the infectious period, while effects which increase disease induced mortality will tend to decrease the infectious period. It is also important to note that the magnitude of the helminth effects on these disease parameters is likely to vary across hosts as a consequence of differences in individual helminth burdens. Although such variation will affect how individual effects translate to the population level, in this review we focus on an "average" helminth effect when prevalence is relatively high, as is typical of many wild populations.

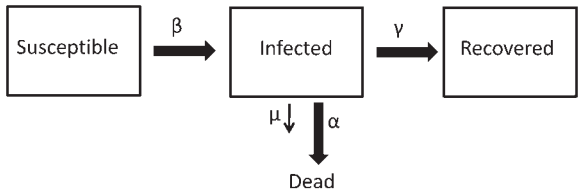

Fig. 1 A basic Susceptible-Infected-Recovered (SIR) compartment model which classifies individuals in the host population with respect to microparasite infection status, and defines the rate at which individuals move from one state to the next. The disease transmission rate (β) reflects the rate at which hosts enter the infected class, whereas the recovery (γ) and death rates (α = disease-related mortality, μ = natural mortality) reflect losses from the infected class. Pathogen invasion is only possible when pathogen transmission exceeds pathogen loss via host death or recovery from infection (i.e., $R_0 > 1$); and helminth coinfection may alter these rates simultaneously in ways that affect pathogen invasion ability. Helminth infection may increase the likelihood of disease transmission by suppressing immune responses aimed at limiting microparasite replication within the host, thereby increasing the susceptibility of uninfected hosts. In addition, higher microparasite replication rates in infected hosts may increase the infectious dose transferred to susceptible individuals, enhancing the likelihood of disease transmission during contact between susceptible and infected individuals. Furthermore, Increased pathogen replication within the host may speed up disease progression, increasing the disease-related mortality rate (α). On the other hand, compromised host immunity may slow down clearance of the infection, reducing the recovery rate (γ) from infection.

Many studies in laboratory animals and humans have quantified mechanisms by which helminth coinfection may affect the individual host response to microparasite infection, and in many cases these mechanisms map directly onto parameters relevant for quantifying effects on microparasite dynamics. Our synthesis of recent literature reveals three important patterns (Table 1). First, helminth coinfection can have profound effects on key parameters influencing microparasite dynamics and invasion ability. Across many host–helminth–pathogen systems, helminths have been shown to affect host susceptibility, infectiousness or individual infection risk, morbidity or mortality, and clearance rate. Second, these effects occur predominantly in the directions predicted by helminth-induced Th1–Th2 cross-regulation or immunosuppression. Helminth infections tend to increase microparasite

Table 1 Effect of helminths on transmission parameters of microparasite infections

Microparasite	Host	Helminth	β	α	γ	Net effect on R_0	References
Bordetella pertussis	Mouse	*Fasciola hepatica*	↑	=	↓	⬆	Brady et al. 1999
Citrobacter rodentium	Mouse	*Heligomosomoides polygyrus*	↑	↑	↓	⬆	Chen et al. 2005
influenza A virus	Mouse	*Trichinella spiralis*	=	↓	=	⬆	Furze et al. 2006
lymphocytic choriomeningitis virus	Mouse	*Schistosoma mansoni*	↑	↑	↓	⬆	Edwards et al. 2005
Leishmania major/Leishmania mexicana	Mouse	*Taenia crassiceps/Litmosoides sigmodontis*	↑/↓	↑/↓	n/a	?	Lamb et al. 2005; Rodriguez-Sosa et al. 2006
Plasmodium chabaudi/Plasmodium yoelii	Mouse	*Schistosoma mansoni/Litomosoides sigmodontis*	↑	↑	↓/=	?	Yoshida et al. 2000; Briand et al. 2005; Graham et al. 2005; Sangweme et al. 2009;
Plasmodium falciparum	Human	*Schistosoma mansoni/haematobium*	↑/↓	=		?	Sokhna et al. 2004; Briand et al. 2005; Lyke et al. 2005; Nmorsi et al. 2009; Sangweme et al. 2010
Plasmodium berghei	Mouse	*Schistosoma mansoni/Litomosoidessigmodontis*	↓	↓	=	⊘	Specht et al. 2010; Waknine-Grinberg et al. 2010
Mycobacterium leprae	Human	gastrointestinal helminths	↑	↑	n/a	⊘	Diniz et al. 2010
Toxoplasma gondii	Mouse	*Fasciola hepatica*	=	=		⊘	Miller et al. 2009
Mycobacterium bovis BCG/*Mycobacterium tuberculosis*	Mouse	GI nematodes/Schistosomes	↑	↑/=	↓/=	?	Erb et al. 2002; Elias et al. 2005; Frantz et al. 2007
HIV	Human	GI nematodes/filarial nematodes Schistosomes	↑/=	↓/=	n/a	?	Wolday et al. 2002; Elliott et al. 2003; Brown et al. 2004; Gallagher et al. 2005; Modjarrad et al. 2005; Hosseinipour et al. 2007; Walson et al. 2008;
Mycobacterium tuberculosis	Human	GI nematodes/Schistosomes	↑	↑/=	n/a	?	Brown et al. 2006b; Co et al. 2007; Neto et al. 2010.

Note. The table includes helminth–microparasite coinfection studies published between 2000 and 2010 (identified using the Science Citation Index, Thomson Reuters). With the exception of malaria, we included studies on gastrointestinal helminths, lymphatic worms, and schistosomes for all microparasites. For malaria, only schistosomes and filarial worm studies were included due to the large volume of studies found. Only studies that included explicit or implicit measures of immune-mediated helminth effects on disease transmission efficiency (β), disease-related mortality rate (α), and/or recovery rate (γ) were included. All studies presented were observational or experimental studies in humans and mice. Measures of β included direct measures of individual infection risk (incidence), and indirect measures such as immunological proxies for susceptibility and infectiousness (e.g., lack of Th1 responsiveness in coinfected individuals), increased parasitemia or viremia. Measures of α included direct comparisons of mortality in coinfected versus singly infected hosts, and indirect measures of morbidity using immunological (e.g., HIV: CD4 cell count), pathological (e.g., TB lung lesions), clinical (e.g., malaria: Anemia, hepatosplenomegaly), and condition (e.g., weight loss) indicators. Where present, the microparasite clearance rate, γ, was measured directly. For persistent infections which hosts do not clear, n/a is listed in the appropriate cells in the table. Upward arrows indicate positive effects of helminths on disease parameters, i.e., helminths increase microparasite transmission efficiency, disease-related mortality rate and/or pathogen clearance rate. Downward arrows indicate negative effects of helminths on disease dynamic parameters, i.e., helminths decrease disease parameters. Equal signs indicate that no effect of helminths on disease parameters was detected. If effects on a parameter were not assessed (i.e., no data), this is denoted as a blank cell. The helminth effects listed represent the most commonly observed effect direction (effect observed in ≥67% of references listed). Where there was no clear consensus, the two most common results are included. The net effect of helminths on microparasite R_0 is assessed qualitatively by combining the effects of helminths on microparasite transmission efficiency, disease-related mortality and recovery rate, according to $R_0 = \beta/(a + \mu + \gamma)$. Net effects on R_0 are only specified for host–helminth–pathogen systems where the direction of helminth effects was clear-cut. Question marks designate cases where there was no consensus on the effects of helminths on β, α, and/or γ.

transmission (β) and progression, reflected as a higher disease-related mortality rate (α), and slower recovery rate (γ), but these modifications of disease parameters do not necessarily occur in lock-step. Different combinations of parameter modifications are observed across host–helminth–pathogen systems and among studies. Third, there are some interesting exceptions to these patterns. For example, helminths appear to decrease transmission and mortality rates of virulent cerebral malaria (Specht et al. 2010; Waknine-Grinberg et al. 2010, but see Legesse et al. 2004) and influenza (Furze et al. 2006) in mouse hosts. Such differences in the direction of helminth effects on microparasite transmission and progression may be understood in the context of the primary mechanisms by which the microparasite causes morbidity and mortality in the host. When the pathogen imposes inflammation-mediated damage (immunopathology), helminths may protect the host from damage by dampening excessive Th1 immune responses, whereas the same Th1 suppression will exacerbate disease progression for pathogens inflicting direct (nonimmune-mediated) damage on the host. Helminth effects on the dynamics of microparasitic diseases may thus emerge from several distinct immunological mechanisms acting on different combinations of transmission-relevant parameters. Below, we develop a framework to explore the most commonly observed combinations of helminth effects.

Consequences of coinfection for disease dynamics: A predictive framework

A simple conceptual model highlights how the SIR framework can be used to assess the net effects of coinfection on the probability of disease invasion, and provides some insight on potential sources of variation in the outcome of helminth–microparasite interactions. The model considers all three parameters central to determining a pathogen's R_0 that can be altered by helminth coinfection (Fig. 1). Importantly, because helminth coinfection can both extend the duration of infectiousness by depressing recovery rates, and truncate the infectious period by enhancing mortality, the infectious period emerges as a key parameter that can lead to variability in disease dynamics in different contexts. For example, under most circumstances a pre-existing helminth infection that induces strong cross-regulatory and/or immunosuppressive effects on the host should increase microparasite transmission via increases in host susceptibility and infectiousness (Table 2). However, differences in the persistence or severity of disease can affect whether coinfection leads to a net increase, decrease, or no change in a microparasite's infectious period. For an acute infection in which disease can end with either the elimination of the pathogen or death, coinfection may alter host recovery, mortality, or both. If the infection is severe, the effect of coinfection on the infectious period will be the sum of the effects on recovery and mortality, where negative effects on infectious period via increased host mortality may counterbalance positive effects via decreased host recovery, potentially resulting in little net change in the infectious period (Table 2). In this case, the effects of coinfection on microparasite R_0 are driven primarily by changes in transmission. On the other hand, for an acute infection where disease is typically mild and the majority of hosts recover, the duration of infectiousness is most strongly influenced by the recovery rate. Thus, if coinfection slows down the recovery rate, then the net effect on infectious period is positive, and coupled with positive effects on transmission, the outcome may be a strong facilitative effect on R_0 (Table 2). Alternatively, for a chronic infection in which the pathogen persists for a long period of time within the host, and recovery is uncommon, the effects of coinfection on the infectious period will be dominated by changes in disease-induced mortality. In the case of a severe chronic infection, coinfection may reduce the infectious period by increasing host mortality. The negative effect on infectious period will moderate positive effects on transmission, potentially dampening any overall effect of coinfection on microparasite R_0. When a chronic infection is mild on the other hand, and unlikely to cause mortality, the infectious period loses its significance and the net effect of coinfection on microparasite, R_0 is driven by changes in transmission, as is the case for severe acute infections (Table 2).

Our conceptual model is a qualitative assessment of helminth effects on microparasite R_0, so we make the simplifying assumption that the effects of helminths on different parameters (transmission, disease-induced mortality, recovery) perfectly counterbalance one another (Table 2). In actuality, the relative magnitude of these effects will determine net effects on R_0, and effects may "add up" differently in different contexts. Nevertheless, our model provides useful insight about why there should be variation in the degree to which helminth coinfection affects microparasite invasion ability, and under what circumstances such variation may arise. Strong effects of helminth coinfection on disease dynamics are likely to be most evident for microparasites that cause mild infections, and for those that are typically nonpersistent or acute. Interestingly, these

Table 2 Relative effects of helminth coinfection on parameters that influence the pathogen basic reproductive number (R_0) when microparasites vary with respect to persistence and severity

Microparasite type	Parameters: Transmission rate (susceptibility and infectiousness) β	Infectious period[a] α	γ	$1/(\mu+\alpha+\gamma)$	Net effect on R_0	Representative microparasites
Acute						
Mild	↑	⊘	↓	↑	⬆	Rubella, mumps, rift valley fever in wildlife
Severe	↑	↑	↓	⊘	↑	Ebola, cholera, west Nile virus
Chronic						
Mild	↑	⊘	⊘	⊘	↑	Herpes viruses, lyme disease, brucellosis, leprosy
Severe	↑	↑	⊘	↓	↑	Tuberculosis, human immunodeficiency virus

Note. Effects of helminths on component values (α and γ) are shown with outlined symbols (arrows or null sign) and the summed effect [$1/(\mu+\alpha+\gamma)$] is shown with solid symbols.

[a]Infectious period is a function of the natural mortality rate (μ; not affected by coinfection), the disease-induced mortality rate (α), and the recovery rate (γ).

patterns are tentatively borne out in our literature review (Table 1). When the effects of helminths on distinct microparasite transmission parameters are considered in combination, the predicted net effects on R_0 are more pronounced for mild acute (*Bordetella pertussis, Citrobacter rodentium,* influenza, lymphocytic choriomeningitis virus) compared to mild chronic (*Toxoplasma gondii, Mycobacterium leprae*) or severe acute (*Plasmodium. berghei*) infections. This is interesting because it provides a basis for identifying diseases for which endemic helminth infections are most likely to facilitate the invasion of incoming microparasites, or alter patterns of microparasite incidence and prevalence. For example, although helminth coinfection may have detectable effects on individual morbidity and mortality due to TB in the developing world (Elias et al. 2005; Co et al. 2007), the likelihood that helminths influence the R_0 of this moderately severe chronic disease may be much lower than for a mild chronic infection like leprosy. Paradoxically, where helminths exacerbate disease severity, coinfection outcomes that are strictly negative from an individual perspective (i.e., increased individual mortality) may actually lead to positive consequences from a population-level perspective (i.e., decreased pathogen invasion potential). These effects highlight the inherent difficulty in predicting population-level outcomes from individual-level data in the absence of an ecological framework.

Our framework is also useful for considering how extrinsic factors such as the environment may influence the effects of helminth coinfection on disease dynamics. In particular, environmental conditions that affect resource availability and allocation within the host may play a critical role in the outcome of coinfection by affecting the magnitude of helminth-induced effects. Malnutrition and food restriction are known to have strong negative effects on immune function in humans and other mammals (Chandra 1996; Martin et al. 2007). Moreover, energy limitation may influence the directionality of Th1–Th2 polarization, with low energy intake potentially tipping the scales in favor of a Th2 response and high energy intake tipping the scales in favor of a Th1 response (Long and Nanthakumar 2004). Thus, under poor environmental conditions when resources are extremely limited, a host may have insufficient resources to adequately maintain a number of core body functions, including immunity, at optimum levels (Fig. 2a). Consequently, the effects of coinfection on all three transmission-relevant parameters may be strongly magnified (Fig. 2b). In direct contrast, when environmental conditions are good and resources levels are high, helminth coinfection may have negligible effects on disease parameters if Th1 immunity remains at near optimum levels (Fig. 2). Interestingly, because hosts may prioritize growth and self-maintenance (e.g., tissue repair, body mass maintenance) over immunity under suboptimal conditions (e.g., Eraud et al. 2008); (Fig. 2a), effects of coinfection on disease-related mortality may typically come into play only under severe resource limitation. This leads to the prediction that facilitative effects of helminths on microparasite invasion ability (R_0) may be most pronounced under intermediate resource conditions, less detectable under good conditions, and potentially dampened or even reversed under extremely severe conditions if disease-related mortality swamps out effects on transmission and recovery (Fig. 2b). This result is

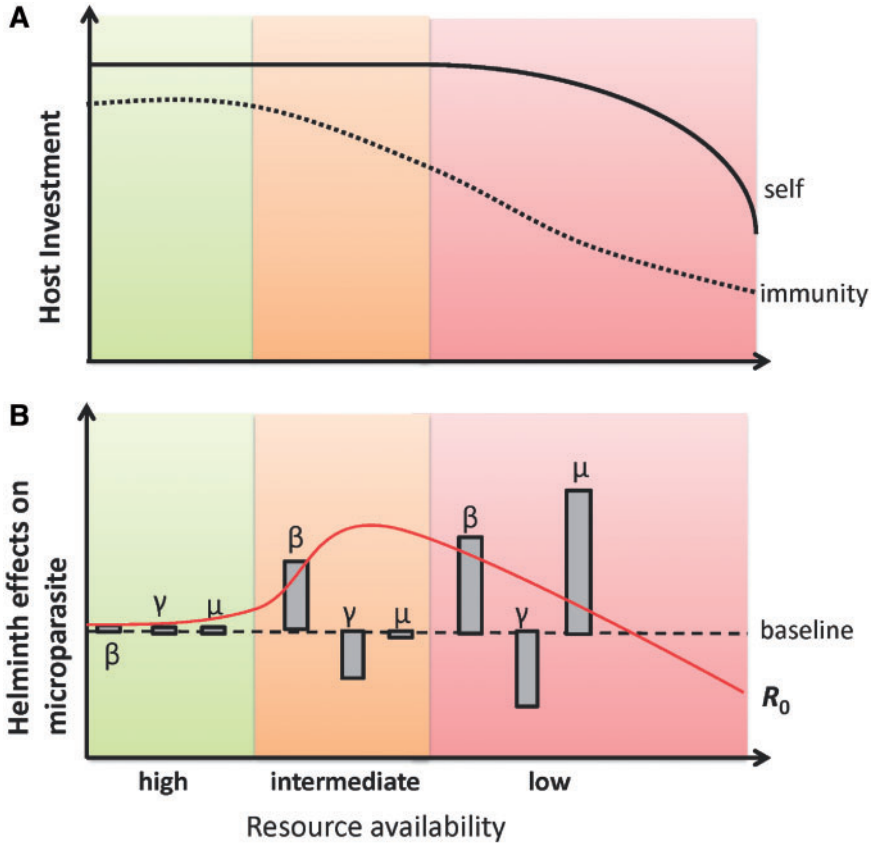

Fig. 2 Heuristic representation of hypothesized effects of resource availability on (**A**) host investment in self-maintenance versus immunity; and (**B**) effects of helminth coinfection on microparasite transmission parameters. β = microparasite transmission coefficient; γ = recovery rate from microparasitic infection; μ = disease-related mortality rate; line = R_0. Hosts prioritize investment in self over immunity under resource limitation. Consequently, immune-mediated effects of helminths on microparasite transmission and recovery rate are observable before effects of coinfection on mortality become evident, along a gradient of declining resource availability. As a result, helminth-induced facilitation of a microparasite peaks under intermediate resource conditions; by contrast as resource availability declines to very low levels, helminths may inhibit microparasite invasion (R_0).

somewhat nonintuitive because effects on individual hosts may be most severe and most easily detected under conditions of severe resource limitation. However, as was the case for mild versus severe infections, increased severity at the individual level will tend to dampen effects at the population level.

Coinfection and disease dynamics in the wild: African buffalo as a case study

Connections between the effects of helminths on individual hosts and disease outcomes at the population level are beginning to be made in the literature. For the African buffalo, a combination of cross-sectional, experimental, and modeling approaches have been used to examine the effects of gastrointestinal nematode infections on bovine tuberculosis (*Mycobacterium bovis,* TB), both in terms of individual-level disease parameters and microparasite invasion potential (R_0). Key results emerging from this work are that nematode infection is capable of depressing the host Th1 response (Ezenwa et al. 2010), suggesting that helminth coinfection is likely to increase general microparasite susceptibility. Effects of nematodes on infectiousness are less clear. Among individuals infected with TB, less severe coinfection with nematodes was marginally associated with weaker Th1 responses to TB antigen challenge (Ezenwa et al. 2010), possibly indicating that for TB-infected animals, stronger antinematode defense is accompanied by weaker control of concurrent TB infections. If this is the case, TB may progress faster in these animals resulting in higher levels of infectiousness. In combination, strong nematode effects on host susceptibility to TB infection and possible effects on infectiousness should translate into an increased TB transmission rate. As TB is a chronic infection, the role of recovery from the disease is negligible, thus coinfection is likely to alter the infectious period solely through changes in disease-

related mortality. Indirect evidence suggests that nematode–TB coinfection may accelerate buffalo mortality via synergistic effects on host body condition (Jolles et al. 2008). As such, coinfection may truncate the infectious period by increasing the mortality rate.

The potential positive effects of nematodes on TB transmission and negative effects on disease-induced mortality set the stage for nematodes to affect TB dynamics in buffalo. When disease dynamic models were used to evaluate whether these combined effects could explain patterns of infection in a free-ranging buffalo population, model results showed that observed patterns of nematode and TB prevalence depended on both effects acting in concert (Jolles et al. 2008). Furthermore, a more detailed model examining the potential for nematodes to alter the R_0 of TB showed that for buffalo populations exposed to nematodes, nematode effects on TB susceptibility tend to increase R_0 while effects of disease-related mortality tend to decrease R_0 (Ezenwa et al. 2010). Ultimately, the relative magnitude of the two effects will determine the net outcome for disease invasion. The model described above showed that changes in the TB transmission rate >50% (due to nematode effects on TB susceptibility) would be sufficient to facilitate TB invasion by driving the R_0 of TB above one (Ezenwa et al. 2010). Further work is needed to determine whether observed nematode effects on host Th1 immunity translate into changes in the TB transmission rate that are sufficient to alter TB dynamics. To evaluate the magnitude of the transmission effect in buffalo or other coinfection systems, longitudinal experimental studies where changes in immunity in response to coinfection are directly linked to the incidence of disease will be required. The need for such long-term manipulative studies highlights one advantage of an increasing research focus on wild animal populations (Pedersen and Babayan 2011).

Finally, the buffalo study system provides preliminary empirical support for a role of the environment in creating variability in the net effect of helminth coinfection as explored in our conceptual model (Fig. 2). Specifically, Th1 responses in buffalo, measured as circulating IFNγ levels, were found to be lower in the dry season compared to the wet season (Ezenwa et al. 2010), and a Th1–Th2 trade-off was only detectable during the dry season (Jolles et al. 2008). Although these patterns are based on a single-annual cycle and are therefore preliminary, taken together they suggest that environmental conditions that affect resource availability (e.g., seasonality) may create temporal variability in the magnitude of helminth-induced immunosuppression in natural populations (Fig. 3). This provides support for the idea that facilitative effects of helminth coinfection on the invasion of microparasites may be enhanced under some environmental conditions and relaxed under others.

Conclusions and future directions

Accumulating evidence from clinical studies, experimental animal models, and wildlife studies point to potentially profound effects of helminth coinfection on the dynamics of microparasitic infections. Most studies to date have evaluated the effects of coinfection on individual host susceptibility, morbidity, and mortality, but our knowledge base for predicting the outcomes of such effects at the population level is still slim. Only rarely have helminth effects on transmission-relevant parameters been combined with dynamic models to predict disease outcomes (e.g., Jolles et al. 2008; Lloyd-Smith et al. 2008; Ezenwa et al. 2010; Gibson et al. 2010), but the use of models to extrapolate to the population level is essential because simultaneous effects of coinfection on multiple parameters may have nonintuitive consequences. This is particularly relevant for disease control strategies. For instance, based on evidence that helminth infections may exacerbate the risk and prognosis of some microparasitic diseases, the use of antihelminthics as part of an integrated strategy for controlling diseases such as TB, malaria, and HIV in developing countries is currently being debated (Eziefula and Brown 2008; Hotez 2009). However, parasite control interventions that improve individual outcomes by reducing morbidity or mortality have the potential to increase disease incidence at the population level via effects on the infectious period. On the other hand, if reductions in host susceptibility and infectiousness (i.e., transmission) are the dominant coinfection effects, then substantial buffering of disease risk may be achieved for the whole population, not just treated individuals.

In this review, we outline a conceptual framework that we hope will provide a useful starting point to guide the exploration of links between individual and population effects. We identify two key aspects of pathogen biology, persistence, and severity, as potential axes for predicting the outcome of helminth–microparasite coinfection, with effects on disease dynamics more pronounced for acute and mild than for chronic and severe microparasite infections. In addition, we show that fluctuations in resource availability may also play a central role in determining coinfection outcomes. Importantly, considering the

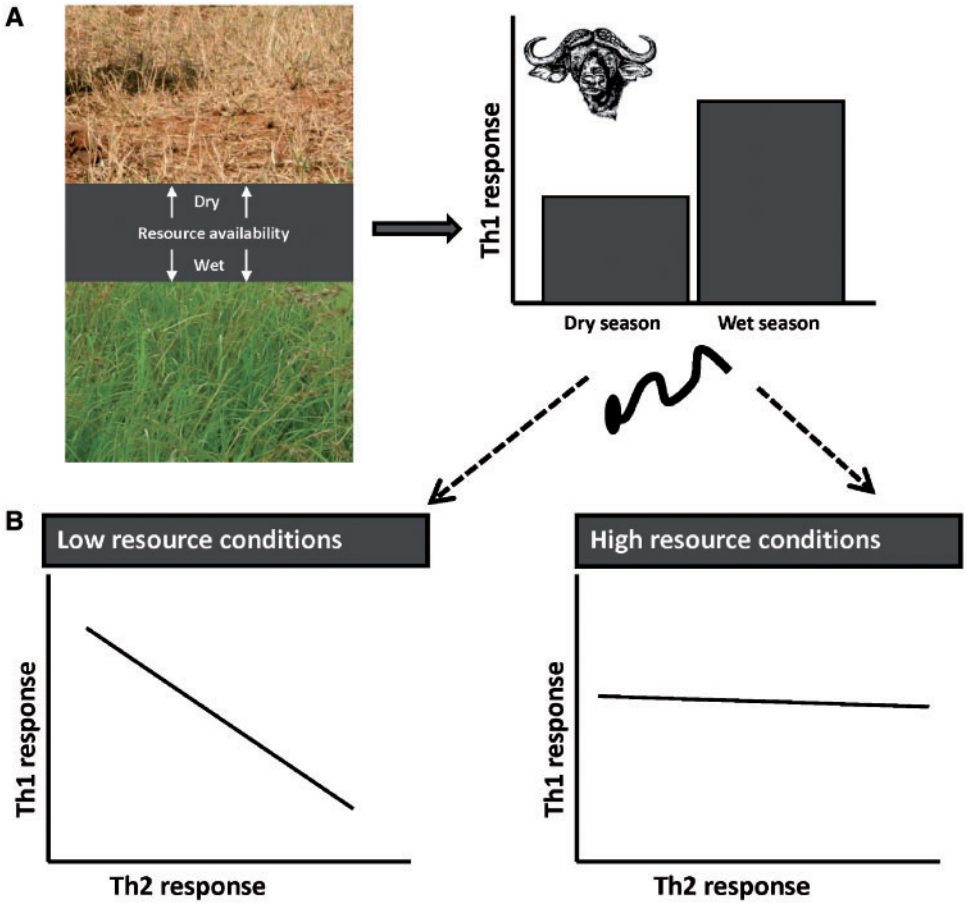

Fig. 3 (**A**) In African buffalo, variation in resource availability in the dry and wet season may underlie observed seasonal variation in Th1 immune responses. (**B**) Seasonal variation in the magnitude of Th1 immune responses may create differences in the degree and detectability of immune-tradeoffs under low versus high resource conditions.

magnitude of immune effects, and the relative investment by the host in self-maintenance under different resource levels, leads to the prediction that the strongest positive effects of coinfection on microparasites may be observed under intermediate levels of resource availability or moderate environmental conditions (Fig. 2).

To improve our understanding of population-level effects of coinfection, and increase our ability to predict outcomes of interventions aimed at coinfecting parasites, more studies integrating individual-level transmission data with disease dynamic models are needed. In particular, studies estimating the full complement of relevant disease parameters (i.e., transmission, disease-induced mortality, recovery) along with disease dynamic outcome measures (e.g., incidence of infection, equilibrium prevalence, rate of spread) will facilitate the bridging of individual- and population-level effects. In addition, our estimates of the effects of coinfection on disease parameters could benefit from longer study time frames, accounting for short- and long-term changes in immune responses throughout the time course of infections by both helminths and microparasites. Considering dynamical feedbacks will also be important since over the longer-term, helminth dynamics, as well as microparasite dynamics, may change as a consequence of coinfection. Ultimately, evaluating the performance of dynamic coinfection models will require experimental studies manipulating coinfection in replicated populations and measuring microparasite infection dynamics as response variables. Wildlife study systems are uniquely positioned to provide this essential experimental validation of disease dynamic theory because experiments on populations are feasible in many systems, whereas similar experiments in laboratory settings suffer from a lack of realism, and human population studies are subject to tighter ethical constraints. Finally, progress on understanding the mechanisms underlying variability in the effects of coinfection on microparasite dynamics will depend on targeted comparisons among a

broader range of microparasites, comprising of gradients in pathogen biology (e.g., disease persistence and severity); carefully designed longitudinal field studies tracking natural variation in environmental conditions and resource variability; and experiments manipulating both resource availability and coinfection status. Such data, when integrated using theoretical models, will go far toward providing the predictive understanding of coinfection needed to inform animal and public health policies.

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