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Immunity, host physiology, and behaviour in infected vectors

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When infection alters host behaviour such that the pathogen benefits, the behaviour is termed a manipulation. There are several examples of this fascinating phenomenon in many different systems. Vector-borne diseases are no exception. In some instances, as the term implies, pathogens directly interfere with host processes to control behaviour. However, host response to infection and host physiology are likely to play important roles in these phenotypes. We highlight the importance of considering host response and physiology from recent work on altered host-seeking in malaria parasite-infected mosquitoes and argue that this general approach will provide useful insights across vector-borne disease systems.

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Introduction

Across taxa and transmission routes, there have been many documented cases of host behaviours that change with infection [1,2]. Currently, any change in host behaviour associated with infection that benefits the pathogen (here used as a general term for an infectious agent) is broadly categorized as manipulation. This categorization is currently applied regardless of the mechanisms that lead to that change, the role of the host in these behaviours, or how the change in behaviour affects the fitness of the infected host. Thus, even if a change in behaviour is a consequence of host adaptive response or pathology, it can be classified as manipulation [3,4]. The argument underpinning this broad definition is that any change in host behaviour elicited by the pathogen (even if this behaviour is the result of an adaptive host response) will be selected for if it enhances transmission.

This definition can be problematic if it is misinterpreted to mean that all host behavioural changes are the result of active and direct action on the part of the pathogen. Indeed, the word manipulation casts the pathogen in the role of puppet master, dynamically pulling on the host's strings. In some instances, evidence supports this narrative. Pathogens can alter behaviour directly by interacting with the host tissues [3,5], secreting substances that act directly on the host nervous system [5], or high jacking host cells and tissues to express these modulators [6–9]. For example, evidence suggests that the parasite *Toxoplasma gondii* increases dopaminergic activity by directly producing an enzyme required for the synthesis of L-DOPA (a dopamine precursor) in its mouse host [10]. Increased dopamine levels have been associated with changes in fear perception, resulting in a reduced anti-predatory behaviour, which is thought to increase parasite transmission success in this tropically transmitted parasite [Reviewed by Ref. [11]]. These types of neuropharmacological manipulations produce many of the dramatic and novel behavioural phenotypes most commonly associated with manipulation [2].

However, the host can also play a large role in these changes, and more recent work has demonstrated that pathogens may indirectly alter behaviour by interacting with host tissues [5]. Some of these include psychoneuroimmunological changes in host behaviour, which derive from ancient bidirectional connections between the immune and nervous systems [9]. For example, it has been proposed that neuro-inflammation in response to infection, rather than direct pathogen interference, is responsible for altered behaviours in infected crustaceans

[12]. The behavioural phenotypes that derive from perturbations in these networks are often difficult to separate from generalized sickness behaviours [5].

Manipulation and vector feeding behaviour

Unlike classic manipulations leading to completely novel behaviours, such as those observed in *Cordyceps*-infected ants [13] or crickets carrying hairworms [14], changes in infected vector behaviour are for the most part changes in the degree and timing of normal behaviours. Notably, many behavioural changes in vectors are associated with feeding related behaviours (Table 1). For the purposes of this review we are focusing on changes in vector behaviour and not changes in the attractiveness of hosts [15–18]. These feeding events are both a point of contact between infectious vectors and susceptible hosts and intimately intertwined with major vector life history events such as reproduction.

Clarifying mechanisms of altered phenotypes is particularly important for vector-borne diseases (VBDs). Even minimal changes in vector behaviour in the small proportion of the population responsible for transmission can have large implications for pathogen transmission and human health [19]. Further, identification of the mechanisms responsible for behavioural change may lead to novel methods for targeting infected individuals and developing tools for manipulating vector behaviour to decrease transmission.

Details of the mechanisms by which pathogens alter vector behaviour are scarce. Changes in feeding efficiency have been linked to parasites physically blocking or inhibiting vector host functions to accomplish manipulation. For example, *Leishmania* parasites secrete a gel that blocks the feeding apparatus of sand flies [20]. Similarly, plague bacilli form a biofilm that blocks a portion of the flea midgut, resulting in repeated attempts at feeding and increased pathogen transmission [21]. Less, however, is known about the mechanisms driving the changes in host seeking patterns and persistence. Recent work in the malaria-mosquito system has highlighted the potential importance of host physiology in changes to vector feeding behaviour. We propose that changes in host physiology with infection are likely to play an important role in VBD systems and should be a priority for investigating the underpinning mechanisms of behavioural change associated with infection.

Table 1

Examples of vectors that exhibit altered feeding behaviours when infected with pathogens they transmit. There are many ways that pathogens alter vector physiology. Here we specifically focus on changes in host feeding behaviour as opposed to other behavioural changes (*e.g.*, dispersal), host physiological processes (*e.g.*, immunity) or host life history traits (*e.g.*, survival). These behaviours have been grouped into feeding efficiency (probing, regurgitation, ingestion, engorgement), host-seeking (response to host stimuli), and host-attack persistence (the probability that a vector attempts to bite multiple hosts or a single host multiple times). In some examples, direct mechanisms have been identified (yes or "Y"). In others, while the mechanisms have not been identified ("N"), they are known to be specific to infection with a particular pathogen as opposed to a general response to immune challenge. In still other cases, the response has been found to be non-specific and to involve host physiology. In these cases it is unclear whether indirect manipulation or simply a host response is responsible for altered behaviour. In a surprising number of cases, including economically and medically important pathogens, the specificity or role of the host in infection associated changes in feeding behaviour has not been investigated (indicated as "?")

Study	Vector/pathogen	Feeding behaviours altered by infection	Potential direct mechanism identified?	Specific to infection with VB pathogen?	Role of vector physiology?
[21]	Fleas/plague	Feeding efficiency	Y	Y	N
[20,38,39]	Sandflies/*Leishmania*	Feeding efficiency	Y	Y	N
[40,41]	Tsetse Flies/*Trypanosoma*	Feeding efficiency and host-attack persistence	Y	Y	N
[29–31,32•,42–45]	Mosquitoes/malaria parasites	Feeding efficiency	Y	Y	N
[46]	Mosquitoes/malaria parasites	Host-attack persistence and feeding efficiency	N	N	?
[25,26,27••]	Mosquitoes/malaria parasites	Host-seeking (however see Ref. [35])	N	N	Y
[47]	Mosquitoes/malaria parasites	Host-attack persistence	N	Y	?
[48•]	Mosquitoes/filarial parasites	Host-seeking	N	N	?
[49]	Mosquitoes/dengue Virus	Feeding efficiency	N	?	?
[50]	Mosquitoes/dengue Virus	Host-seeking	N	?	?
[50]	Mosquitoes/dengue Virus	Host-attack persistence	N	?	?
[51]	Mosquitoes/LaCrosse virus	Feeding efficiency	N	?	?
[52]	Midges/vesicular stomatitis virus	Feeding efficiency	N	?	?
[53]	Aphids/barley yellow dwarf virus	Host reference	N	?	?
[54]	Thrips/tomato spotted wilt virus	Feeding efficiency	N	?	?
[55]	White flies/tomato spotted wilt virus	Feeding efficiency	N	?	?