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Transmission consequences of coinfection: cytokines writ large?

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Coinfection of a host by multiple parasite species is commonly observed and recent epidemiological work indicates that coinfection can enhance parasite transmission. This article proposes an immunoepidemiological framework to understand how within-host interactions during coinfection might affect between-host transmission. Cytokines, immune signalling molecules with a fundamental role in the amplification of antiparasitic effector mechanisms, provide a useful way to simplify immunological complexity for this endeavour – focusing on cytokines offers analytical tractability without sacrificing realism. Testable predictions about the epidemiological consequences of coinfection are generated by this conceptual framework.

Extrapolating from the individual to the population

Understanding how within-host processes influence between-host transmission represents a major challenge in parasite ecology and applied biomedicine [1–5]. Coinfection (see Glossary) makes this even more of a challenge given the complex interactions that are often observed when multiple parasite species infect a single host [6–13]. Alterations in disease severity because of coinfection have recently been reviewed [14,15] and debated [16–18] in *Trends in Parasitology*, and detailed immunological interactions have also been examined [8–10]. The complementary aim of this article is to explore how processes within the coinfected host affect the transmission of parasites from one host to the next.

Epidemiological evidence indicates that parasite transmission can be strongly affected by coinfection. For example, over a fifteen year period in Kisumu, Kenya, nearly a million excess malaria cases (10% of the total) have been attributed to HIV coinfection; during the same time frame, malaria-attributable HIV infection was estimated at 5% [19]. Increased malaria prevalence in HIV-positive hosts might be due to increased susceptibility to malaria [20] and/or a tendency to sustain high parasite densities [21]. Such observations have led to the suggestion that bednets or other malaria prophylaxis might be best used by HIV-positive adults [22]. Malaria transmission potential could also be enhanced by helminth coinfection because gametocyte density reportedly increases with the number of helminth species that are present within the host [23].

Cytokine biology might provide a useful framework in which to understand the impact of coinfection upon parasite transmission. Cytokines work as a common currency underlying a myriad of immune transactions, including the selection of immune effector mechanisms. By reducing the complexity of an immune response to a few simple measures, the focus on cytokines proposed here might enable integration of detailed immunological investigations at the individual level with ecological and epidemiological studies at the population level. Such linkage across scales – which is intractable without simplifications – could be crucial to understanding disease emergence and developing effective measures of control [4].

A cytokine-based approach to coinfection

Cytokines are secreted signalling molecules that, in concert with membrane-bound molecules, enable communication among cells of the immune system during both innate and adaptive responses to infection [24]. Cytokines

Glossary

Basic reproductive number (R_0): the standard measure of parasite transmissibility. This measures the average number of secondary cases caused by a typical infectious individual in a completely susceptible population.
Coinfection: simultaneous infection of a host by two or more parasite species.
Duration of infection: see Infectious period.
Infectious period: interval of time during which an infected host is shedding infectious stages of a parasite or is capable of transmitting the parasite to susceptible hosts.
Infectiousness: a property of an infected host. This indicates the relative likelihood of transmitting the parasite to other host individuals.
Intensity of infection: a measure of the parasite burden of an infected host. Typically, this will vary over the course of the infection and might be related to the infectiousness of the host.
Species jump: transmission of a parasite from one host species into another, typically novel, host species.
Superspreader: a highly infectious individual who transmits a parasite to an extraordinarily large number of susceptible hosts (for a precise mathematical definition, see Ref. [49]).
Susceptibility: a property of an uninfected host. This indicates the relative likelihood of becoming infected by a parasite, given exposure to a potentially infectious dose.
Transmission: a population-level process that integrates the susceptibility and infectiousness of the individual members and their contact rates.

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are particularly important for the polarisation [24,25] and amplification [26] of immune responses. As a result, these signalling molecules help to determine which effector mechanisms are employed. For example, T helper (Th)1 cytokines such as interferon (IFN)-γ, Interleukin (IL)-12 and tumor necrosis factor (TNF)-α promote mechanisms (e.g. oxidative bursts or phagocytosis) that control microparasitic infections (i.e. viruses, bacteria, fungi or protozoa) [25,27,28]. Th1 cell activity might be complemented by the recently discovered IL-17 producing Th cells (Th17), which are thought to be involved in the clearance of extracellular microparasites [29]. By contrast, Th2 cytokines such as IL-4, IL-5 and IL-13 promote mechanisms (e.g. mucus secretion, noncytophilic antibody production, eosinophilia or collagen deposition) that fight macroparasitic infections (primarily helminths) [25,27,28]. To prevent the harm that cytokines can do when produced in excess – as recently highlighted by the 'cytokine storms' that threatened the lives of volunteers in an immunotherapy study in London [30] – immunomodulatory cytokines such as transforming growth factor (TGF)-β and IL-10 work to reduce the magnitude of immune responses [31,32]. The influence of cytokines on effector responses is so powerful that many parasites manipulate host-cytokine pathways for their own benefit: TNF-α pathways are exploited by diverse microparasites [33] and TGF-β pathways might be used by macroparasites [34].

For coinfection studies, cytokines offer a functionally relevant, measurable way to simplify the great diversity of cells, molecules, actions and interactions of the vertebrate immune system. Although new immunological cytokines are discovered each year (IL-31 [35], IL-32 [36] and IL-33 [37] are among the latest additions), their functions tend to align with previously described cytokines. A further simplifying advantage of focusing upon cytokines is that their roles are robust across host–parasite systems [24]. In addition, cytokines are readily measurable: for example, in serum or in supernatants of cultured peripheral-blood mononuclear cells. Because cytokines tend to activate effectors rather than attacking parasites directly, the relationship between cytokines and parasite killing is often correlational. For example, in the field, high Th2 cytokine concentrations correlate with rapid expulsion of helminths [38]. Still, such correlations are useful, given that cytokines are more easily measured in live hosts than system-specific downstream effector mechanisms, and yet remain predictive of effector efficacy.

Crossregulation among the suites of cytokines that shape the four major arms of functional immunity – Th1, Th2, Th17 and immunomodulation [39] – is central to understanding immune responses during coinfection. For example, mutual inhibition precludes full Th1 and Th2 responses at the same time and place [27,28] and can impair simultaneous control of microparasites and macroparasites [40–42]. By contrast, when parasite species are cleared by the same effector mechanisms, cytokine responses to one might enhance clearance of the other [43,44]. These interactions occur because cytokines are prone to generating 'bystander' effects, whereby immune responses induced by one antigen or cell type also affect other antigens or cell types [24]. Bystander effects are often thought to be the root cause of alterations in parasitaemia in controlled coinfection experiments [7–10]. Thus, just as polymorphisms at loci that encode cytokines (e.g. IFN-γ [45] or IL-13 [46]) genetically affect the risk of infection, cytokines that are induced by a coinfection can phenotypically alter host resistance to a second parasite species.

As for single-species infections, the efficacy of parasite killing or expulsion during coinfection arises from downstream effects of cytokines on the effector mechanisms that target the parasites in question. For example, the failure of helminth-infected hosts to control lymphocytic choriomeningitis virus replication has been directly attributed to changes in the resistance of hepatocytes to viral infection, which in turn is determined by the cytokine milieu of local liver tissue [41]. Alternatively, poor control of malaria replication can result from helminth-induced changes in the cytokine milieu in which B cells are instructed to produce antibodies: the resultant changes in malaria-specific antibody isotype bias can reduce the efficacy of both primary [42] and vaccine-induced protective immunity [47]. Crucially, the exact downstream details differ greatly from one pair of coinfecting parasites to the next [8–10]. Upstream, cytokine responses are more stereotypical in the face of both parasite and host diversity [24].

Therefore, cytokine data provide a balance between realism and tractability that might prove useful to understanding a broad spectrum of coinfections. When the taxonomic identities of parasites are replaced with their cytokine signatures, for example, it becomes possible to predict the within-host consequences of coinfection for microparasite replication (A. Graham, unpublished). Cytokine data can also be used to predict the transmission of viruses from one cell to another [48]. The next challenge is to 'bridge the gap' between immunology and epidemiology [4] and examine whether within-host cytokine interactions during coinfection are predictive of between-host transmission.

Cytokine interactions as predictors of parasite transmission

To dissect how processes at the individual level scale up to influence population dynamics of parasite transmission, it is useful to break transmission into its component parts (see Glossary). Susceptibility is an individual trait that describes the likelihood that a given dose of parasites will establish and cause infection in that host. Infectiousness of an individual host describes the efficiency with which that individual infects other hosts. All else being equal, infectiousness tends to increase with infectious period and/or intensity of infection. Transmission is a population-level process that integrates the susceptibility and infectiousness of individual hosts within the spatial or social context that underlies host-contact patterns.

The magnitude and type of cytokine response influence host susceptibility and infectiousness. Susceptibility to a given parasite will be affected by cytokine responses that are ongoing at the time of exposure, including responses to pre-existing infections. Infectiousness, however, might depend on the dynamic cytokine response over the course of the coinfection. For example, a pre-existing macroparasite infection that induced high concentrations of Th2

Table 1. Proposed effects of a pre-existing infection on the transmission of an incoming infection

		Does the pre-existing infection induce immunosuppression?[a]	
		Yes[b]	**No**[b]
Is the incoming infection cleared by the same effector mechanisms as the pre-existing infection?[a]	**Yes**[b]	1. Transmission decreased slightly[c] Correct effector mechanisms reduce susceptibility and/or infectiousness	2. Transmission decreased Correct effector mechanisms reduce susceptibility and/or infectiousness
	No[b]	3. Transmission increased Incorrect effector mechanisms combine with immunosuppression to boost susceptibility and/or infectiousness	4. Transmission increased slightly[c] Incorrect effector mechanisms boost susceptibility and/or infectiousness

[a]For example, through any mechanism downstream of the cytokines that is induced by the pre-existing infection.
[b]These classifications represent endpoints of what are likely to be continua.
[c]The net outcome in these scenarios depends on the relative strength of immunosuppression versus effector polarisation, as described in the text.

cytokines could simultaneously reduce the probability of intestinal nematode establishment (i.e. susceptibility) and both the intensity and duration of infection (i.e. infectiousness) [38]. However, because of mutual inhibition between Th1 and Th2 cytokines, the hosts that are most resistant to nematodes might have impaired effector responses against subsequent microparasitic infections. The result is likely to be greater susceptibility to microparasite coinfections and, possibly, greater infectiousness because of high intensity of infection and/or delayed microparasite clearance. If immune polarisation eventually shifts towards Th1 in response to the new infection, then the period of enhanced infectiousness could be brief.

A simple classification scheme might be used to outline the potential influences of cytokines on the transmission of coinfections. There are four main scenarios by which cytokines might mediate interactions among parasite species and affect the transmission potential for an incoming parasite species (Table 1). These scenarios are based on whether the incoming parasites are cleared by the same effector mechanisms as the pre-existing parasites (e.g. Th1 versus Th2) and whether pre-existing parasites induce immunosuppression (e.g. immunomodulatory cytokines). These classifications represent extreme endpoints of what, in reality, are probably continua. Each scenario leads to a prediction regarding the transmission of the incoming parasite species.

Crucially, coinfections can lead to positive covariation between the infectiousness and susceptibility of individual hosts. The result is inflation of the basic reproductive number of the parasite and, thus, increased likelihood of successful establishment in a host population (Box 1). For example, scenario 3 in Table 1 represents an incoming parasite that infects an immunosuppressed host that is also predisposed to the wrong effector mechanisms. The expected result is increased susceptibility to the incoming infection, in addition to increased infectiousness (provided the combined infections do not kill the host). Consequently, coinfection increases the reproductive number for the incoming parasite species and facilitates its transmission through the host population (Box 1). By contrast, scenario 2 of Table 1 represents a host that is not immunosuppressed and whose cytokine milieu makes it predisposed to mount an effective response to the incoming parasite. The resulting prediction is that coinfected hosts will be relatively resistant to the second species and transmission will be decreased. In ecological parlance, these interactions among parasite species span from 'apparent competition' (scenario 2) to 'facilitation' (scenario 3). However, unlike interactions among free-living consumers, these interactions are mediated by the immune system of the host.

In scenarios 1 and 4 of Table 1, the net effects of coinfection depend on the relative strengths of immunosuppression and effector synergy, in addition to any dynamic changes in the cytokine response over the course of infection. In scenario 1, for example, decreased susceptibility to the incoming infection because of the presence of appropriate effector mechanisms could be offset by increased susceptibility because of immunosuppression. In all cases, however, coinfection might alter host susceptibility and infectiousness, thereby altering probability of parasite establishment, rate of transmission, and persistence in the host population (Box 1).

Testable predictions emerge from this conceptual framework. Consider, for example, an incoming bacterial infection for a host that has pre-existing chronic helminthiasis (thus placing the host in scenario 3) versus acute protozoal infection (scenario 2). The prediction from Table 1 – that chronic helminth coinfection would increase bacterial transmission, whereas protozoal coinfection would decrease it – could be tested in several ways. For example, researchers could test for correlations between coinfection status and individual-level transmission data, as collected in retrospective contact-tracing studies [49]. Alternatively, in prospective studies, blood samples could be collected to detect how cytokine profiles correlate with susceptibility, infectious period and infection intensity (although correcting for background variation among hosts could be a challenge). Alongside the clinical and immunological parameters that are measured in well-designed field studies (see Ref. [50] and review in Ref. [5]), perhaps parameters that are relevant to transmission, such as viraemia or helminth eggs per gram of faeces, could be measured.

More direct tests of the predictions in Table 1 could be conducted using randomized experiments. At the population scale, for instance, broad-spectrum anthelmintics or antibiotics could be used to eliminate certain classes of pre-existing infection in randomly selected wildlife or livestock populations, then epidemic parameters (e.g. growth rate, final outbreak size or even transmission potential) for other parasites could be compared for treated and control populations. At the individual scale, infectious dose and transmission experiments for 'parasite 2'

Box 1. Coinfections can alter the odds of disease emergence

Immune-mediated interactions among parasites might influence the likelihood of disease emergence in a host population. Consider a host population in which a given infection, parasite 1, is established at prevalence p, where $0 < p \leq 1$. How might the prevalent infection influence the invasion of a second infection, parasite 2?

As a simple model of this situation, the host population is divided into two groups: individuals infected by parasite 1 and uninfected individuals. Let f be the relative susceptibility to parasite 2 of individuals infected by parasite 1. That is, given exposure to parasite 2, the probability that the individual becomes infected by parasite 2 is multiplied by f if they are already infected by parasite 1 (so $f > 1$ indicates increased susceptibility, $0 < f < 1$ indicates reduced susceptibility, and $f = 1$ indicates no effect of coinfection). Similarly, let φ be the relative infectiousness (with respect to parasite 2) of individuals already infected with parasite 1. Changed infectiousness could arise from changes in infection intensity, infectious period, frequency of contact with uninfected hosts or efficiency of shedding.

All factors that influence transmission of an infection combine to determine its basic reproductive number R_0, which is defined as the expected number of secondary cases that are caused by a typical infectious individual in a wholly susceptible population. The value of R_0 strongly influences the epidemiological dynamics of an infection and if $R_0 < 1$ the infection is unable to invade. If parasite 2 has reproductive number $R_{0,2}$ in a population that is unaffected by parasite 1, then its reproductive number in a population that is affected by parasite 1 (which we denote $R_{0,2/1}$ or 'R_0 of parasite 2, given parasite 1') is (Equation I) (see Ref. [63]):

$$R_{0,2/1} = (1 - p + p\, f\varphi)R_{0,2} \qquad \text{[Eqn I]}$$

Figure I shows variation in $R_{0,2/1}$ with p, f and φ, with the resulting probability of successful invasion of parasite 2 into a host population affected by parasite 1. Invasion probability depends strongly on the prevalence of parasite 1, particularly when $R_{0,2/1}$ is near the threshold value of 1. This indicates that the influence of coinfections on emergence risk can vary greatly because of fluctuations or cycles in the epidemiology of parasite 1. Qualitative effects of coinfection on susceptibility and infectiousness are predicted in Table 1 for our four main scenarios of interaction. Precise values of f and φ for any particular system will depend on the dynamic time course of immune interactions, the relative strength of immunosuppression and cytokine polarisation, and other biological details.

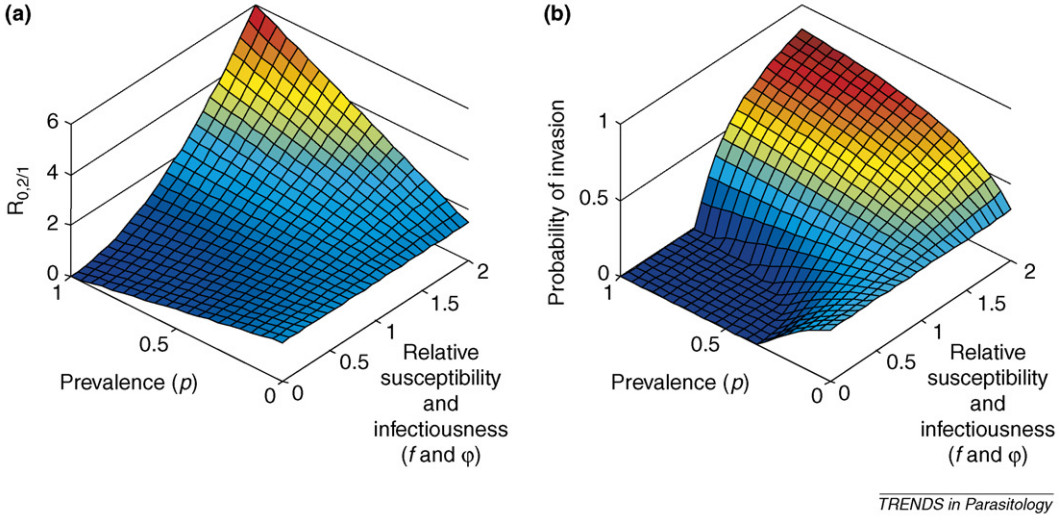

Figure I. Coinfection can alter the basic reproductive number and probability of invasion of parasites. Reproductive number (a) and probability of invasion (b) for parasite 2 in the presence of coinfecting parasite 1. In these figures $\varphi = f$, so the influence of coinfection on susceptibility and infectiousness is assumed to be the same, although generally they can differ. The reproductive number for parasite 2 in the absence of coinfection is $R_{0,2} = 1.5$. The probability of invasion represents the chance that introduction of a single infectious case will cause a major outbreak of parasite 2. When $R_{0,2} \leq 1$ there is no chance of successful disease invasion and when $R_{0,2} > 1$ the invasion can fail because of stochastic die-out when the number of infected individuals is small. The invasion probability is calculated as $1 - 1/R_{0,2/1}$ as appropriate for an infection with exponentially distributed infectious period and a single index case [63].

could be conducted for animal subjects stratified into three groups: one group infected with 'parasite 1', one with cytokines that have been artificially manipulated to mimic immune responses to 'parasite 1' (e.g. viral infection of constitutively IL-4 producing mice [51] to mimic helminth coinfection) and one control group. Clinical trials for cytokine-blocking drugs (such as those analysed in Ref. [52]) present an opportunity to address similar questions in humans – for example, a test of the direct influence of cytokines on transmission in a controlled setting by comparing epidemiological data for naturally circulating parasites in the treatment and control groups of the study.

As with any simplification of a complex natural system, there are certain phenomena not included in the framework of Table 1. Foremost, system specificities such as anatomical sites of infection, routes of transmission or direct involvement of pathology (e.g. anaemia [23]) are likely to be key determinants of the transmission consequences of certain coinfections. In addition, immune response magnitude might have complex implications for transmission. Just as immunosuppression could boost infectiousness by increasing the duration and intensity of infection or reduce it by causing host death, immunopathology has the potential to enhance or reduce parasite transmission [53] because excessive cytokine responses can kill both hosts and parasites [32]. Moreover, important epidemiological consequences could arise from genetic recombination among coinfecting bacterial [54] or viral [55] species. Notwithstanding such complexities, the simple framework proposed here is a step towards generating testable predictions regarding coinfections based on the ability of cytokines to affect host susceptibility and infectiousness. Framing and testing immunoepidemiological predictions is a crucial step towards understanding how the immune system operates in natural populations [4].

Impact of host heterogeneity on immunity to coinfection

Immune responses depend on many host characteristics, such as age, breeding status and gender, and these factors have demonstrable effects on immunity in laboratory conditions and in the wild [56]. Although the influence of heterogeneity in each of these traits can be studied in isolation, in empirical systems or using mechanistic theoretical models, a more general (and hence simpler) formulation of the influence of host heterogeneity on transmission of coinfections is outlined in Box 2. A typical consequence of host heterogeneity is a highly aggregated distribution of parasites within the population, such that a minority of hosts carry the majority of parasites. This pattern is sometimes simplified to the so-called 20/80 rule, whereby 20% of the host population usually contribute 80% of the transmission events [57,58]. If these heavily parasitized individuals also experience the majority of coinfections, then immune-mediated interactions like those in Table 1 could lead them to become either highly infectious superspreaders [49] or effective dead-ends for transmission.

Box 2. Coinfections as a source of host heterogeneity

The consequences of host heterogeneities for epidemic dynamics have received attention for vector-borne [57,64], sexually-transmitted [57] and directly-transmitted [1,49] single-species infections. Box 1 includes a simple binary scheme of heterogeneity induced by coinfection, which distinguishes only whether hosts carried parasite species 1. In practice, however, the susceptibility and infectiousness of hosts exposed to parasite species 2 are likely to follow some distribution that is determined by the duration and intensity of the infection by parasite 1, in addition to many other factors. For example, heterogeneity in worm burden within a host population can correlate with quantitative variation in the immune response of hosts that might affect subsequent infections [3,15]. The consequences of coinfection can be studied by first considering the variation in host characteristics that are generated by parasite 1 (through any of the mechanisms discussed in the main text) and then, borrowing from the literature on single-species infections, asking how that variation is reflected in the epidemic dynamics of parasite 2.

As an illustrative example: consider a directly-transmitted parasite with mean transmission rate $\bar{\beta}$ and mean recovery (or disease-induced mortality) rate $\bar{\gamma}$. In the absence of heterogeneity, the basic reproductive number, R_0, would be $\bar{\beta}/\bar{\gamma}$ [63]. However, heterogeneities in transmission and recovery rates will change this according to the so-called moment expansion (a Taylor expansion about the mean [65]) (Equation I):

$$R_0 \approx \frac{\bar{\beta}}{\bar{\gamma}} + \frac{\bar{\beta}}{\bar{\gamma}}\mathrm{cv}(\gamma)^2 - \frac{1}{\bar{\gamma}^2}\mathrm{cov}(\beta,\gamma) \qquad \text{[Eqn I]}$$

where cv() represents the coefficient-of-variation and cov() the covariance. Thus, in a heterogeneous population, R_0 is larger when there is variation in the recovery rate and the transmission and recovery rates are negatively related (i.e. individuals that shed more are infectious longer) (Figure I).

The figure illustrates the consequence of such heterogeneity for a parasite with an arbitrary $\bar{\beta} = 1$ and $\bar{\gamma} = 1$. In the absence of heterogeneity (i.e. the star), R_0 would be 1. Coinfection might generate heterogeneity in recovery rate and, thus, inflate R_0 if coinfected individuals have more prolonged infections. Mildly immunosuppressive infections could increase transmission and slow recovery and, therefore, induce negative covariance and higher R_0. By contrast, strongly immunosuppressive infections might induce a positive covariance between high transmission rates and rapid host mortality and, hence, a reduction in R_0 (the light-shaded area). Note that even moderate heterogeneity induced by coinfection can double R_0 and increase the likelihood of emergence.

This example explores the influence of host heterogeneity upon infectiousness only. In relation to Box 1, a given individual's values for β and γ will determine their infectiousness, φ. Coinfection induced variation in susceptibility, f, can be studied in a similar fashion [66].

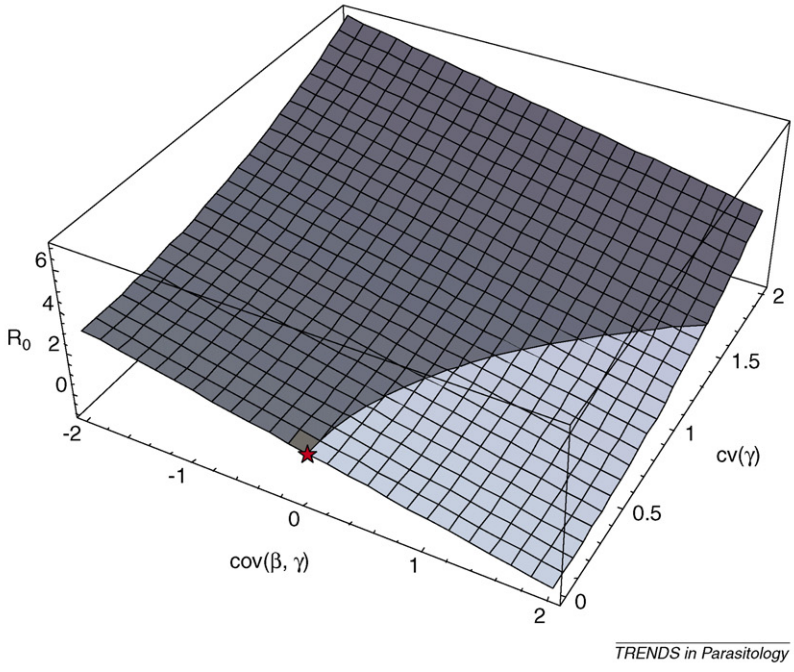

Figure I. Host heterogeneity and the epidemic potential of coinfections. Covariance (cov) between transmission (β) and recovery rate (γ) and the coefficient of variation (cv) of recovery rates (γ) determine the direction in which heterogeneities due to coinfection by parasite 1 alters R_0 for parasite 2. The star represents the case for homogeneous hosts, for which R_0 is assumed to be equal to 1 in this example. Under conditions of host heterogeneity (all points away from the star), R_0 alternatively reaches epidemic proportions (>>1) or is incapable of spreading in the population (<<1).

However, identifying how host heterogeneities affect parasite interactions and subsequent transmission dynamics of coinfection is not trivial. As an example, consider how seasonal infection with the myxoma poxvirus alters the immune response to the gastrointestinal nematode *Trichostrongylus retortaeformis* in a natural population of European rabbits. The intensity of *T. retortaeformis* infection is affected by host age, sex and breeding status [56] and the number of gastrointestinal coinfections (I. Cattadori *et al.*, unpublished and [13]). The intensity and duration of *T. retortaeformis* infection in myxoma-infected rabbits were consistently greater than in virus-negative hosts, which indicates that myxoma coinfection increases both host susceptibility and infectiousness for the nematode (I. Cattadori *et al.*, unpublished). Moreover, because of seasonal outbreaks of myxoma, hosts vary over time in susceptibility to both infections; this further boosts heterogeneity among hosts and, hence, disease persistence in the population (I. Cattadori *et al.*, unpublished and Box 2). These data indicate that to understand fully how immunity to coinfection shapes transmission, researchers must consider how cytokines are modified by spatiotemporal changes in host characteristics.

Therefore, demonstrating a linkage between individual-level causes and epidemic-level effects remains a daunting challenge. There is much work to be done. Realistic simplification of immunological mechanisms to inform mathematical investigations is just one step towards understanding the role of host immunoheterogeneity in the transmission of coinfections.

Concluding remarks

Hosts that are coinfected by multiple parasite species seem to be the rule rather than the exception in natural systems and some of the most devastating human diseases are associated with coinfections that challenge immune response efficacy [12]. However, there is still no consensus about how interspecific interactions among parasites shape their abundance, community structure or dynamics [59]. Cytokines are powerful immune drivers that help to determine susceptibility and infectiousness – properties of individual hosts that, in turn, might facilitate or impede between-host transmission and determine the population-level dynamics of coinfections. This article has explored potential cytokine-mediated consequences of coinfection for parasite transmission. A key emphasis has been on the need to examine processes across scales, from molecules to populations, using an integrated immunoepidemiological approach [4].

Understanding the epidemiological consequences of coinfection could lead to new recommendations for population-level control strategies. These include targeted distribution of bednets to HIV-positive people [22] and less-intensive selection of livestock for resistance to gastrointestinal helminths, if constitutively high Th2 responses [60] increase susceptibility to coinfecting microparasites. More generally, if coinfection status is a good predictor of infectiousness, then the framework proposed here could help to address the recognized challenge of identifying potential superspreaders for targeted control measures [49]. Another important forum for application of these insights is the interpretation of vaccine trials. In some settings, helminth coinfection reduces the efficacy of vaccines against microparasites [9] and coinfection-mediated effects on transmission could be potent confounders, if not accounted for, in those analyses.

Even moderate host heterogeneities introduced by coinfection can yield substantial epidemiological effects (Box 1 and Box 2). Coinfections could, thus, increase vulnerability to the emergence of new parasites by facilitating species jumps [61], if the coinfected portion of a population provides favourable conditions for an emerging parasite to adapt to a new host species [62]. These considerations warrant further research, particularly given current concerns about zoonotic emergence of human diseases. In summary, appropriate and cost-effective decision making in biomedicine arguably must take coinfection into account [12], both at the clinical level of the individual host [14,15] and at the epidemiological level of the population of hosts.

The issues addressed in this article open many channels for future research. In terms of the 20/80 rule [57], are the 20% of hosts who are transmitting 80% of a given parasite species disproportionally likely to be coinfected with other species? Coinfection has already been identified as a leading cause of superspreading events based on case reports for human diseases [49] but the within-host mechanisms that drive that effect are unknown. What factors determine the epidemiological consequences of cytokine dynamics over time during coinfection? How are our predictions altered when immunopathology has a key role in transmission or host mortality? More generally, what can be learned by pursuing the analogy between immunological interactions and principles of competition and facilitation from community ecology [62]? Addressing these questions will represent real progress towards the integration of immunology and epidemiology – a goal that is plainly necessary [4] but stubbornly elusive.

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