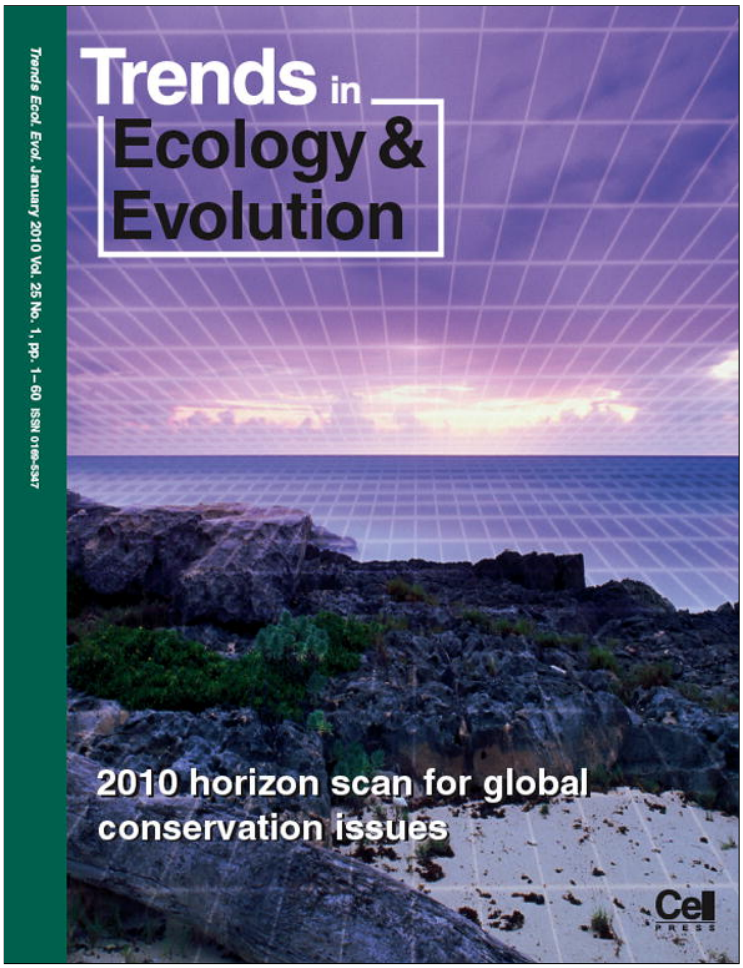

Opinion

Disease spread, susceptibility and infection intensity: vicious circles?

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Epidemiological models and studies of disease ecology typically ignore the role of host condition and immunocompetence when trying to explain the distribution and dynamics of infections and their impact on host dynamics. Recent research, however, indicates that host susceptibility should be considered carefully if we are to understand the mechanism by which parasite dynamics influence host dynamics and vice versa. Studies in insects, fish, amphibians and rodents show that infection occurrence and intensity are more probable and more severe in individuals with an underlying poor condition. Moreover, infection itself results in further deterioration of the host and a 'vicious circle' is created. We argue that this potential synergy between host susceptibility and infection should be more widely acknowledged in disease ecology research.

Variable host susceptibility: too important to ignore

Explaining and predicting the transmission, dynamics and distribution of infectious disease is fundamental to public health, animal husbandry and biological conservation. A key element, clearly, is host susceptibility: the more susceptible the hosts, the more rapid and widespread will be the spread of disease. Yet epidemiologists and disease ecologists have often neglected variation in host susceptibility. There can be sound practical reasons for doing so, but as we argue here, such neglect might also seriously hinder understanding of infection dynamics.

In particular, we illustrate the mechanism by which host susceptibility and disease can act in synergy, generating vicious circles at both the individual and population levels. Individuals in poor general physiological condition (see glossary) might be more susceptible to infections, which further weakens their condition, and so on. Populations in poor average condition might exhibit higher prevalences of infection, increasing the risk of further infections, with further deterioration in condition. This escalating polarisation between the sick and the robust could have important implications for the dynamics of disease and its impact on host dynamics.

Variations in host susceptibility have often been neglected in interpreting observational data. Observational studies can demonstrate associations but cannot establish causality. Yet, the interpretation of such associations has tended to see the pathogen as the putative cause and low survival or fitness as its effect. For example, an association between cowpox virus infection and lower survival in wild field voles (*Microtus agrestis*) has recently been demonstrated, at both the individual and population level [1]. This finding suggests that cowpox is having a detrimental effect on the animals. However, it is also possible that the voles that became infected were the ones in poorer condition, and, thus, would have had poorer survival even in the absence of cowpox. Hence, the dynamics of cowpox might in part be reflecting the dynamics of host condition. Similarly, Bewik's swans (*Cygnus columbianus bewickii*) naturally infected with low-pathogenic avian influenza virus have poorer migration performance compared to uninfected individuals of the same population [2], an association that might reflect harmful effects of the virus but could equally reflect increased susceptibility to infection in individuals in poorer condition (see also Refs. [3–5]). Indeed, the potential for misinterpretation in these studies could be compounded by detection bias; diagnosing the infection might be more probable in individuals in poor condition if they shed more pathogen particles or do so for longer. The possibility of

Glossary

Adaptive immune system: arm of the immune system (largely or entirely confined to vertebrates) that confers specific defences following pathogen exposure. This immunity is acquired after several days of initial exposure and is responsible for immunological memory (acquired immunity to previously exposed pathogens).
Co-infection: concomitant infection by more than one pathogen.
Condition: general physical and physiological status of a host. A measure of the aptitude of an individual for performing all those functions vital to its fitness. In human and veterinary medicine, it is usually measured using generic indices of health (e.g. from haematology or plasma biochemistry, or an even more general measure such as body-mass index, etc.).
Cross-immunity: phenomenon that results when the immune response exerted against one parasite is also effective against a different parasite, resulting in antagonistic interactions between parasites during concomitant infections.
Immunocompetence: ability of the immune system to counter and limit an infection.
Infection: invasion of a host by a parasite, followed by parasite proliferation or development. For the purposes of this article, no distinction is made between infection and infestation.
Infection intensity: number (concentration) of parasites infecting a host.
Infectiousness: capacity of an infected host to transmit the infection following contact with a susceptible host.
Innate immune system: arm of the immune system that confers nonspecific defences in the absence of previous pathogen exposure.
Parasite or Pathogen: in disease ecology, an organism (virus, bacteria, protozoan, helminth, etc.) that parasitizes a host. Here 'parasite' and 'pathogen' are used interchangeably.
Parasite aggregation: heterogeneity in the distribution of parasites among hosts in a population beyond what would be expected by chance alone (a random distribution). In aggregated distributions, most of the parasites of a given species are present in relatively few of the hosts.
Susceptibility: proneness to becoming infected and weakness to oppose infections; the opposite of resistance.

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lower fitness being a cause rather than a consequence of infection is generally acknowledged in these studies, but it is usually overshadowed by the general message that the lowered fitness is an effect exerted by the pathogens.

Neglect of variability in susceptibility might also result in erroneous interpretation of laboratory data, especially if these interpretations are used to draw conclusions about natural populations. Individuals from captive colonies are usually maintained in homogeneously good condition, an unparalleled experience to that of individuals in nature; and genotypic heterogeneity is also typically much greater in wild than in captive populations. It is not surprising, then, that a study using gypsy moths (*Lymantria dispar*) showed that heterogeneity in the susceptibility of the moths to a virus was much greater in feral populations than in laboratory reared larvae [6]; and that this difference resulted in dissimilar viral transmission dynamics. Also, a recent study on haematological dynamics in wild field voles showed that even when the highly variable red blood cell counts (one measure of condition) were at their highest in the field, they were lower than in voles kept in an animal house (abundant food and fewer pathogens) [7]. Clearly, it could be dangerous to assume that data on infection susceptibility from such laboratory-reared animals is relevant to natural populations.

Heterogeneity in susceptibility, and other related host characteristics, has also typically been neglected in theoretical studies. From the earliest attempts to model health problems [8–10], a strong emphasis has been placed on the role of contact between susceptible hosts and infectious agents (either other hosts or free-living infectious particles). When there is direct transmission between hosts, the rate at which susceptible individuals become infected is generally assumed to be dependent on either the density or proportion of infectious individuals in a population [9–13] (see Box 1 for an explanation of the basics of disease modelling), with the dependence captured by a transmission function incorporating a transmission coefficient. Important implicit components of the transmission coefficient include the contact rate between hosts, and the probability of infection given pathogen exposure, which itself incorporates both host susceptibility and host infectiousness [13]. Most disease models assume a single transmission coefficient for all individuals in a population. Hence they assume, in effect, invariable susceptibility, infectiousness and contact rate.

Most models, therefore, are unable to capture the potentially different outcomes resulting from variable heterogeneity in these host characteristics. Lloyd-Smith *et al*. [14], however, have pointed out that predictions from models that do incorporate such variability can differ sharply from those using only 'average' values. With heterogeneity, disease outbreaks are less probable. However, the outbreaks are likely to expand rapidly when they do occur. As these authors note, such predictions echo the experience of the SARS outbreak in 2003, where individual 'superspreaders' of disease were apparent, and where many cities escaped whereas a few suffered explosive epidemics. Moreover, those models which have incorporated such heterogeneities have tended to focus on human infections [15]; and, therefore, they have not included a key characteristic of many wildlife populations: that both average susceptibility and variation in susceptibility are themselves likely to be dynamic, varying in particular with host density and/or the availability of host resources. This omission can have even more profound, though as yet unexplored, consequences.

Box 1. Constant transmission coefficients

Epidemiological models generally describe the rate at which susceptible individuals (S) become infected (I), usually expressed as the force of infection [10,12], $\lambda(I)$. For simplicity, here we assume that infected hosts are also infectious. With directly transmitted infections, $\lambda(I)$ depends on the number of susceptible hosts and the per capita transmission rate (the rate of transmission *per* susceptible host). In turn, the per capita transmission rate is usually proportional, first, to the contact rate, k, between susceptible and infectious hosts, and also to the probability, p, that a contact that might transmit infection actually does so. The probability, p, itself depends on the infectiousness of infectious hosts and the susceptibility of susceptible ones. That is:

$$\lambda(I) = k\ p\ S.$$

The contact rate between susceptible and infectious hosts can itself be broken down further into two components: the contact rate, c, between a susceptible individual and *all* other hosts, and the proportion of those hosts that are infectious, I/N, where N is the total number of hosts. Our expanded equation is now:

$$\lambda(I) = c\ p\ S\ I/N.$$

The most common assumption (*density-dependent transmission*) is that the contact rate c increases in proportion to the density of the population, N/A, where A is the area occupied by the population. Assuming, again for simplicity, that A remains constant, the Ns in the equation then cancel, all the other constants can be combined into a single constant β, 'the transmission coefficient', and the equation becomes:

$$\lambda(I) = \beta\ S\ I.$$

By contrast, it can be argued that for sexually-transmitted (and probably 'socially-transmitted') diseases, the contact rate is approximately constant: the frequency of contacts is independent of population density (*frequency-dependent transmission*). This time the equation becomes:

$$\lambda(I) = \beta'\ S\ I/N,$$

where the transmission coefficient again combines all the other constants but this time acquires a 'prime', β', because the combination of constants is slightly different.

Crucially, though, note that whatever the nature of transmission, the transmission coefficients, β and β', are assumed to be applicable to the whole population, and their components, susceptibility, infectiousness and per capita contact rate, are, therefore, also effectively assumed to be invariable within the population. Although there has been work developing different models of disease transmission and dynamics (see examples in McCallum et al. [12]), there is a paucity of data on these dynamics that allow assumptions such as constant transmission coefficients to be tested. Here we argue that not acknowledging the variability in the components of the transmission coefficient might, in some cases, lead to invalid modelling of infection dynamics.

Variable host condition: variable host susceptibility

Infection with microparasites (viruses, bacteria, fungi and protozoa) is traditionally studied as a dichotomous variable (i.e. individuals are classified as infected or uninfected) [16]. However, following exposure to a pathogen, a continuum of outcomes might be seen, ranging from failure of the infection to progress to overwhelmingly high infection intensity. (Variations in the intensity of infection are much more commonly considered for macroparasitic pathogens, such as helminths and arthropods [17].)

The outcome will depend partly on the pathogen (e.g. pathogenicity, infective dose), but it could also depend on the integrity and vigour of the host's defences against infection.

In vertebrates, these defences consist of physical and chemical surface barriers (e.g. epithelia and lisozyme), components of the nonspecific innate immune system (e.g. complement system and phagocytes) and the specific adaptive immune system (e.g. antibodies and lymphocytes) [18]. In the physiological economy of a host, the extent of resource allocation to immunity and surface barriers depends on nutrient availability and competing physiological demands [19–21]. Distinct trade-offs related to age, co-infection, etc., determine differential investment in the various compartments of the immune system [22–24], but given identical life history circumstances, it is reasonable to assume that good condition will better prepare an individual to oppose and/or limit infection. The more 'healthy' a host, the more hostile an environment a parasite will face. Therefore, the influence of general host condition on intrinsic susceptibility, and as a result on infection dynamics within the host, could be substantial. The following studies support this contention.

Sequential data, obtained by taking repeated samples from the same individuals, show evidence of an important role for host condition in natural parasite-vertebrate systems. Free-ranging field voles with low haematological indicators of condition (red blood cell and lymphocyte levels) were more likely to show elevated haematological indicators of infection (neutrophilia and monocytosis) when re-sampled one month later [25]. In the same populations, host condition specifically influenced proneness to infection with the endemic cowpox virus, particularly among males [26]. At times when a susceptible male with good body condition had a relatively low probability of becoming infected, one with poor body condition was twice as likely to contract cowpox; and if this male was also anaemic, the chances were almost quadrupled.

Variation in non-inherited susceptibility has also been examined in populations of invertebrates. Field experiments that investigated transmission of nuclear polyhedrosis virus in African army-worm larvae (*Spodoptera exempta*) found that susceptibility was crucially dependent on previous rearing conditions; larvae reared under crowded conditions were more resistant to infection, whereas larvae reared solitarily were less resistant [27]. Also, a model that accounted for noninherited phenotypic differences in host susceptibilities to the bacteria *Pasteuria ramosa* provided the best explanation for infection patterns in water fleas, *Daphnia magna* [28].

Variable host condition: variable infection intensity

Infections of hosts in poor condition might also be of higher intensity because parasites would encounter less opposition to their survival and proliferation. In support of this hypothesis, Blanchet *et al.* [29] found that the extent of infection of rostrum dace fish (*Leuciscus leuciscus*) with the copepod *Tracheliastes polycolpus* was dependent on the growth rate of the fish before infection. The burden of *T.polycolpus* and the fin degradation that resulted were better explained by models that considered growth rate as a cause (growth before infection) than as a consequence of the parasitism (growth during infection). Similarly, a longitudinal observational study in wild field voles [30] showed that individuals developing high levels of *Trypanosoma microti* parasitaemia tended to be those that prior to the infection had very low lymphocyte counts, an indication of poor immunological investment.

It is generally acknowledged that heterogeneity in susceptibility is one reason why macroparasites tend to be aggregated in host populations [17]. Clearly, whereas intensities of microparasitic infection are much less commonly monitored, we might expect them to be similarly aggregated.

The synergy between host susceptibility and infection: a vicious circle

Recently, Pedersen and Greives [31] conducted an experimental study where replicated populations of white-footed mice (*Peromyscus leucopus*) and deer mice (*Peromyscus maniculatus*) received either food supplementation, a long-lasting antiparasitic drug effective against nematodes and ectoparasites, both treatments, or neither. Finding that the interaction term drug $\times$ supplementation was significant, they demonstrated, at the population level, that the impact of parasites on rodent abundance was exacerbated in the absence of food supplementation; and that the effect of food supplementation was much greater when combined with antiparasitic treatment. This reveals a synergy between parasites and resources; together they are more influential on population dynamics than the sum of either effects alone. Studies at the individual level might help elucidate the mechanisms behind such synergy.

There is an extensive body of literature relating food resources to physiological condition and immunocompetence. For example, at high densities, rodents are limited in their resources [32], which has a negative impact on their physiological condition [7,32]. Numerous studies in humans have revealed that even moderate protein-energy malnutrition affects the integrity of physical barriers (skin, mucosal protection) and weakens every component of the immune system [33,34]. Nutrient deficiency (whether by resource limitation or from sequestration by parasites) jeopardises the immune response because of the shortage of essential elements (e.g. to produce antibodies), and owing to induced immunosuppression via glucocorticoid stress hormones [35,36]. Pedersen and Greives [31], in their experiment, found that food supplementation and partial removal of parasites significantly lowered glucocorticoid levels.

Not only can poor host condition predispose individuals to infection; infection itself can have a detrimental effect on condition. Besides their specific pathogenic effects, parasites extract host resources and induce a nutritionally demanding immune response [19,20]. There is a clear potential for synergy: poor condition predisposes individuals to infections, which further reduces the condition of the host, which further predisposes the host to infection, and so on. Thus, as previously noted, at the individual level, low haematological indicators of condition precede elevated levels of haematological indicators of infection in wild field voles. However, those individuals with high

indicators of infection subsequently experience a decline in their indicators of condition [25]. Furthermore, because individuals in a poorer condition are expected to have infections of greater intensity, the resulting deterioration in condition is likely to be even more marked for infections in individuals with a preceding impoverished condition.

In support of this, rostrum dace that had lower growth rates before infestation with *T. polycolpus* developed heavy burdens of this ectoparasite, which gave rise to a greater impact on concomitant growth rates and more severe fin degradation [29]. Likewise, field voles with decreased indicators of immunological investment developed high intensities of *T. microti* parasitaemia, and subsequently, further declines of these indicators were observed [30]. Similarly, an experimental infection study of recently metamorphosed common toads (*Bufo bufo*) with the fungus *Batrachochytrium dendrobatidis* found that body mass before exposure (a sign of vigour) was strongly correlated with survival [37]; infected toads were much more likely to die if their body mass prior to infection was low. Most probably, infection intensity is both a cause and consequence of the host condition [25,29]. Being in good condition is important in controlling infections. Equally, controlling infections is essential in maintaining good condition.

Undoubtedly, the occurrence of these vicious circles will depend in part on the host-parasite system. For example, in parasites with complex life cycles, where the definitive host feeds primarily on the intermediary host, it is perhaps unlikely that poor host condition precedes high infection intensities, since if a definitive host in good condition feeds more, it will tend towards greater exposure to the parasite.

Vicious circles at different levels

These vicious circles clearly have the potential to give rise to a polarisation between the healthy and robust, on the one hand, and the increasingly weak and sickly on the other. Furthermore, such vicious circles, and such polarisation, can occur both at the individual and the population level (Figure 1).

At the individual level

As illustrated above, whereas a host in good condition might be able to counter and limit pathogens because of the functionality of its defences, a host in poor condition will defend itself poorly against infections, which might then also be of higher intensity. This could, in turn, result in host defences being overwhelmed and condition deteriorating further. Moreover, the vicious circle could influence the interaction between a host and its parasite community. The adaptive arm of the immune system in vertebrates will attempt to limit an infection by mounting a specific response, which in some cases confers life-long immunity to the pathogen in question [18]. However, parasite communities are rich and diverse [38], and an infected individual, or a recovered or recovering one that survives an infection, might be left poorly prepared to effectively oppose other pathogens, except in cases where there is cross-immunity or an antagonistic interaction between parasites because of competition between them

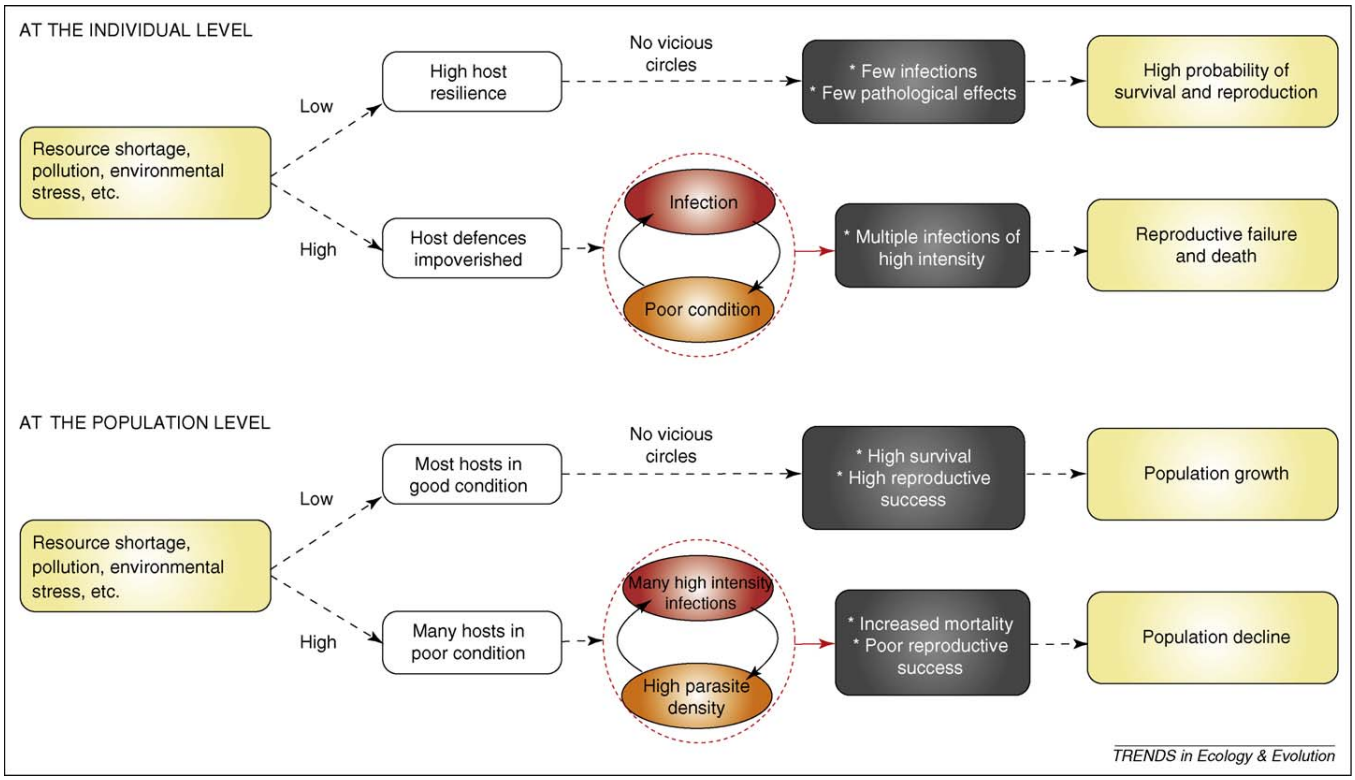

Figure 1. Synergy between condition and infection: vicious circles at the individual and population levels. Small initial differences in host condition caused by resource shortage, competition, climate change, etc., can become exaggerated and populations might become 'polarised' into the weak and the strong. An individual with an impoverished condition is more prone to developing infections that are also more likely to be severe, with a resulting increasing deterioration in condition that can eventually and substantially affect its performance and survival. At the population level, a great proportion of individuals in poor condition will cause both a large number of infections and more severe infections, resulting in pathogen exposure dose being greater, with a consequential greater impact on host dynamics.

[39,40]. However, in general, previous infections do not protect against new hetero-specific infections, even when parasites belong to the same group [41]. The resulting scenario for a host in poor condition is thus greater vulnerability to the whole parasite community, triggering a vicious circle where host health becomes increasingly impoverished and severe infection generally more probable, which might eventually lead to death (Figure 1). Consistent with this, a study of house martins (*Delichon urbica*) found that individuals infected with two types of *Plasmodium* parasites had higher burdens of chewing lice and worse body condition than birds with single-infections [42]. Similarly, a negative association between gastrointestinal nematode prevalence and body condition in African buffalo (*Syncerus caffer*) was observed only if there was a concurrent *Mycobacterium bovis* infection [24].

At the population level

As individuals in poor condition are not only more likely to become infected by pathogens, but also more prone to high infection intensities, they might be the most important source of infection to others. Consequently, in a population with a large proportion of individuals in poor condition, there is likely to be not only a high prevalence of infection but also a large number of infections of high intensity, which will in turn result in greater pathogen density. Prevalence, too, can be increased simply because infections are longer lived in individuals in poor condition (though the opposite, ephemeral transmission as a result of premature death, is also possible [43]). Pathogen density, in turn, is a key component of disease transmission and infection dynamics, as evidenced by experiments with micro- and macroparasites (e.g. [44,45]). Greater pathogen density causes more infections and the negative loop is triggered (Figure 1).

These vicious circles acting at two levels would, as a consequence, have an impact on population dynamics such as those observed by Pedersen and Greives [31] in mice. Lochmiller, some time ago, proposed that underlying immunocompetence might be a key factor regulating natural populations [46], arguing that increased proneness to infections results in population declines owing to morbidity and mortality. Here we propose that the vicious circle is the mechanism by which this regulation might occur. Studies in mammals have provided data that support this hypothesis insofar as improved host condition has been found to be positively correlated with survival [47–49]. Recent evidence from invertebrates is also consistent with this idea. Population declines of western tent caterpillar (*Malacosoma californicum pluviale*) were strongly associated with a general deterioration in larval quality [50].

Conclusions and recommendations

The synergy between host susceptibility and infection has important implications. First, host condition could influence a major focus of attention in disease ecology: the relationship between pathogen prevalence and host density. Variation in condition is itself related to host abundance and dynamics [7,32]. Abundant resources and good condition favour population growth, but condition is then often lowest when host abundance has been high (or soon after) and competition for resources is intense. In addition, pathogen prevalence will often be highest at higher host abundances, simply because of the density-dependence of infection dynamics (see Box 1) [17]. If, though, as we argue, the probability of infection is substantially condition-dependent, greater contact rate would not be the sole explanation for the observed density-dependence of prevalence. High host densities would cause not only greater contact but also poorer condition, with resultant increased susceptibility and greater pathogen production. This hypothesis is supported by results from the experiment with African army-worms, described above [27], which indicate that host density might affect the 'susceptibility' component of viral transmission rather than the 'contact' component (rearing conditions, and not density per plant in the experiment, affected pathogen transmission). Stress as an alternative explanation of the density-dependence of prevalence has also been tested experimentally in mallards (*Anas platyrhynchus*) [51]. Ducks in a stressed state because of either crowding or a glucocorticoid injection showed greater numbers of nematodes at necropsy than infected non-treated controls. Endemic pathogens that are normally tolerated might become more pathogenic following high host densities, because host resistance is impaired. This notion could be key to understanding the mechanism by which parasites regulate animal populations [52]. Indeed, insects seem to have evolved a mechanism that anticipates this triple interaction between host abundance, susceptibility and disease (termed 'density-dependent prophylaxis'), because when some species are reared under crowded conditions, they are significantly more resistant to infections than those reared solitarily [53,54].

Second, the vicious circle could have a substantial influence on parasite abundance. As noted, the greater infection intensities suffered by individuals in poor condition make them very important sources of disease, contributing greatly to parasite density. This is relevant, for example, in understanding the ecoepidemiology of human and livestock diseases that have a wildlife reservoir. At high reservoir host densities, the mechanisms described will produce high parasite densities, and exposure to the pathogen will be greatest. Also, it is increasingly acknowledged that many populations include 'superspreaders' of disease [14]. The vicious circle clearly has the potential to generate such superspreaders.

A third important implication concerns biological conservation. It is now well recognised that infectious diseases represent a considerable threat contributing to biodiversity loss [55,56]. Although it has been posited that pathogens might not be able to drive their hosts to extinction because they would 'fade out' when host density is below a threshold that is crucial for disease persistence [12] (except for cases where transmission is frequency-dependent [57]); we should note that pathogens are not independent entities but are part of a rich parasite community. Hence, host populations that survive the impact of specialist pathogens are then left vulnerable to density-independent generalists and opportunistic environmental pathogens. The fate of a wild animal population, then, might depend on the

proportion of individuals that are prone to developing vicious circles. This can have important consequences for the effects of other factors on the population (e.g. resource shortage or predation). Environmental stress (caused by habitat destruction, pollution, climate change, etc.) might cause a large proportion of the population to be vulnerable, and thus (otherwise tolerated) native parasites could become a health threat for wildlife. The vicious circle might become a vicious spiral, trending towards population extinction.

We have emphasised that the intensity of parasitism can be both cause and effect in its interaction with host condition. Hence, establishing cause-effect relationships or the impact of a specific pathogen poses a challenge that warrants the exploration of novel approaches. For example, when studying a single pathogen, it can be important to take into consideration the remainder of the parasite community, since infection with one pathogen might indicate not only proneness to infection by other, possibly undiagnosed pathogens, but also a disproportionate probability of concomitant infection with those pathogens. The net effect observed might, then, not be that of the focal parasite alone but of all those concomitant infections. Moreover, observational studies, besides controlling for potential confounders in the study design and analysis (e.g. other pathogens), should whenever possible use sequential data, where a measure of host condition prior to infection can be included. Experimental approaches should also consider including measures of host condition. Finally, the concepts presented here alert us to the value of studying disease as a continuous variable (i.e. infection intensity), rather than in simple terms of presence and absence.

There is a need for interdisciplinary research to improve our understanding of the role of host susceptibility in infection and of potential vicious circles. Developing and assessing metrics that allow us to measure the general condition of hosts, their immunocompetence, and the aptitude of specific compartments of the immune system, are crucial if we are to become able to incorporate host susceptibility into disease ecology research.

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