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Responding to infection affects more than just the host

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An infection triggers a dramatic suite of changes in host physiology and behavior. While seemingly localized, the host response affects many other organisms, both within and beyond the boundaries of the host's body, with far-reaching ecological implications. Here, I call for more awareness and integration of those potential 'off-host' effects.

The initial host response to infection

The immune system comprises barrier, surveillance, and effector systems, whose jobs are to deter and eliminate invasion by foreign (non-self) elements. When activated, immune cells release molecules that activate and attract additional immune cells. The immune response can remain localized but also have effects in locations far away from the infection site. While seemingly constrained to the host, these local and systemic responses to infection affect many other organisms (Figure 1). Here, I provide an overview of those 'off-host' effects and their potential consequences, so that researchers in disparate fields can explicitly consider those effects in future studies.

The effects on offspring

An example of an off-host effect is that of maternal immune activation (MIA). Activation of the maternal immune system during gestation has been causally linked with neuropathology and altered behaviors in the offspring [1] and can impose long-term effects on offspring immunity [2]. The effects of MIA on offspring phenotype are driven by the maternal immune response and therefore extend to oviparous animals, which can, for example, transfer maternal defenses such as antibodies into their eggs [3]. The impacts of MIA on offspring immunity can be negative, such as an increased predisposition to inflammatory disorders [2]. However, effects can also be positive by enhancing antimicrobial defenses and therefore decreasing offspring susceptibility to infectious diseases [2,3], which could help to decrease disease prevalence in the population. Thus, the physiological responses to infection affect not only hosts, but also their offspring.

The effects on the microbiome

Host immune responses to infection can also affect communities of organisms that inhabit the host, such as the microbiota. For example, infection with HIV, along with the associated inflammatory response, leads to changes in the relative abundance of microbial communities of the gut [4]. Changes to the microbiota can, in turn, affect immune responses and increase susceptibility to infection by opportunistic microbes [5], as well as affect aspects of the host that provide cues regarding its infection status: behavior [5] and odor [6]. For instance, interactions between microbiota and host cells, as well as metabolites produced by the microbiota, communicate with the central nervous system in ways that can elicit changes to behaviors [5]. Some of those behavioral changes (e.g., locomotor activity, exploratory behavior) could then influence space use and social encounters, therefore having additional off-host effects.

The effects on the behaviors and physiology of others

Sickness cues such as behaviors and odors are also directly altered by the inflammatory response and its effects on neurophysiology and metabolism [6]. Sick animals are often lethargic and eat and drink less than healthy animals, which by itself can reduce patterns of movement, contamination of common resources (e.g., water holes), and social interactions. Thus, the immune response of one animal can affect how that animal spreads pathogens. Given the effects of inflammation on host behavior and physiology, infected hosts can potentially be easily detected by other animals. Sickness cues can thus lead to infected hosts being avoided by others to reduce their likelihood of becoming infected [6]. Reduced interactions with parasitized conspecifics have been observed across several taxonomic groups, often through avoidance but in extreme cases also through aggression and even eviction from the social group. Interestingly, parasites can also manipulate host physiology and behavior in ways that enhance parasite reproduction and transmission. The response to infection by certain pathogenic bacteria leads infected fruit flies (*Drosophila melanogaster*) to increase the emission of odors that attract other flies, enhancing the transmission of those bacteria to healthy flies [7]. Independently or combined, the behavioral changes experienced by infected hosts and the behavioral responses of healthy animals towards infected hosts should strongly affect the spread of contagious pathogens.

In some instances, however, avoiding parasitism can carry large costs for fitness. For example, certain parasite avoidance behaviors can increase predation or reduce mate attraction, creating trade-offs [6]. Captive animals may not be able to avoid diseased cage mates. The activation of anticipatory physiological responses is an additional and taxonomically widespread response to the presence of infected animals that may be important in these situations [8]. As an illustration, healthy canaries (*Serinus canaria*) that were allowed to observe canaries infected with *Mycoplasma gallisepticum* (a bacterial infection that causes swollen or crusty eyelids) developed immune responses [9]. Exposure to disgusting stimuli is also known to elicit physiological responses in humans and other primates (see [8] for an overview on disgust). Some

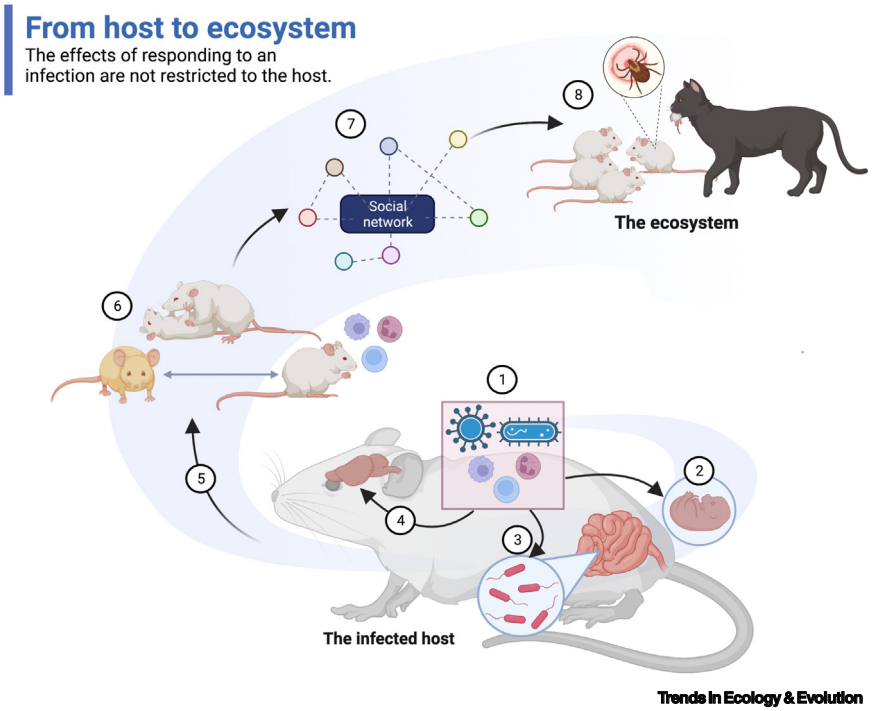

Figure 1. The host reactions triggered as a response to a pathogen lead to effects that go beyond the host. Immune responses produced on the detection of an invader (1) can impact other organisms living inside the host, such as a developing embryo (2) or commensal bacteria (3). In addition, those immune responses affect and activate distant organs in the host (4), including other immune organs, as well as the nervous, endocrine, digestive, and reproductive systems. Through their effects on host behavior and physiology, those systemic effects can produce sickness cues (5). Conspecifics perceive those cues, with demonstrated effects on their behavior and physiology (6). Combined, changes in host and conspecific behavior affect patterns of social interaction (7) within and between species. Changes in the aggregation patterns of a population can have cascading effects on disease transmission through alteration of direct contacts, space and resource use, food chains, disease reservoirs, and vector distribution, ultimately impacting biodiversity and ecosystems (8). Not all feedbacks alluded to in the text are represented, for simplicity. Created with Biorender.com.

studies suggest that, like MIA, when these anticipatory responses occur in mothers they can also affect offspring. For instance, pregnant mice housed across from mice infected with *Babesia microti* (a vector-transmitted parasite, and therefore not directly transmissible) had offspring that showed reduced parasite load faster upon infection than the offspring of mothers housed across from healthy mice [10]. It is thus possible that these anticipatory responses help to protect animals (or their offspring) from infection or reduce infection burden.

Combined, the behavioral and physiological responses to the presence of infected hosts have the potential to alter social networks, and hence how infectious diseases travel through populations. The altered movement and aggregation patterns resulting from changes in the behavior of hosts and groupmates, as well as effects on host and offspring immunity and mortality, can also impact the distribution and density of parasites, disease vectors, disease reservoirs, predators, prey, and availability of resources (Figure 1), with consequences for biodiversity, ecological networks, and human welfare. To illustrate the feedback on human welfare, we can consider the example of the effect of parasitic chytrid fungi, including *Batrachochytrium dendrobatidis* (Bd), on global amphibian declines. Amphibian diets include mosquitos and flies, which are critical vectors of important human diseases such as malaria, dengue, and yellow fever. Bd-driven amphibian decline is associated with increased malaria incidence in Central America [11].

Challenges and importance of considering off-host effects

Integrating these cascading effects and their feedbacks seems essential to understanding the impacts of infections both within and beyond the host. Some of the interactions described have the potential to affect how we do science (Figure 2). For example, if experimental control animals shift their behavior or physiology because they are perceiving and responding to the presence of infected animals, do they really constitute the type of control desired? Given that the microbiome affects behavior and physiology, what, then, is the consequence for research findings of giving experimental animals antimicrobial drugs as they arrive at the animal facility? These factors are also likely to affect issues of replicability in science.

Our recent experience with the coronavirus disease 2019 (COVID-19) pandemic also underscores the importance of understanding these intersections. The way in which the behaviors of sick or susceptible individuals were altered during the pandemic, whether due to debilitated health, self-imposed limited contact, or governmental or local guidelines, is already having notable consequences for both population immunity and the transmission of other infectious diseases [12]. While the incidence of most directly transmitted diseases (e.g., influenza, measles, norovirus) was severely reduced during the lockdown, changes in seasonal patterns of some diseases occurred (e.g., earlier onset of flu season) as restrictions were lowered. In addition, despite being key to slow disease spread, the build-up of susceptible, uninfected children stemming from reduced contacts might have resulted in a surge in respiratory

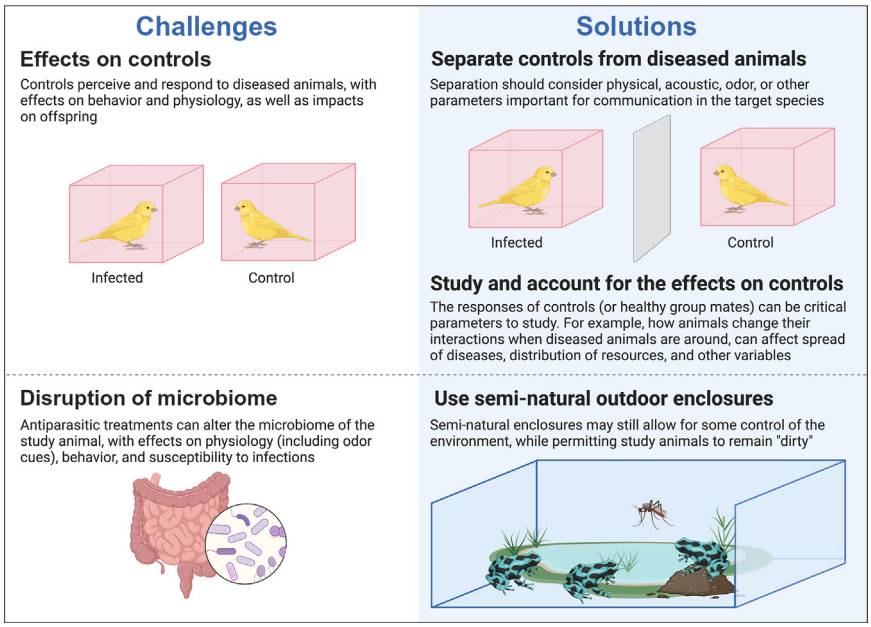

Figure 2. Challenges driven by 'off-host' effects, and potential solutions. It is important to be aware of how off-host effects may impact experimental outcomes. Sometimes, it may be desirable to reduce the presence of off-host effects, while for other questions those effects may be critically important to study. Potential solutions are proposed for some of the challenges highlighted in the text. Created with Biorender.com.

syncytial virus in that population [13]. Finally, the pandemic also illustrated how anthropogenic activities, such as the consumption of and trade in wildlife, create opportunities for pathogen spillover events. Since zoonotic spillover and infectious disease outbreaks should continue to intensify in response to climate change [14] and to other anthropogenic impacts on biodiversity (e.g., land-use change, overharvesting) [15], awareness of the potential feedbacks described here will be critical to predict how infectious hosts, populations, ecological networks, and ecosystems will respond to the challenges.

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Declaration of interests

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