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Effects of malaria infection on mosquito olfaction and behavior: extrapolating data to the field

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Vector-borne pathogens have been shown to influence behavioral and other traits of their hosts and vectors across multiple systems, frequently in ways that enhance transmission. In malaria pathosystems, *Plasmodium* parasites have been reported to alter mosquito physiology, fitness and host-seeking behavior. Such effects on vector behavior have obvious medical relevance given their potential to influence disease transmission. However, most studies detailing these effects have faced methodological limitations, including experiments limited to laboratory settings with model vector/pathogen systems. Some recent studies indicate that similar effects may not be observed with natural field populations; furthermore, it has been suggested that previously reported effects on vectors might be explained by immune responses elicited due to the use of pathogen–vector systems that are not co-evolved. In light of these developments, further work is needed to determine the validity of extrapolation from laboratory studies to field conditions and to understand how parasite effects on vectors affect transmission dynamics in real-world settings.

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Introduction

Evidence from a wide range of studies suggests that vector-borne pathogens frequently manipulate host–vector interactions in ways that influence transmission [1–11]. In human disease systems, extensive research has focused on interactions between malaria parasites (*Plasmodium* spp.) and their mosquito vectors because of their profound impacts on global health [12–18,19••,20–22,23•,24••,25••,26]. Malaria transmission may potentially be affected by parasite effects on several different aspects of the host–vector interaction, including the host-seeking and feeding behavior of infected mosquitoes, as well as the relative attractiveness of infected and uninfected hosts to vectors [2] (Figure 1). Furthermore, there is considerable evidence, emerging primarily from laboratory-based studies, that malaria parasites do indeed influence such interactions [12,14,17,18,19••,20–22,23•,24••,26,27••,28•], and this work has potentially important implications for understanding malaria transmission and consequently for disease control efforts [29,30•]. Here we discuss key issues regarding the extrapolation of past findings to predict transmission under real-world conditions [31–33] and highlight the pressing need for additional research on this topic.

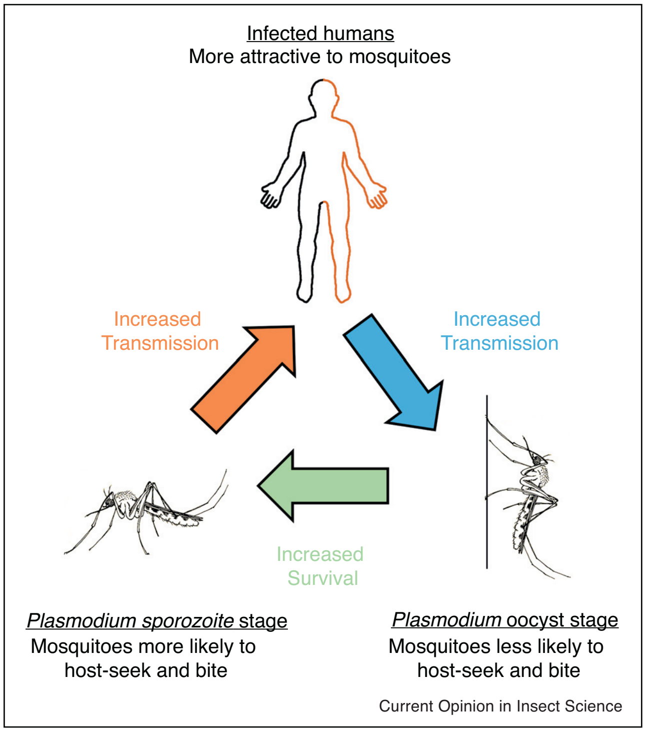
Evidence for *Plasmodium* manipulation of mosquitoes

Several laboratory studies have explored the possibility that *Plasmodium* parasites might influence mosquito feeding behavior, and a majority have reported such effects, including increased likelihood, frequency, persistence and duration of probing by infected mosquitoes (Table 1) [12,14,18,22]. Meanwhile, only two studies reported no effects of infection status on relevant traits, including the duration of probing and blood meal size [17,34]. Interestingly, the reported effects on mosquito behavior were observed exclusively during the transmissible sporozoite stage of the parasite's life cycle but not during the earlier, non-transmissible oocyst stage, consistent with the hypothesis that such effects reflect active manipulation by the parasite to enhance transmission. It has also been suggested that a decrease in biting behavior during non-transmissible stages may benefit the parasite, as feeding entails a risk of vector mortality [3,29]. Studies examining short- and mid-range host-seeking by *Plasmodium*-infected mosquitoes have reported a similar pattern of effects, with mosquitoes showing increased flight activity and attraction to hosts when the transmissible stage of the parasite is present but a decrease in these behaviors when only the non-transmissible stage is present [19••,20,24••,26]. Such findings have important implications for disease control, as they suggest that current models may significantly underestimate the intensity of transmission in the field and that incorporating the observed effects could conceivably lead to a three–fivefold increase in predicted transmission rates [29,30•].

Can mosquito immune responses explain behavioral alterations?

As noted, the findings discussed above are broadly consistent with parasite manipulation; however, recent

Figure 1



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Examples of behavioral alterations observed in malaria-infected mosquitoes and humans which may affect the transmission cycle. At the oocyst stage, malaria parasites are non-transmissible; at the sporozoite stage they can be transmitted by biting.

findings raise questions about this interpretation [19••,35]. *Plasmodium* infection has many effects on mosquito physiology (*e.g.*, increased reproductive costs, altered metabolism, and changes in lifespan), many of which are mediated by the mosquito's immune response to infection [2,36–40]. The demonstration by Cator *et al.* that inoculation with heat-killed *Escherichia coli* caused behavioral and electrophysiological changes in *Anopheles stephensi* mosquitoes similar to those reported following infection by *Plasmodium yoelii* suggested that immune responses might play an important role in mediating effects of infection on mosquito behavior [19••], and these authors speculated that the effects of a general immune response, rather than active manipulation by the parasite, could explain many of the behavioral effects previously reported from *Plasmodium* systems, possibly due to adaptive behaviour on the part of the mosquito to overcome the immune challenge. Consistent with this possibility, a follow-up study from the same group linked *E. coli* immune challenge to changes in insulin signalling that might potentially affect the sensitivity of olfactory receptor neurons [27••]. While these findings raise questions about the interpretation of previous results, they are not necessarily incompatible with the hypothesis that *Plasmodium* infection alters mosquito behavior in ways that influence transmission, as it is plausible that the parasite might exploit the natural immune responses of the vector in order to manipulate behavior, and there may also be *Plasmodium*-specific effects that remained unexplored. However, the questions raised by these recent findings highlight the need for more information about the exact nature of the behavioral effects that occur in natural populations.

The potential significance of parasite-vector co-evolution in natural systems

Until recently, only a few studies from the 1990s had examined the interaction between *Plasmodium* infection and mosquito biting behavior in field systems [13,15,16]. For example, Koella *et al.* collected mosquitoes from huts and found that those infected with *P. falciparum* displayed higher levels of engorgement and were more likely to contain blood taken from more than one host compared to uninfected individuals [13,15]. Meanwhile, a similar study by Wekesa *et al.* reported a positive effect of infection on the percentage of field-collected mosquitoes probing hamsters in the laboratory [16]. As each of these studies used mosquitoes collected directly from the field, the stage of *Plasmodium* infection was unknown, and host-location behavior was not examined.

In contrast to these early field studies – and the majority of previous laboratory studies discussed above [12–16,18,19••,20,22,24••,26] – a recent study by Vantaux *et al.* examining the effects of *P. falciparum* on *Anopheles coluzzii* behavior in naturally co-occurring populations reported no evidence of parasite effects on mosquito feeding behavior or on short- or long-range host-seeking in laboratory choice tests [25••]. The authors of this study hypothesized that the divergence of their findings from previous studies might be related to co-adaption between the parasite and its vector in natural populations, or rather to the lack thereof in most laboratory-based study systems, which frequently employ non-sympatric and co-evolved pathogen and vector models. Given the previously discussed observation that behavioral effects are often mediated by mosquito immune responses, such effects might well be heightened if responses are stronger when mosquitoes are infected by novel parasite strains; however, this would not explain differences previously reported for different species of field-collected mosquitoes [13,15,16], raising the possibility of variation across different species of *Plasmodium*/mosquitoes.

There is clear evidence of local adaptation in some *Plasmodium*-vector systems [41,42]. For example, sympatric infections of *P. falciparum* in *An. gambiae* resulted in lower infection prevalence compared to foreign ones [43]. Furthermore, infections in laboratory settings have been shown to lead to higher parasite burden in the vector than that observed under field conditions [44], and there is also evidence that the intensity of infection by *P. falciparum*