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Emphasizing the ecology in parasite community ecology

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In natural systems, individuals are often co-infected by many species of parasites. However, the significance of interactions between species and the processes that shape within-host parasite communities remain unclear. Studies of parasite community ecology are often descriptive, focusing on patterns of parasite abundance across host populations rather than on the mechanisms that underlie interactions within a host. These within-host interactions are crucial for determining the fitness and transmissibility of co-infecting parasite species. Here, we highlight how techniques from community ecology can be used to restructure the approaches used to study parasite communities. We discuss insights offered by this mechanistic approach that will be crucial for predicting the impact on wildlife and human health of disease control measures, climate change or novel parasite species introductions.

The need for a mechanistic understanding of parasite communities

Emerging infectious diseases present one of the most pressing issues facing human health and wellbeing in the 21st century. In response, there has been substantial progress in understanding disease transmission and the regulatory effects of parasites on host populations [1,2]. However, these studies have focused mainly on one-host–one-pathogen systems, whereas hosts are typically infected by multiple parasite species [3,4]. Interactions between co-infecting parasite species within individual hosts determine host fitness, the severity of disease symptoms, the release of infective stages into the environment and, ultimately, the epidemiology of each parasite species within the host population. Furthermore, understanding the mechanisms shaping within-host parasite communities is vital for the design of disease control programmes; control approaches that only consider one parasite species in isolation might have unpredictable consequences for disease caused by co-infecting species [5]. Therefore, if we are to make accurate predictions concerning how parasite communities respond to perturbations, it is necessary to understand the mechanisms by which the component species interact within individual hosts.

To date, parasite community ecology has been highly descriptive, driven by pattern-based analyses at the host population level. Broadly, two main approaches have been adopted to examine parasite communities, although these are not mutually exclusive. The first classifies parasite communities based on patterns of species occurrence (presence and absence data) and tests for community structuring by comparing observed species distributions against null models [6–8]. The second approach quantifies pairwise associations between species, inferring interspecific interactions from correlations in species abundance [9–11] or more complex models that control for biotic and abiotic factors [5]. However, although these approaches provide a basic description of parasite communities at the host population level, they provide little mechanistic insight into the within-host processes shaping these patterns. Whereas parasite studies at the host population level are the most accessible, they might not reflect the level at which the key processes that structure parasite communities occur. Patterns of parasite association at the host population level could reflect more fundamental processes occurring at the within-host level. However, owing to inherent complexities within each host, it might not be possible to infer the magnitude or even existence of these processes from population-level data.

Fortunately, there is a precedent for identifying fundamental processes underlying noisy ecological patterns. The broader field of community ecology also began by classifying communities based on patterns of species abundance. However, this field has since developed more mechanism-driven approaches, resulting in a better understanding of the processes that drive patterns of species diversity and community functioning. Recently, analytical tools developed in community ecology have been applied to other fields (e.g. invasion biology [12] and the impact of contaminants on ecosystems [13]), and we believe that they can also be applied to parasite communities. Specifically, we argue here that techniques from community ecology can shed light on the direct and indirect processes that structure within-host parasite communities. These approaches enable us to address issues such as the impact of control strategies on non-target parasite species and the likelihood of infectious disease emergence in humans, domesticated animals and wildlife.

Representing within-host parasite communities as interaction networks

To obtain a mechanistic understanding of parasite communities, we need to consider the network of interactions (both direct and indirect) that occurs between parasite species within an individual host. In community

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ecology, there has been a recent surge of interest in the use of interaction networks, covering issues including network structure [14,15], the consequences for community stability [16,17], how to parameterize networks [18–21] and network responses to perturbations [15,21,22]. Applying these approaches to within-host parasite communities will provide a deeper insight into the causes and consequences of parasite community structure than is available using current methodologies.

The most common interaction networks in community ecology are food webs, which incorporate explicit trophic structure and directionality such that primary producers (basal level) are consumed by species at the intermediate level, which are in turn, consumed by predators higher up the network. We suggest that within-host parasite communities can be represented in a similar fashion, incorporating trophic structure in terms of the resources of the host that the parasites consume and the components of the immune response of the host that attack infecting parasites. Here, we illustrate this with a hypothetical within-host parasite network comprising three trophic levels (Figure 1): host resources, the parasite community and the host immune system.

Level 1: host resources

The basal level is defined by host resources, which can be a specific component that parasites feed on (e.g. blood), or the physical space available (e.g. within the gastrointestinal tract). Parasite feeding or growth depletes resources and debilitates the host, indirectly affecting other parasites within the community.

Level 2: the parasite community

The second level includes all parasites (both micro- and macroparasites) that infect the host. Where possible, parasite species should be placed into functional guilds of similar species (Figure 1). Defining guilds can be controversial but, as has been previously recommended [23–25], we suggest they should be based on functional similarity of species rather than on taxonomic classifications. In particular, parasite guilds can be defined in terms of a shared niche, where species differentiate themselves along three major axes: (i) a resource axis (e.g. what resources do the parasites feed on?); (ii) a location axis (e.g. where do the parasites occur within the host?); and (iii) an immunological axis [e.g. what components of the immune response of the host (Box 1) do the parasites stimulate?]. The location of a parasite along each of these axes defines its niche and parasites occupying similar niches (i.e. occupying similar locations, consuming similar resources and stimulating comparable host immune responses) can be placed in the same guild. However, there is a degree of subjectivity in the definition of guilds and it should be seen as a simplifying approach. Frequently, individual species will occupy their own unique guild.

Level 3: host immune system

The third level comprises the immune system of the host (Box 1), which is analogous to a predator trophic level in community ecology food webs. This predator–prey analogy of host immunity–parasites is frequently adopted for modelling the within-host dynamics of single pathogen species,

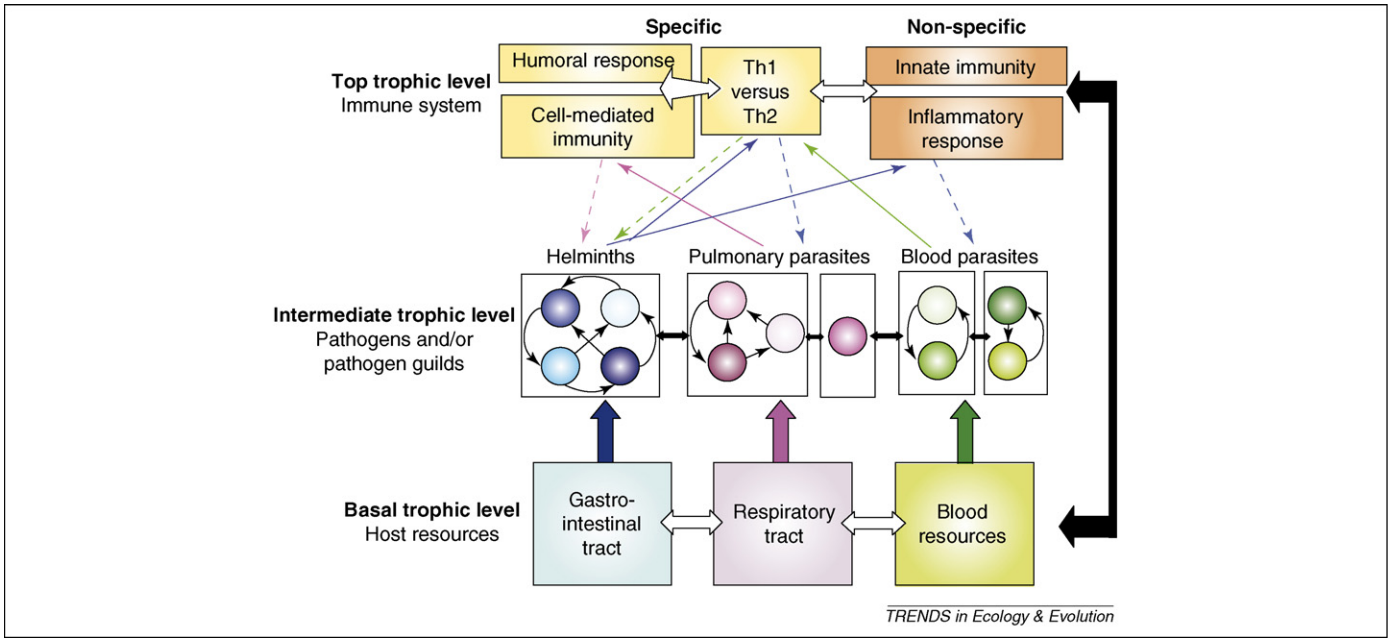

Figure 1. A hypothetical within-host parasite community interaction network. We define the within-host parasite interaction network with three levels of explicit trophic structure; given that parasites consume resources of the host for development, reproduction and transmission, and the immune system acts as a predator destroying the infecting pathogens. The basal level is defined by the host resources, analogous to the primary producers in a typical free-living food web. However, by contrast, host resources are inextricably linked to each other (white arrows) because the fitness and survival of the host depends on all resource components. The intermediate level comprises the parasites (colored circles) and parasite guilds that infect the host. Pathogens that consume similar resources, share a locality within the host and are attacked by the same components of the immune system can be considered parasite guilds (boxes), in which direct interactions between parasites are most probable (unidirectional arrows). Parasite guilds can comprise a single species. The vertical arrows represent the flux of energy from host to pathogen. The top trophic level represents the diverse responses of the immune system that vary in their degree of specificity. Here, we highlight a few common components (boxes), and use solid colored arrows to represent the aspects of the immune system that target each parasite or parasite guild, whereas the dashed arrows represent the top-down indirect interactions of co-infection parasites, mediated by the immune system.

Box 1. Essential immunology for ecologists

The immune system is a complex network of functions that define the ability of the host to defend the body against parasites and pathogens. The two main lines of defence, innate and adaptive immunity, are differentiated by the specificity and strategy of their response; but they both include cellular and molecular tools to defend the host from invaders. The major task of the innate immune response is to provide a rapid, nonspecific attack on parasites via the cellular response of phagocytosis and the molecular response of complementation proteins and interferons (INF). Adaptive immunity is parasite specific, stimulating both the humoral (antibody production and immune memory) and cell-mediated response (targeting infected host cells). Parasites can be attacked by several components of the immune system, and their route of infection, location within the host and parasite type will determine the scope of the response. Although there are components of the immune system that specialize in the clearance of intracellular parasites (i.e. bacteria and viruses), different components eliminate macroparasite extracellular infections (i.e. those caused by worms, protozoa and fungi).

Th1 versus Th2 immune response

One important mechanism that gives rise to indirect immune-mediated interactions within a host is driven by the T-helper type 1–type 2 (Th1–Th2) (CD4+ T-helper cell) tradeoff. Stimulated by the introduction of a parasite and the associated circulating cytokines, one arm of the response is enhanced, whereas the other is downregulated. This tradeoff leads to dynamic interactions when hosts are co-infected with several parasite species. The Th1 immune response is stimulated by intracellular viral antigens and develops a primarily cell-mediated response, resulting in a specific cytokine profile [interferon-γ (INF-γ), tumor necrosis factor β and interleukin 2 (IL-2)]. This profile activates cytotoxic T cells, macrophages, B cells and natural killer cells. By contrast, extracellular antigens usually stimulate the Th2 immune response, which leads to a different cytokine profile (IL-4,5,6,9,10 and 13). The Th2 response triggers a primarily humoral response and increases activation of mast cells and eosinophils (which tend to target larger parasites such as helminths) [46,47]. This leads to the Th1 response primed to target intracellular viral and bacterial pathogens, whereas the Th2 response focuses on parasitic or macroparasite infections. In laboratory mouse models and humans, there has been an extensive amount of work to investigate this competitive response and its effect on the infection and pathogenesis of several parasites [46,48,49].

where the immune response 'consumes' the pathogen [26]. This trophic level can be divided into different components of the immune system (i.e. cellular response, humoral response and T-helper cell types; Figure 1, Box 1), akin to a suite of generalist and specialist predators, with potential interactions between them.

Given the explicit trophic structure of the parasite community ecology network, it is possible to construct *a priori* hypotheses about potential links between co-infecting parasite species within an individual host. The mechanisms driving these interactions can be direct or indirect, positive or negative and have been the subject of several reviews [3,4,27]. Direct interactions can occur through interference competition, where the physical presence of one species affects the fitness of a co-infecting species. These interactions are most likely to occur among species within a parasite guild, as they share a similar location in the host and consume the same resources (Table 1). Given the trophic structure of the parasite community network outlined earlier, there are two main routes of indirect interactions between co-infecting parasites. Both these routes have similarities with mechanisms of interspecific interactions in free-living communities. The first involves a 'bottom-up' interaction, where two (or more) species compete for a common host resource (Table 1). This is akin to classic resource competition in community ecology, mediated by the abundance of the shared resource [28]. The second main route of indirect interaction among co-infecting parasite species is a 'top-down' interaction, acting via the immune system of the host (Table 1; [3,27]). Different components of the immune system target particular types of invading parasites and these responses vary in their degree of specificity (Box 1). Therefore, the strength of an immune-mediated interaction among co-infecting parasites can depend on the type of immune response solicited and the degree of cross-reactivity among parasites.

Within-host parasite networks differ from free-living communities in at least one important way. Species in free-living food webs that are separated by more than one trophic level do not typically interact directly, but are mediated through links in the food chain (e.g. a trophic cascade [29,30]). However, in parasite networks, the basal (host resources) and top (immune system) trophic levels are inextricably linked because they are components of the

Table 1. Examples of within-host parasite interactions

Interaction type	Details	Example	Refs
Direct			
Negative	Interference competition (e.g. for space) between species sharing a similar physical location	Establishment and egg output of the barber pole worm *Haemonchus contortus* is reduced by concomitant sheep stomach worm *Ostertagia circumcincta* infection, owing to changes in GI tract physiology	[40]
Positive	Mechanical facilitation	Feeding action of the fish louse ectoparasite *Argulus coregoni* increases susceptibility to the pathogenic bacterium *Flavobacterium columnare*	[41]
Indirect			
Negative	Resource competition (bottom-up interaction)	In the tea tortix *Adoxophyes honmai (Adho)*, competition with *Adho* nucleopolyhedrovirus for host resources dramatically reduces *Adho* entomopoxvirus replication and growth	[42]
	'Apparent competition' (top-down interaction) between antigenically similar parasite species	Cross immunity of the nematode *Graphidium strigosum* from acquired resistance of the hairworm *Trichostrongylus retortaeformis* in wild rabbits *Oryctolagus cuniculus*	[5]
Positive	Immuno-suppression	Infection with the nematode *Heligmosomoides polygyrus* leads to increased parasitemia, host mortality and lower vaccine efficacy of the malarial parasite *Plasmodium chabaudi* in mice *Mus musculus*	[43,44]
	Th1–Th2 tradeoff (Box 1)	*Onchocerca volvulus* (the causative agent of African river blindness) can inhibit immune responses to the TB bacterium *Mycobacterium tuberculosis* via the Th1–Th2 tradeoff in humans	[45]

Box 2. An example of the within-host parasite community network: parasites of humans

Humans, particularly in the developing world, can be co-infected with a variety of deleterious parasites: ~40.3 million people are currently infected with HIV/AIDS [50], >33% of the population worldwide has TB [51], and >25% has soil-transmitted helminths (e.g. *Ascaris*, *Ancylostoma*, or *Trichuiris*) [52]. Here, we present a subset of human parasites in a within-host community network (Figure I). This approach enables predictions of the broader consequences of single-parasite treatment programs and provides evidence for coordinated multi-parasite treatment strategies (Box 3).

Malaria (*Plasmodium* spp.) versus lymphatic filariasis (*Wucheria brancrofti*)

Spatial GIS analysis demonstrates reciprocal negative associations between the prevalence of *Plasmodium* spp. and *Wucheria brancrofti* [(a) in Figure I], owing to internal factors (e.g. within-host immune-mediated competition) or external factors (e.g. vector distribution) [53].

Between helminths

Hookworm *Ancylostoma* spp. interact synergistically with other soil-transmitted helminths (e.g. *Ascaris lumbricoides* and *Schistosoma mansoni*) [(b) in Figure I]. These species co-occur more often then expected [54], owing to immune modulation or reduced cellular activity during helminth co-infection [55]. Conversely, *A. lumbricoides* and *S. mansoni* interact antagonistically, with decreased worm intensities during co-infection, possibly through a general anti-helminth immune response [54].

Malaria (*Plasmodium* spp.) versus helminths

Plasmodium infection in children can be significantly increased and more virulent owing to concomitant infection with soil-transmitted helminths [56,57], and malaria is frequently associated with heavily *S. mansoni*-infected children [58] [(c) in Figure I]. These interactions affect the ability of the host to mount long-term immunity. Helminths elicit a non-cytophilic (non-cellular) antibody response comprising immunoglobulins IgG2, IgG4 and IgM, whereas effective malaria responses are driven by cytophilic (cell-associated) responses, which elicit the dominate antibodies against bacterial and viral antigens (IgG1 and IgG3) [56].

HIV/AIDS versus soil-transmitted helminths

Helminth infections can cause chronic immune activation and skew the immune response to upregulate the Th2 response [59]. HIV has higher rates of infection and replication within Th2 cells, such that gastrointestinal helminth infection can increase the likelihood of HIV infection, and can quicken the rate of clinical disease progression and mortality [60] [(d) in Figure I].

Helminths versus TB (*Mycobacterium tuberculosis*)

Schistosoma mansoni and soil-transmitted helminths stimulate the Th2 immune profile and IgE antibody levels, which can stimulate reactivation of latent TB infections and disease expression [61] [(e) in Figure I].

HIV versus all other parasite species

HIV infection specifically targets and depletes CD4+ cells, compromising the host immune response [50,61] and leading to a bottom-up indirect interaction (resource competition). This illustrates the physical connection of basal and top network levels to host fitness [(f) in Figure I].

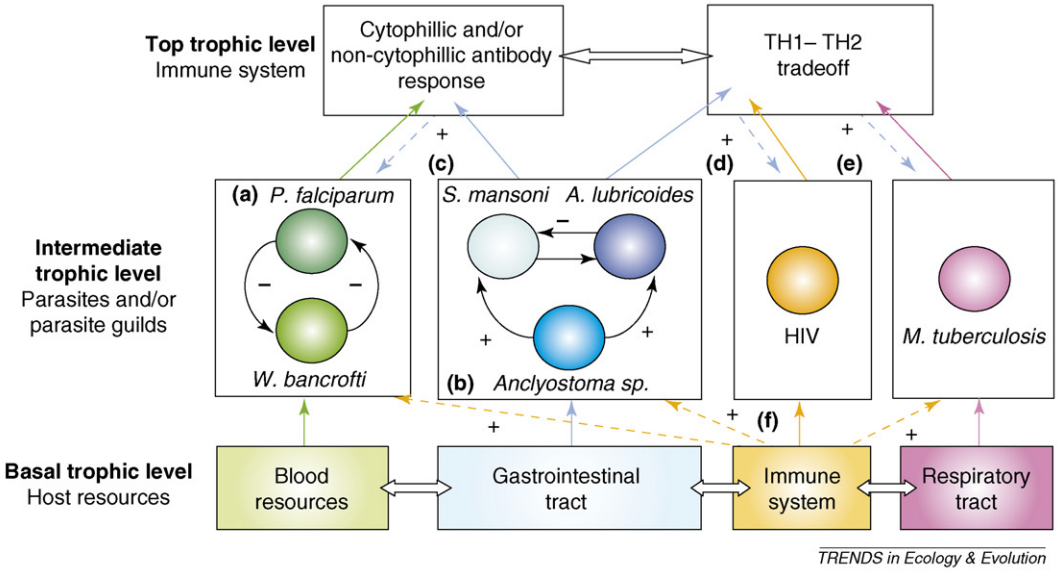

Figure I. A simplified human–parasite community interaction network. Following the schematic of the hypothetical interaction network (Figure 1, main text), we present a subset of the community of human pathogens and their interaction network within an individual host. The basal level represents specific host resources, and the bidirectional white arrows between resources illustrate the link between each component and host fitness. The colored arrows represent the flux of energy from host to pathogens, the intermediate level of the network, whereas the dashed arrows represent a bottom-up, or resource-mediated interaction. Direct interactions between parasites within a guild (boxes) and between guilds are represented by the black arrows. The top level, host immune response, is represented by two components (antibody responses and Th1–Th2 tradeoffs) that differ in their specificity. Top-down (immune-mediated) indirect interactions between parasites are illustrated by solid colored lines from one parasite to the immune response, and the reciprocal dashed colored line indicates the parasite that is affected by the interaction. The effect of the interactions is denoted by +/–. The labels (a)–(f) refer to the coordinated multi-parasite treatment strategies that are discussed in the box text.

same host individual. For example, red blood cells (at the basal level) and white blood cells (at the highest level) both originate from the same stem cell population. As a result of this direct link between the top and bottom trophic levels, failure of one component can severely compromise the entire network and, thus, host fitness.

Applying tools from community ecology to analyze parasite community ecology interaction networks

Network analysis techniques applied to community ecology have shown that community stability is determined by the distribution and strength of interactions within a network [31–33]. The structure of free-living

communities is often characterized as 'scale-free', where most species interact weakly via long indirect pathways, but a few species act as 'hubs', interacting with many species [14,15]. Recent analyses have shown that these scale-free networks are more stable to perturbations than are randomly assembled networks [15,34], although the removal of one highly connected 'keystone' species can significantly compromise community stability [35]. Empirical studies of parasite communities at the population level often conclude that most pair-wise interactions between species are weak and, thus, are not important in structuring parasite communities [6,36,37]. However, analyses of community ecology interaction networks suggest that it is precisely these weak, indirect interactions that are crucial for maintaining community stability. Although this seems encouraging, in terms of the robustness of parasite communities to small perturbations, broad-scale parasite species removal through disease control programmes could increase mean interaction strengths, potentially destabilizing the community [34]. This instability could lead to unpredictable consequences for other, co-infecting parasite species.

Recently, analytical tools developed in community ecology have demonstrated that network topology has important implications for determining how a community will respond to species removals. For example, Ebenman and Jonsson [22] describe how community viability analysis (CVA) can quantify the risk of secondary species loss following removal of a given species from a community. Applying CVA to within-host parasite communities would enable predictions of how co-infecting parasite species will respond to a focal species removal through a disease control programme.

One major difficulty with describing within-host parasite communities is how to estimate interaction strengths. There are several analytical tools in community ecology that enable interaction strengths and network structure to be determined from a range of semi-quantitative and qualitative data. Gotelli and Ellison [19] used experimental manipulation of species abundance and 'path analysis' [28] to fit competing models of network structure statistically to macroinvertebrate abundance data of pitcher plant communities. Similarly, for within-host parasite communities, experimental manipulations of parasite abundance would provide an estimate of *per capita* impacts of the focal species on other species in the network. As such, disease control programmes of humans or domestic animals can provide a useful starting point (Box 2). These programmes are the equivalent of large-scale ecological manipulations where a targeted parasite taxon is removed from the community. Ideally, subsequent monitoring programmes would measure the response of both the target parasite species as well as other, co-infecting parasite species. Different *a priori* models of community structure, possibly based on laboratory studies of interspecific pairwise associations, could then be tested against these data to determine the best-fitting description of the parasite community. Similar model-fitting approaches have been used in analyses of plant communities to determine the intensity and importance of interspecific interactions even within non-manipulated communities [38]. Applying such an approach to within-host parasite communities would enable testable predictions of how indirect interactions affect the dynamics of each component species within the community.

Finally, if interaction strengths cannot be estimated from the data, techniques exist in community ecology that provide insight into the response of the community to perturbations. These qualitative approaches, such as 'loop analysis' [39], specify potential interspecific interactions in terms of direction alone (i.e. +/0/−). A community matrix can be constructed between all species pairs, and matrix stability and species-specific responses to a perturbation can be measured. These analyses also can highlight potentially unpredictable responses where further empirical work should be directed [39]. In addition, 'fuzzy cognitive maps' [21] have recently been used for ecological communities, and can also be applied to within-host parasite communities. These matrices weight qualitative interactions by their relative strength (e.g. incorporating the degree of immunological cross-reactivity between parasite species), and loop analysis can then be used to determine the probable response of each parasite species to the invasion or removal of a co-infecting parasite.

Conclusions and future directions

The interactions of co-infecting parasites within individual hosts will have profound effects on host fitness, parasite transmission and the response of target and non-target parasite species to imposed control strategies. If we are to make progress in controlling infectious diseases, we need to continue to expand from the one-host–one-parasite framework and consider the potentially complex dynamics of multi-host–multi-parasite communities. Currently, parasite community ecology studies focus on host population-level data to infer interactions among parasites. This approach does not provide insight into the within-host mechanisms underlying the observed patterns (i.e. direct or indirect interactions, mediated by resources or the immune system). The ultimate consequences of these mechanisms are likely to be highly nonlinear owing to the combination of various density-dependent, possibly time-lagged direct and indirect interactions throughout the parasite community ecology network. Without an understanding of these mechanisms, we cannot predict the overall effect of parasite removal or addition to the fitness or the growth of the host and transmission of other co-infecting parasites. Therefore, although parasite community ecology studies have provided much information about the broader patterns of parasite community structure, many key questions remain (Box 3).

Many of these key questions relate to how the within-host parasite community will respond to perturbations (e.g. parasite species removal through disease control programs or the invasion of novel parasites into existing communities). As such, they can be addressed by applying the tools from community ecology described earlier that explicitly enable predictions of the response of ecological communities (either free-living or within-host) to perturbations, even in the absence of quantified estimates of interaction strengths. Ultimately, however, we need to move from simply observing parasite communities to

Box 3. Future directions and outstanding questions

Can we predict the impact of a control programme on non-target parasites?
Within-host interspecific parasite interactions will alter both the efficacy of treatment programmes and the impact on other co-infecting parasites [5]. Therefore, understanding the mechanisms underlying interspecific interactions can change the focus of disease control programs, and reveal novel avenues of research. For example, a single oral dose of an antihelminthic (US$0.02) might reduce susceptibility to HIV and progression to AIDS [60], as well as decrease the burden of childhood malaria infections [56]. Alternatively, relatively benign parasites might be able to suppress more pathogenic parasites (e.g. phage therapy [62]).

How does parasite community structure affect individual parasite fitness?
Interspecific interactions can be dynamic and density dependent, such that the abundance of one parasite affects the fitness of a co-infecting species. If interactions are immune mediated, the effect of the interaction might be lagged in time, and can depend on the condition of the host. Therefore, models of parasite evolution or host–parasite coevolution should consider feedback between co-infecting species created by within-host interactions.

How does parasite community diversity affect the invasibility of a novel pathogen?
A major question in community ecology is how community complexity affects its stability and resilience to invasion [63]. Similarly, a key question for parasite community ecology is whether parasites can invade existing communities, resulting in host shifts and the emergence of novel infectious disease. If we understand within-host interactions, we could predict which interactions affect parasite invasion and how certain parasites can affect their rate of spread.

How does parasite community composition affect host fitness?
Interspecific interactions can change the within-host parasite community, affecting host population size and dynamics. For example, increases in TB infection might have driven the decline in leprosy by reducing the cell-mediated response associated with controlling leprosy and TB infection, leading to a faster disease progression and death in leprosy-infected individuals [64].

How do parasite interactions affect the host's immune response to mixed infections?
Within-host parasite interactions can affect the ability of the host to produce a lasting immune response. For example, the differences in dynamics of HIV infection between developed and undeveloped countries might be due to chronic immune activation in places where humans suffer from consistent infection with diverse parasites throughout life [60,61].

conducting the necessary large-scale field experiments that will provide insight into the mechanisms driving relationships between co-infecting parasite species. It is only then that we can make real progress in reducing the burden of disease around the world.

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