

# Reciprocal effects between host phenotype and pathogens: new insights from an old problem

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**Relationships between the host phenotype and pathogen infection are assumed to reflect either causes or consequences of the infection. In fact, these processes are likely to co-occur, even in the same phenotypic traits. For example, hosts with high ingestion rates have a higher growth rate but are also more infected by trophically transmitted pathogens that subsequently reduce the host growth rate. Here, we briefly review the empirical evidence suggesting reciprocal effects in host–pathogen interaction. We then provide a ‘verbal’ model that aims to predict how reciprocal effects can bias our interpretation of the relationship between host phenotype and pathogen infection. Finally, we outline technical avenues for explicitly considering reciprocal effects in the future and discuss their fundamental and applied implications.**

## The importance of host phenotype in parasitology

In the field of parasitology, it is well established that the phenotype (see [Glossary](#)) of infected and uninfected individuals often differs [1–3]. Because these differences are the tractable output of the intimate interaction between a pathogen and its host, studying them is central to applied aspects of parasitology, such as epidemiology and medicine [4]. Their exploration is also important for understanding the pivotal role of pathogens in host evolutionary ecology [2] and on ecosystem functioning. For example, phenotypic alterations in hosts infected by manipulative pathogens modify host population ecology, apparent competition processes, food web structure, and energy and nutrient flow between habitats, as well as favouring habitat creation [5].

The mechanisms behind the apparent relationship between host phenotypes and pathogens are traditionally categorized into two kinds of mutually exclusive processes: the first considers pathogen infection as a cause of subsequent phenotypic variation; the second considers pathogen infection as a consequence of phenotypic variation. This view, although undoubtedly valid in many cases, is an oversimplification (or is at least incomplete)

because several phenotypic traits can both control the rate of infection and be reciprocally affected in their expression by the infection process. A relationship between the host phenotype and pathogen infections could then reflect reciprocal effects between host phenotype and pathogen infection ([Box 1](#)). Although reciprocal effects are well recognized and are sometimes mentioned as alternative hypotheses [3,6–8], they are rarely explicitly considered, and their implications for the ecology and evolution of host–pathogen relationships remain largely unexplored. Here, we aim to review evidence for reciprocal effects, explain why omitting them can lead to fallacious interpretations and highlight their importance for our understanding of the ecology and evolution of host–pathogen interactions. We also outline the future research needed to underpin this recurrent, but unsolved, topic.

## How many traits are influenced by reciprocal effects?

Reciprocal effects occur when, for a given host–pathogen interaction, a phenotypic trait controls the infection rate and is then affected by the pathogen ([Box 1](#)). Although few researchers have explicitly investigated host–pathogen interactions for reciprocal effects (however, see Refs [3,6–8]), several examples deserve consideration.

## Glossary

**Capture-marking-recapture:** a method commonly used in ecology to estimate population size, for example. It consists of marking individuals and following the presence or absence of those marked individuals in a given study area.

**Encounter filter:** defined as the probability of contact between a pathogen and a potential host.

**Hormone:** a chemical compound released by cells that affects cells in other parts of the body. In animals, hormones are often transported in the blood. They participate in the development of secondary sexual characteristics.

**Manipulative pathogens:** parasites that induce phenotypic changes (morphology, behaviour, physiology, and so on) in their hosts that increase the probability of their transmission from one host to another and/or ensure that propagules will be released in an appropriate location.

**Phenotype:** any observable characteristic or trait of an organism, such as its morphology, development, biochemical or physiological properties, or behavior.

**Secondary sexual characteristics:** phenotypic traits that are genetically and/or environmentally based and appear in sexually mature animals. They often differentiate between the sexes, but they rarely have a direct reproductive function and are believed to be the results of sexual selection.

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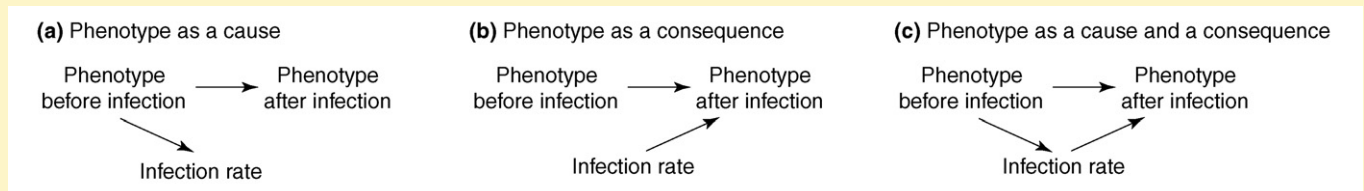
**Box 1. Reciprocal effects in a nutshell**

Some particular host phenotypes are more infected than others, either because they are more exposed to pathogens or because they are less able to resist infection (Figure 1a). In addition, pathogens can affect the host phenotype through their pathogenic effect (Figure 1b). For a given host–pathogen interaction, reciprocal effects occur when a single phenotypic trait controls the infection rate and is then affected by the pathogen (Figure 1c). This means that both causes and consequences underlie the observed relationship between host phenotype and pathogen infection (Figure 1c). Hence, mechanisms behind this relationship can be explained only if reciprocal effects are explicitly considered.

The possibility of reciprocal effects occurring has been proposed repeatedly [3,6–8]. Reciprocal effects can be accounted for by performing controlled experiments in which hosts are experimentally infected, but this approach often masks reciprocal effects that are present in naturally infected hosts. Masking reciprocal effects could preclude an understanding of natural host–pathogen dynamics,

which limits our ability to provide a full explanation for patterns observed in natural settings.

Not all phenotypic traits are concerned by reciprocal effects. Notably, phenotypic traits that represent an ‘innovation’ from a host point of view (i.e. a new phenotype that can only be observed after infection by a given pathogen) cannot be affected by reciprocal effects. For example, in the case of manipulative parasites, certain phenotypes only appear in the host population while the parasite is infecting the host (and sometimes, only when the parasite has reached a developmental stage at which it becomes infective to its final host). For example, the reverse phototaxis observed in *Gammarus pulex* occurs only when this intermediate host is parasitized by certain acanthocephalan parasites and the parasites have reached a certain developmental stage [49]. These cases are generally assumed to be convincing evidence that the infection is the cause and not the consequence of the altered phenotype.

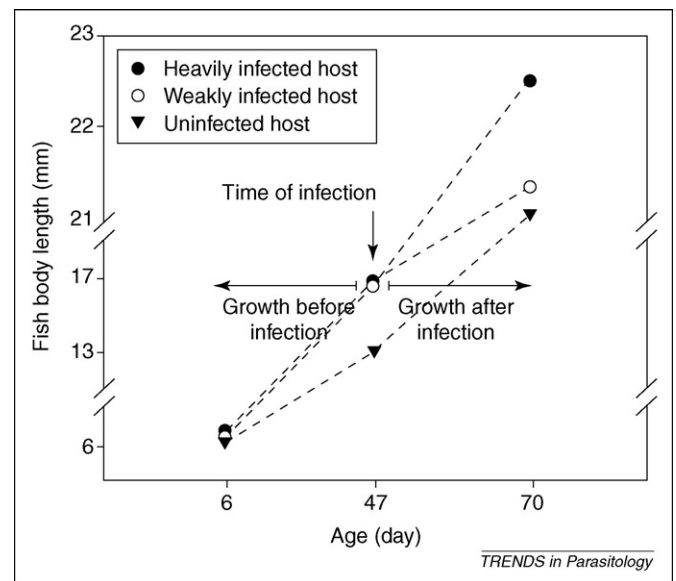


**Figure 1.** Relationships between the phenotype of the host before infection, the phenotype of the host after infection and infection rate. (a) The relationship between host phenotype and infection rate reflects a cause of infection. (b) The relationship between host phenotype and infection rate reflects a consequence of infection. (c) The relationship between host phenotype and infection rate reflects both a cause and a consequence of infection; reciprocal effects occur.

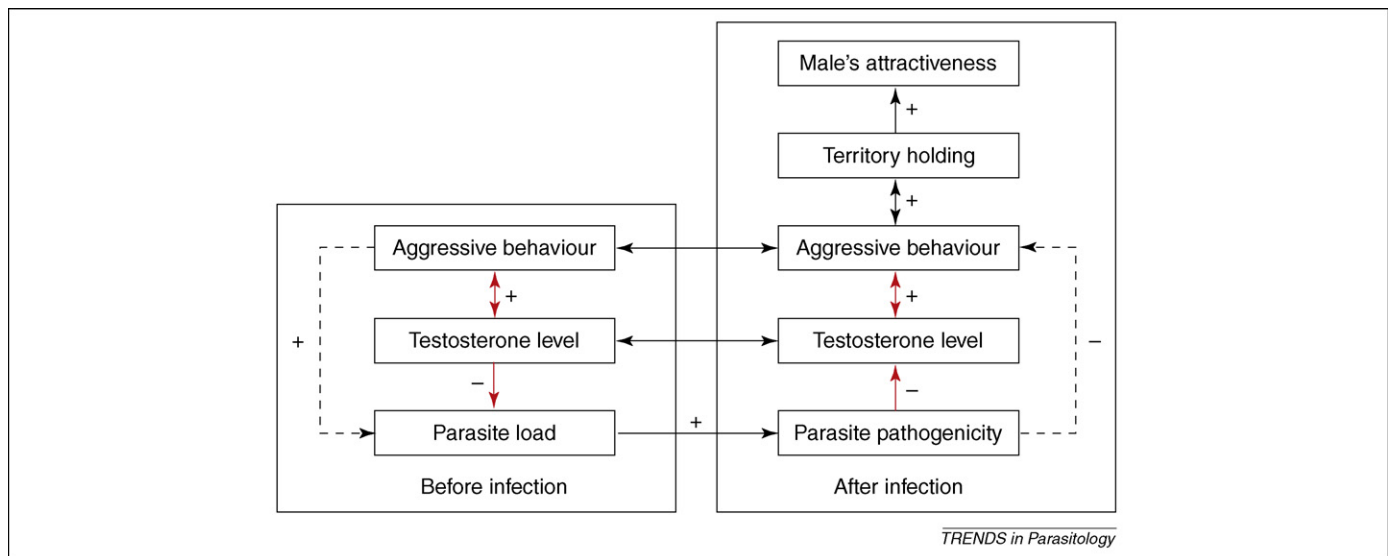
The first example concerns a host–parasite system involving an endoparasite (the cestode *Proteocephalus tetrastomus*) and its fish host (the rainbow smelt, *Osmerus mordax*). Bourque *et al.* [9] demonstrated a pattern of host gigantism holding true for fish that were weakly infected by the parasite (i.e. at a given age, weakly infected hosts were bigger than uninfected hosts) but not for heavily infected hosts (Figure 1). To understand these intriguing patterns, Bourque *et al.* [9] back-calculated the growth rate of rainbow smelt both before and after the period of parasite infection using otoliths (internal solid fish structures) as a growth marker. By doing so, they found firm evidence for both causes and consequences of parasite infection. Indeed, they first demonstrated that infected hosts (both weakly and heavily infected) were individuals that had a high growth rate before the period of infection (Figure 1). This probably reflects either that a high growth rate correlates with a high ingestion rate of the fish’s main prey (a copepod), which is the intermediate host of this parasite, or that a negative genetic correlation between host growth rate and resistance to this parasite exists in this population. They then showed that the parasite negatively affected the hosts’ growth rate, but only for heavily infected hosts (Figure 1). Overall, this means that the pattern of host gigantism observed for the weakly infected host was solely a cause of a covariation between ingestion rate and infection, whereas the pattern observed for heavily infected hosts resulted from a combination of the cause and consequence of infection [10].

Secondary sexual characteristics (SSCs), such as the tail of the peacock, are also prone to being affected by reciprocal effects of pathogens. Indeed, SSCs are typically costly for individuals, and those who invest a lot of energy in them frequently become more susceptible to infections that can, in turn, negatively affect the elaboration of SSCs [11,12].

Female sticklebacks (*Gasterosteus aculeatus*) have evolved a preference for males with red breeding coloration. Paradoxically, the red pigments are acquired through eating copepods rich in carotenoids, which are also intermediate hosts for several parasites. Thus, the intensity of red



**Figure 1.** Relationships between the growth rate of rainbow smelt (*Osmerus mordax*) and the infection level of the cestode *Proteocephalus tetrastomus*. In this system, infection by *P. tetrastomus* first appeared in the population when the potential hosts were 47 days old. The growth rate back-calculated before this date thus represents the pre-infection growth rate of fish that will be ‘weakly infected’, ‘heavily infected’ or ‘uninfected’ (‘growth rate before infection’). All the fish were caught in the same area and were, hence, all exposed to the parasite. The growth rate back-calculated after the 47th day represents the post-infection growth rate of ‘weakly infected’, ‘heavily infected’ and ‘uninfected’ fish (‘growth rate after infection’). Knowing these three variables (growth rate before and after infection and timing of infection) has enabled Bourque *et al.* [9] to tease apart causes and consequences in this host–parasite relationship. Redrawn, with permission, from Ref. [9].



**Figure 2.** Possible pathways between aggressive behaviour, testosterone level and parasite infection in the red grouse (*Lagopus lagopus scoticus*) and the parasite *Trichostrongylus tenuis*. Double-headed arrows indicate covariance between traits, and single-headed arrows indicate causal relationships. Covariance and correlation can be either positive or negative. The trade-off involving testosterone, aggression level and parasite infection is highlighted in red. In the red grouse, as well as in many lekking species, high levels of testosterone lead to holding territory and, hence, attracting females. We have separated the physiological pathways that are hypothesized to occur before infection and after infection. In this example, the two pathways might lead to reciprocal effects between aggressive behaviour and infection level.

breeding coloration is indirectly associated with an increase in prior parasite exposure [13,14]. A reciprocal effect is possible because experimental studies suggest that harmful effects of specific parasites reduced the intensity of red breeding coloration in males [15]. This example suggests that important fitness-affecting traits, such as SSCs, are also prone to reciprocal effects.

A long-term study conducted on the British red grouse (*Lagopus lagopus scoticus*) and its main parasite, *Trichostrongylus tenuis* [16], offers another example in which reciprocal effects probably occur between testosterone levels, parasite infection and aggressive behaviour (Figure 2). In the red grouse, testosterone mediates a trade-off between the level of aggression and immunity; high levels of testosterone favour male aggression, which enhances holding territory and, hence, the ability to attract females [17]. In turn, this decreases immune function and, hence, resistance to parasites [18–20] (Figure 2). A natural difference in aggression existing before infection, therefore, might be seen as an indirect cause of susceptibility to infection (Figure 2). However, reciprocal effects should occur in the red grouse because it has been demonstrated that parasite infection reduces the level of male aggression [21]; in that case, changes in aggression become a consequence of parasite infection (Figure 2). This example assumes that circulating testosterone can fluctuate in an individual according to its phenotypic condition. Although not directly concerned with host–pathogen relationships, this assumption parallels recent findings in animal physiology [22,23]. Indeed, Safran *et al.* [22] have demonstrated that circulating androgens affect plumage ornaments in barn swallows (*Hirundo rustica*) and, reciprocally, that changes in plumage ornaments affect the temporal course of the circulating hormones. As for host phenotype and pathogen infection, a relationship between phenotypic attributes and physiological parameters could underlie causes, as well as consequences.

### Box 2. Reciprocal effects as a way of determining the ‘pathogen effect size’

Disentangling the causes and consequences of the relationships between the host phenotype and pathogen infection enables evaluation of whether reciprocal effects occur and are relevant for evaluating what we refer to as the ‘effect size’ of the pathogen. In statistical terms, an ‘effect size’ is the magnitude of an effect. By extension, for a given host–pathogen interaction, we define a ‘pathogen effect size’ as the magnitude of the effect the pathogen has on the host phenotype, while taking into account the possible reciprocal effect of this same host phenotype on the level of pathogen infection. Considering reciprocal effects would lead to four main patterns of pathogen effect sizes. These four patterns are illustrated by a theoretical graph in Figure 3. The first two patterns include interactions in which the phenotype of the host before infection does not determine the future level of infection (i.e. the mean phenotypic value before infection is equal between [future] infected and [future] uninfected individuals; Figure 3a). In this case, the pathogen can either affect the phenotype of its host (i.e. non-null pathogen effect size; Figure 3d) or not (i.e. null pathogen effect size; Figure 3c). The two other patterns include interactions in which the phenotype of the host before infection determines the future level of infection. The mean phenotypic values before infection here differ between (future) infected and (future) uninfected individuals (i.e. phenotypic variation is a cause of infection; Figure 3b). In this case, not considering this causal relationship could lead to two kinds of bias in the measurement of the pathogen effect size. The first kind of bias arises when both causes and consequences occur; in this situation, the pathogen can either exacerbate (if the pathogen has a synergistic effect on the host phenotype) or diminish (if the pathogen has an antagonistic effect on the host phenotype) the phenotypic difference that pre-existed before infection (non-null pathogen effect size; Figure 3f). The second kind of bias arises when only causes occur (i.e. the pathogen has no pathogenic effects); in this situation, one could conclude that there is a notable pathogen effect while, in fact, none exists (i.e. null pathogen effect size; Figure 3e). Ignoring these possible reciprocal relationships would undoubtedly lead to incorrect interpretation of the consequences of pathogen infection on host phenotypes (i.e. over- or under-estimation of the pathogen effect size).

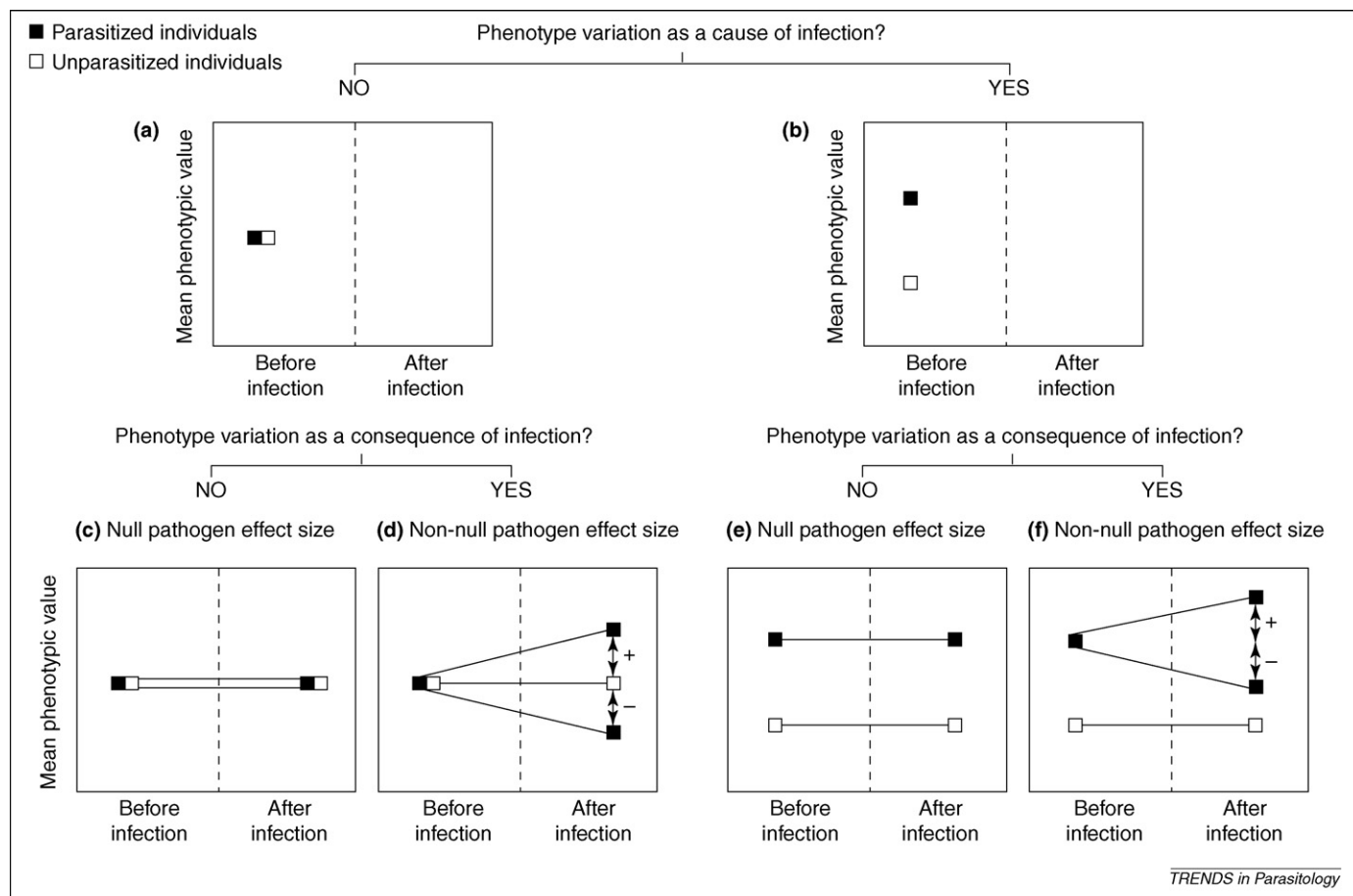
Similar reciprocal effects are expected for interactions involving sexually transmitted pathogens (STPs). The spread of such pathogens is closely linked to the sexual behaviour of hosts [24–26]. Risky sexual behaviour, such as high mating frequencies or mating with at-risk partners, is known to facilitate the spread of STPs, both in humans and in others animal [25–29]. Evolutionary ecologists have established that the efficiency of transmission could also be increased through the manipulation (by the pathogen) of the host's sexual behaviour [26]. Notably, some insect pathogens have developed strategies that cause the mating behaviour and/or success of their hosts to be enhanced (for a review, see Ref. [26]). For example, female *Musca domestica* infected by the fungus *Entomophthora muscae* are more sexually attractive than uninfected females, in part because the fungus swells the abdomen of infected females (a trait that is associated with higher fecundity in this species) [30]. Disentangling the causes and consequences of STPs has very important implications for understanding their epidemiology [31,32].

These few examples suggest that reciprocal effects might concern a large diversity of host phenotypic traits, such as growth patterns, morphology, physiology and

behaviour. This means that for many candidate traits, the relationship between host phenotype and pathogen infection can be highly dynamic and underlie both causes and consequences. As detailed in the next section, considering this possibility not only has semantic purposes but also has important fundamental consequences (Box 2).

### The importance of reciprocal effects

Ignoring the possibility of reciprocal effects might bias the interpretation of the relationships between host phenotype and pathogen infection. Considering reciprocal effects leads to four main theoretical patterns that correspond to several measurement biases, including overestimation or underestimation of the ability of the pathogens to modify the phenotype of their host (Box 2, Figure 3). If reciprocal effects are ignored, the conclusions that can be drawn from data collected after hosts have been infected can be fallacious. Hence, the questions that scientists should aim to answer are: does the phenotype of the host determine the level of infection? And does the level of infection determine the host phenotype? These questions are comparable to the 'chicken-egg dilemma' and are crucial to measure what we refer to as the 'pathogen effect size' (i.e. the magnitude of



**Figure 3.** Reciprocal effects between host phenotype and pathogen infection. This conceptual model includes the possibilities that parasite infection can be a cause of changes in the host phenotype, a consequence of variation in the phenotype or both at the same time (i.e. reciprocal effects). The figure shows how the mean phenotypic value (i.e. the mean value of a phenotypic trait measured for a given host population) of the infected (black squares) and uninfected (white squares) hosts evolved from the period before infection to the period after infection. The existence of reciprocal effects can be verified using a two-step hierarchical reasoning. In a first step (a–b), we ask whether variation in the host phenotype was a cause of the pathogen infection. If yes (a), the mean value of the phenotypic trait being considered (before infection) should differ between individuals that will become infected and those that will be uninfected. Knowing that, the second step (c–f) consists in asking whether the parasite infection has a consequence on the host phenotype. This leads to four patterns of pathogen effect size that correspond to different measurement biases (Box 2): two patterns [(c) and (e)] belong to the category 'null pathogen effect size' (i.e. the parasite has no consequence on the phenotype of the host), and the other two to the category 'non-null pathogen effect size' [as indicated by the double-headed arrows showing variation around the mean in (d) and (f) (i.e. the parasite has a consequence on the phenotype of the host)].



the effect of a pathogen on its host phenotype; Box 2, Figure 3).

Given the measurement biases that are inherent to reciprocal effects, we feel the time is ripe to go from theoretical considerations to the empirical assessment of reciprocal effects. The difficulty of evaluating both causes and consequences in natural settings and, thus, calculating a pathogen effect size is probably the main reason why the reciprocal effects between host phenotype and pathogen infection are understudied. Indeed, detecting and evaluating such reciprocal effects requires following individuals of known phenotypic status both before and after infection has occurred.

### How to study reciprocal effects in host–pathogen interactions

It is commonly assumed that experimental infection of the hosts under laboratory conditions should overcome the possibility for reciprocal effects (e.g. Refs [33–35]). However, a common pitfall is that, in general, all the potential hosts are individually housed and then exposed to the pathogens, so that the encounter rate is equalized among hosts (e.g. Refs [34–36]). By doing this, researchers force what has been termed the ‘encounter filter’ [2], biasing or even masking the fact that in nature, not all hosts have the same probability of encountering pathogens. To solve this problem, we propose that future laboratory studies fully integrate this phenotypic difference in pathogen encounter rate for evaluating the pathogen effect size (Box 2) on the host phenotype. This can be achieved through three independent steps. First, individual phenotypic differences among potential hosts must be measured before infection. Phenotypic traits to be investigated are strikingly dependent on the mode of pathogen transmission. For example, growth rate or behavior related to food acquisition can be investigated in the case of pathogens that are transmitted trophically. Individual differences can be measured when each individual is reared alone and/or in a group (depending on the trait of interest). Second, when exposure to the infection takes place, it is most important that individuals should be kept in a group during exposure, so that the individual probability of encountering the pathogen’s infective stages is as close as possible to the natural probability of such an encounter. Third, individual phenotypic differences must be measured for a second time after infection. This final step is aimed at comparing the phenotypes of infected and uninfected hosts. Such an approach [6,37] has proved to be powerful for detecting reciprocal effects between activity behavior of a fish species (*Salvelinus fontinalis*) and the load of an ectoparasitic copepod (*Salmincola edwardsii*).

Currently, technological refinements to the development of capture-marking-recapture (CMR) techniques [38] present an opportunity for following individuals during their lifetime (i.e. longitudinal studies) and, hence, for resolving reciprocal effects under natural conditions. Marking procedures can be adapted to an increasingly large number of taxa [39,40] and can be of very long duration and high accuracy (e.g. Ref. [40]). For example, marking has been used to test the effects of influenza A virus on the body condition and the behaviour of migrating

waterbirds [41,42]. These studies, however, highlight a major difficulty of the CMR approach [8,41] – namely, controlling for initial pathogen infection. Indeed, it will still be difficult to ensure that at the beginning of the marking, individuals are free of the target pathogen species, unless marking can be done at a stage of development at which individuals are not prone to infection [8]. For instance, juveniles are often less prone to infection than adults because they have been in contact with pathogens to a limited extent [2]. Ideally, marking procedures should be performed before infection so that both causes and consequences of infection can be inferred. Another possibility would be to couple laboratory rearing with marking procedures. The phenotypic status of laboratory-reared individuals, for example, could be monitored throughout the rearing period (when individuals are free of the target pathogen species) and then monitored in the wild, once the individuals have been released (to allow a natural infestation). It is worth noting that such an approach must be accompanied by appropriate statistical analyses to avoid misleading interpretation [43].

Although technically demanding, evaluating the strength of reciprocal effects in the laboratory and in the wild seems resolvable, particularly if new tools such as CMR are used. By so doing, new perspectives on host–pathogen interaction will be highlighted, and this should have several concrete applications in diverse research fields.

### Concluding remarks and future directions

Pathogens and host phenotypes can have reciprocal effects on each other, and considering such a possibility is a very important step for estimating the effect size of pathogens on the phenotype of their hosts. Such reciprocal effects are currently overlooked, which is surprising given that the possibility for the existence of reciprocal selective pressures is incorporated into most current co-evolutionary theories [44]. Given the ubiquity of pathogens in natural ecosystems [45,46], this reasoning would apply to a large proportion of living organisms.

Not to consider reciprocal effects between hosts and pathogens might bias our interpretations of the relationships between host phenotype and pathogen infection and, thus, the ecological and evolutionary inferences that can be drawn from them. Taking on board reciprocal effects has many theoretical and applied implications, ranging from the study of population dynamics and sexual and natural selection to the prevention of disease outbreaks. Beldomenico *et al.* [7] demonstrated recently that hosts and their pathogens sometimes embark on a ‘vicious circle’, whereby poor condition predisposes hosts to infections, which further reduce their condition, and so on. This special case of reciprocal effects has been suggested to be central to predicting the dynamics of certain host populations [47].

An immediate challenge will be to gather more information on the range of phenotypic traits that are involved in reciprocal effects. Because they are diversified and complex phenomena, one single method or model cannot totally describe them. Another major challenge will be to overcome the technical limitations that currently prevent researchers from investigating host–parasite relationships for reciprocal effects in the field. For example, longitudinal

studies for small-bodied species are currently not conceivable because of technical limitations with marking procedures. We also need to understand the causes of diseases to decrease the suffering they engender. Traditional medical approaches rarely consider the problem within an ecological–evolutionary framework. One step towards resolution would be to increase awareness among medical scientists of the reciprocal effects that are likely to be encountered in ascribing infectious causation. Health sciences are still grappling with the crypticity of infectious causation (e.g. certain cancers [48]). Developing principles and approaches that could facilitate recognition of reciprocal effects would undoubtedly benefit a large community of scientists. The resolution of these questions promises, sooner or later, to reorient medical research. We hope this article will motivate scientists to consider our reasoning in their future studies.

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