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Host location by arthropod vectors: are microorganisms in control?

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Vector-borne microorganisms are dependent on their arthropod vector for their transmission to and from vertebrates. The ‘parasite manipulation hypothesis’ states that microorganisms are likely to evolve manipulations of such interactions for their own selective benefit. Recent breakthroughs uncovered novel ecological interactions initiated by vector-borne microorganisms, which are linked to different stages of the host location by their arthropod vectors. Therefore, we give an actualised overview of the various means through which vector-borne microorganisms impact their vertebrate and arthropod hosts to ultimately benefit their own transmission. Harnessing the directionality and underlying mechanisms of these interactions driven by vector-borne microorganisms may provide tools to reduce the spread of pathogenic vector-borne microorganisms.

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Introduction

Microorganisms are considered an important part of the extended phenotype [1]. Indeed, the holobiont concept has been proven to extend to the health and behaviour of organisms across the tree of life [2,3]. (Micro) organisms inherently have a selfish nature, driven by the fundamental urge to ensure the spread and transmission of their genes [4]. Not all (micro)organisms can ensure this by themselves, and many depend on environmental factors or interactions with other organisms, often across different kingdoms. For instance, pollinators are instrumental in the evolutionary success of many plants by spreading their pollen, enabling plant reproduction [5]. Also, arthropod-vectored viruses, bacteria, protozoa and parasites (from now on referred to as vector-borne microorganisms) are dependent on arthropod vectors for their survival, spread, transmission and reproduction and thereby their evolutionary success [6].

At least three principal players, all with different interests, are involved in the spread of vector-borne microorganisms: i) the vector-borne microorganisms themselves; ii) the arthropod vector, which serves as an intermediate host and enables spread and transmission of the vector-borne microorganisms and iii) the vertebrate host where the vector-borne microorganisms replicate and/or sustain themselves [7,8]. Arthropod vectors are under selection to find a blood host to complete their lifecycle, whilst vertebrate hosts are under selection to become inconspicuous, acquire defensive traits or perform defensive behaviours against arthropod vectors due to the pathogenic microorganisms they may carry and the subsequent fitness costs these pathogenic microorganisms potentially bring [6,9,10]. Because vector-borne microorganisms are dependent on the success of their arthropod vectors, this increases the evolutionary pressure on vector-borne microorganisms to ensure their own spread or infectivity.

According to the ‘parasite manipulation hypothesis’, vector-borne microorganisms likely evolved intricate ways to manipulate the interactions between their arthropod vectors and vertebrate hosts to favour their own evolutionary success [11,12]. Indeed, vector-borne microorganisms are known to affect the physiology of their vertebrate host to favour the host preference of subsequent arthropod vectors [13]. In addition, arthropod vectors are subjected to alterations in their own physiology and homeostasis after infection by vector-borne microorganisms [8], which are known to extend to behavioural alterations [14]. These alterations may modify the vectorial capacity of the arthropod hosts, to the benefit of the vectored microorganisms [6,11,12].

Here, we delve into the various means through which vector-borne microorganisms impact their vertebrate and arthropod hosts to ultimately benefit their own transmission. Both the cues emitted by vertebrates, as well as several behavioural parameters of the arthropod vector potentially play a key role. We focus on the interactions involving pathogenic vector-borne microorganisms due to their role in the epidemiology of various emerging and established diseases globally [7,15]. Nevertheless, invertebrates and plants may also be similar victims of vector-borne diseases, with vector-borne microorganisms altering the homeostasis and behaviour of hosts and/or vectors [6,16]. Finally, we discuss current knowledge gaps and uncover innovative ways to harness the directionality of these interactions driven by vector-borne microorganisms, to ultimately reduce the spread of pathogenic vector-borne microorganisms [17].

Vertebrate skin bacteria guide the host preference of arthropod vectors

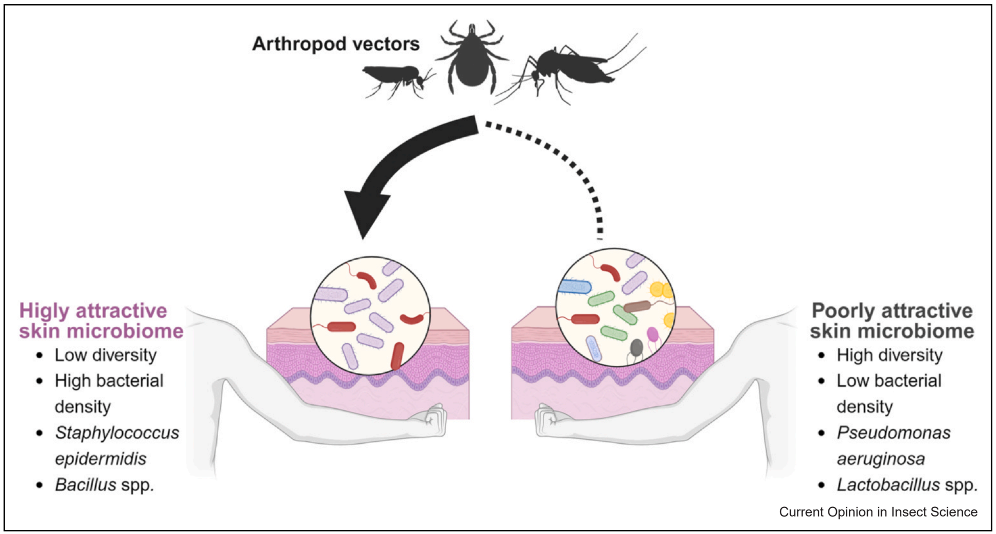
Arthropod vectors have evolved sophisticated sensory systems and foraging strategies to navigate their environment in search of blood hosts. When foraging, they use a layered foraging strategy in which they subsequently navigate from habitat to host, using the most reliable cues depending on their proximity to potential blood hosts [14,18]. At short range, body odours play a large role in the host preference of arthropod vectors, which are largely produced by microorganisms resident on the vertebrate skin [19]. Anthropophilic mosquitoes are often more attracted to blood hosts with bacterial communities that have a low(er) diversity and a high(er) bacterial density [20–22]. In addition, the presence of several specific bacterial species or strains may increase or decrease mosquito preference strongly (Figure 1) [21,23,24].

Similar patterns have been shown for interactions between different vertebrates, like mice and primates, and mosquitoes [25–27]. Triatomine bugs, which may vector the causal parasite of Chagas disease, are also attracted by odours produced by similar bacteria (*Staphylococcus* spp.) isolated from the human skin [28]. In addition, biting midges are attracted to volatiles produced by skin bacteria isolated from their sheep host, and again a *Staphylococcus* species was identified as attractive [29]. Regarding other arthropod vectors such as ticks, tsetse flies and lice, knowledge on the link between vertebrate host microbiome and arthropod vector preference is limited (but see Ref. [30]). More studies are needed to confirm whether similar effects of bacterial abundance and diversity also influence host location and host selection by other arthropod vectors.

Vertebrates infected by vector-borne microorganisms have an increased attractivity for arthropod vectors

Because of the important role of skin microorganisms, vector-borne microorganisms affecting the vertebrate skin microbiome can have a substantial impact on the interaction between vertebrates and their arthropod vectors. It is well-established that infected vertebrates become more attractive to arthropod vectors compared to their uninfected conspecifics [13,27]. Indeed, this is attributed to changes in microbial communities affecting vertebrate body odour profiles. For example, mice infected with *Leishmania* parasites have an altered skin

Figure 1



Skin microorganisms impact the host preference of uninfected arthropod vectors. The composition of the skin microbiome and the presence of specific bacterial species or strains impact the preference of arthropod vectors, affecting the attractiveness of uninfected vertebrate hosts.

microbiome, also linked to dysbiosis [31]. The microbiome of *Leishmania*-infected individuals has characteristics of more attractive individuals (as mentioned in section 2; Figure 1). This results in a higher attractiveness for the sandfly vector, increasing the uptake and subsequent spread of the parasite [32]. In addition, individuals infected with *Plasmodium falciparum*, the causal agent of malaria, are known to be more attractive to mosquitoes due to alterations in their body and blood odour [25,33–37], and ticks prefer the odours of *Borrelia afzelii*–infected voles over uninfected voles [38]. Tick bites alter the (local) skin microbiome, which may play a role in the pathogen transmission [39]. However, studies linking arthropod vector preference to the dermal microbiome of pathogen-infected vertebrate hosts are scarce. A direct link between the increased attraction after *Borrelia* and *Plasmodium* infection to alterations of the dermal microbiome is currently still missing and should be the focus of future research.

Zhang et al. pioneered a study linking changes in the dermal microbiome upon infection with dengue virus (DENV) and Zika virus (ZIKV) with body odours [27]. This study demonstrated that arthropod-borne viruses (arboviruses) alter the skin microbiome of a mammalian host to increase their attractivity to mosquitoes in favour of their own transmission. Bacteria increasing the vertebrate host attractivity are enriched after arbovirus infection, leading to increased production of the volatile compound acetophenone, which is shown to be attractive to mosquitoes. This study highlights the mechanism behind this alteration. Arboviruses can downregulate an antimicrobial peptide, favouring the acetophenone-producing bacteria over bacteria in dermal microbiome [27]. In addition, cytokines have been identified to possess antimicrobial properties [40] and play a key role in the antimicrobial defences of vertebrates by regulating immunological processes including those of the skin [41,42]. Cytokines and antimicrobial peptides impact each other bi-directionally [43], and the presence of viruses and/or mosquito saliva modulates the presence of (anti-)inflammatory cytokines [44,45]. Hence, this presents a route through which vector-borne microorganisms may manipulate the composition of the vertebrate skin microbiome for their own benefit (Figure 2b).

Such targeted alterations of the vertebrate host microbiome increase the uptake of vector-borne microorganisms (Figure 2a). We propose that the increased attractiveness of infected vertebrates is not merely a by-product of infection and immunity but results from selection on traits of vector-borne microorganisms favouring host manipulations. Future research should delve into the consistency of microbiome alterations between different vector–host combinations. We propose studies to characterise the dermal microbiome of individuals in vertebrate populations with endemic vector-borne diseases such as malaria, ZIKV, or yellow fever. Identifying the core microbiome of infected individuals will open new avenues for vector control strategies, for example, by selectively targeting enriched bacteria or by inhibiting the production of their attractive cues. A mechanistic understanding of these interactions may also open doors for novel solutions. In the case of DENV/ZIKV manipulations, a supplementation of vitamin A was demonstrated to be a direct solution to compensate for the arbovirus-induced inhibition of the antimicrobial peptide [27]. Future studies should pay special attention to antimicrobial peptides and cytokines of vertebrates, as these are promising targets for vector-borne microorganisms to manipulate the attractiveness of infected vertebrate hosts towards subsequent vectors (Figure 2b).

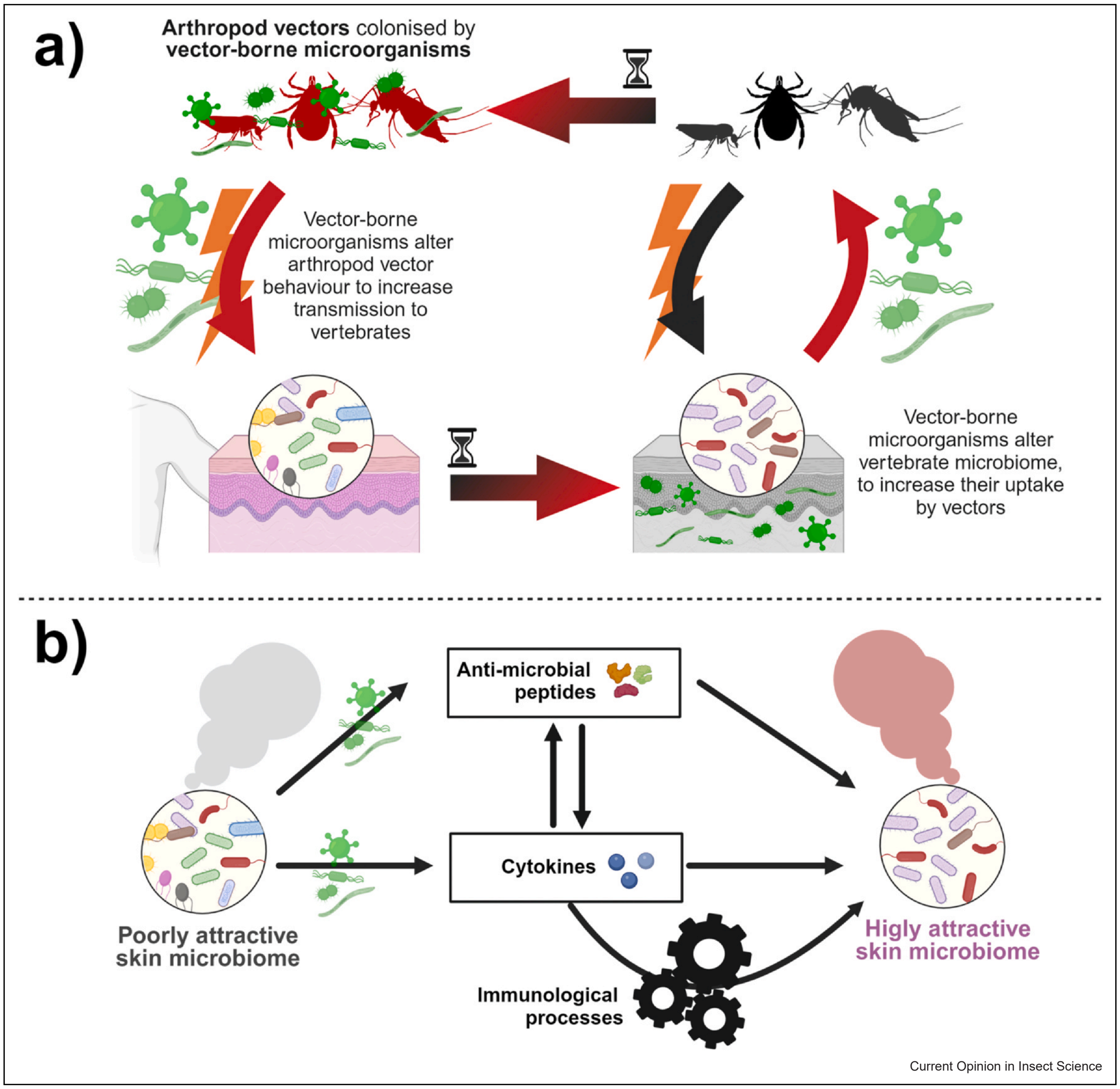
Infected vectors are modulated to favour the transmission of vector-borne microorganisms

When vector-borne microorganisms are ingested by their arthropod vector(s), they must overcome immunity, disseminate themselves throughout the arthropod vector and become resident in the salivary glands (or gut) to initiate their spread [15,46]. Evolutionary pressure likely drives vector-borne microorganisms to improve their transmission to vertebrate hosts, where they can propagate themselves most efficiently. Indeed, numerous studies have shown that infected arthropod vectors exhibit physiological and behavioural changes in a vector-borne microorganism–specific way [47]. Physiological alterations cause changes in resource allocation to increase the longevity of arthropod vector, in benefit of the timeframe length during which vector-borne microorganisms can be spread [12]. Behavioural alterations mainly occur at the host selection and feeding stage of arthropod vector host location and can affect the transmission of vector-borne microorganisms strongly [47]. Below, we discuss the behavioural changes of arthropod vectors driven by vector-borne microorganisms and the impact on the transmission of vector-borne microorganisms.

Vector-borne microorganisms alter the host-encounter rate of arthropod vectors, but not their host preference

Vector-borne microorganisms benefit most when they can manipulate infected arthropod vectors to have i) an increased contact with suitable hosts and ii) a preference for individuals who do not harbour the vector-borne microorganism yet [6,10]. A plethora of arthropod vectors have altered activity patterns after infection by vector-borne microorganisms, leading to increased host contacts (Figure 2a) [36,48,49]. For example, infection by *Borrelia burgdorferi* or tick-borne encephalitis virus increases the activity, mobility and aggressiveness of ticks that promote the transmission of vector-borne microorganisms [50,51]. Similarly, triatomine bugs infected by parasitic protists of *Trypanosoma* spp. were shown to take

Figure 2



Infection by vector-borne microorganisms impacts the characteristics of arthropod vectors and the vertebrate skin microbiome. **(a)** A wide range of arthropod vectors show altered behavioural patterns after infection by vector-borne microorganisms, resulting in increased interactions with potential hosts. After a successful infection by vector-borne microorganisms, vertebrate hosts become more attractive to uninfected arthropod vectors, increasing the spread of vector-borne microorganisms. Lightning bolts indicate the occurrence of host alterations by vector-borne microorganisms to increase their transmission or uptake. **(b)** Putative mechanisms through which vector-borne microorganisms can alter the skin microbiome of vertebrates after infection. Vector-borne microorganisms can alter the presence of antimicrobial peptides and cytokines, which both (in-)directly affect the composition of the skin microbiome.

increased risks during predation, facilitating increased parasite transmission to mammal hosts [52,53]. Arthropod vectors infected by vector-borne microorganisms are known to have an increased sensitivity to host odours compared to uninfected vectors [14,54–56], though the opposite has been shown as well [57,58]. Changes in arthropod vector behaviour are likely dependent on the type, life stage and localisation of the vector-borne microorganism within the arthropod vector [47,49,59] and thus may be less obvious at certain timepoints. For example, the dissemination of DENV into the salivary glands is known to coincide with the invasion of the head and antennae, which are required for the perception of olfactory cues [54]. Thus, manipulations of arthropod vectors may not always be evident at every timepoint after dissemination, and observing manipulations requires attention for the sensory biology of the arthropod vectors.

Besides host affinity, the host selection of arthropod vectors also has a large impact on the transmission rate of vector-borne microorganisms [6]. When vector-borne microorganisms are in control of this part of the tripartite interaction, infected arthropod vectors are expected to prefer uninfected hosts [6], as demonstrated in a plant-insect-virus pathosystem [60]. However, the outcome of several studies makes it seem unlikely that this manipulation exists for vertebrate pathogens. For example, mosquitoes prefer birds infected with the avian malaria parasite *Plasmodium relictum*, regardless of whether the mosquitoes themselves are infected [61]. Similarly, mosquitoes infected with West Nile Virus and La Crosse Virus are not altered in their host preference to favour virus transmission [57,62]. A recent field study found that mosquitoes infected with *Plasmodium falciparum* are even more likely to bite humans who are also infected [63], negatively impacting the transmission rate of *P. falciparum* [6]. Further research is needed to determine if this pattern holds for the interaction between other arthropod vectors and their vector-borne microorganisms. We suggest full-factorial studies involving both infected and uninfected arthropod vectors and their vertebrate hosts, as done by Cornet et al. [61].

Vector-borne microorganisms increase the transmission rate of their arthropod hosts

In concert with host selection, the blood-feeding stage presents a critical window where the influence of vector-borne microorganisms on their arthropod vectors becomes most apparent. The blood-feeding behaviour of infected arthropod vectors most directly affects the transmission rate of vector-borne microorganisms and is thus a high-priority target to be manipulated. While vector-borne microorganisms do not seem to alter the host preference of arthropod vectors, their impact is most evident during the critical blood-feeding stage. A wide range of arthropod vectors, including fleas, tsetse flies, sand flies and mosquitoes, have a disrupted blood uptake mechanism after infection by vector-borne microorganisms [11–13]. Tsetse flies infected by *T. brucei* have a modulated composition of their saliva, hampering their blood-feeding performance. This alteration increases the duration of blood-feeding and thus the likelihood of parasite transmission [64]. Mosquitoes are more persistent in their feeding attempts [59] and have an altered duration and size of bloodmeals after infection by vector-borne microorganisms [65–67]. Such alterations in the blood-feeding stage cause an increased biting and vector competence of arthropod vectors, facilitating an increased transmission of vector-borne microorganisms [12,46,67].

Linking biting behaviour to the infectivity of arthropod vectors is often a difficult task. A key study by Wei Xiang et al. harnessed a close-up video recording setup to analyse the final stages in the host location of DENV-infected mosquitoes [14]. Their findings confirm that DENV-infected mosquitoes have a higher affinity to the vertebrate host but an increased number of probes before blood ingestion and a higher number of unsuccessful bites. Using immunocompromised mice, this study demonstrated that short successive probes already led to transmission of the pathogen, which remains effective after consecutively probing up to three different mice [14]. Sequential (uninfected) bloodmeals also increase the vector competence of arthropod vectors [67,68]. Thus, behavioural alterations induced by vector-borne microorganisms go hand in hand with an increase in the transmission towards their vertebrate hosts.

Beyond visible feeding parameters, the feeding behaviour of arthropod vectors after penetrating the skin has the potential to play an equally large role in the transmission of vector-borne microorganisms [69]. Parameters like salivation time, time to find a blood vessel and blood ingestion time affect the transmission of vector-borne microorganisms [13,46] but are often not directly measured due to their limited visibility. We propose electropenetrography (EPG), often used in plant–insect interactions, as an approach to investigate this currently unknown interface [70]. Using this method, it was already demonstrated that infected arthropod vectors of plant viruses have an altered feeding behaviour to increase viral transmission [71].

Conclusion/discussion: are vector-borne microorganisms in control?

Because of the exploitative nature of the relationship with their hosts, vector-borne microorganisms are bound to alter their host in some way and cause adaptive changes (by-products of physiological activities) [11,12]. When vector-borne microorganisms are in control of the interaction with their host(s), we expect true manipulations to be more evident than adaptive changes. True manipulations differentiate themselves from adaptive manipulations by having i) a clear cause and effect (e.g. targeted products that manipulate host pathways) and ii) strictly must increase the transmission of vector-borne microorganisms [12,72]. We identified various means through which vector-borne microorganisms ultimately benefit their own transmission. To further disentangle whether vector-borne microorganisms are in control of the tripartite interaction, future studies should aim to identify parasite-produced products that manipulate host pathways. This has been demonstrated for *P. falciparum*, which produces a metabolite (HMBPP), inducing red blood cells to release CO_2 and other attractive volatile compounds, increasing the attractivity of the vertebrate blood [37]. This has the potential to increase the attractivity of the vertebrate host, but it is currently unknown how vertebrate (skin) volatiles and mosquito attraction are impacted by such changes. Similarly, we speculate that products of various vector-borne microorganisms target (the production of) antimicrobial peptides and/or cytokines to increase the attractiveness of their vertebrate host [27].

Understanding the interactions driven by vector-borne microorganisms can open new avenues for vector control. The characteristics of poorly attractive microbiomes may be used as blueprint to decrease the attractiveness of vertebrate hosts to arthropod vectors, for example, by using pre- or probiotics to steer the microbiota [73]. Odour-based traps are shown to be an effective intervention to reduce malaria incidence [74]. Traps including characteristic skin microorganisms present on attractive hosts, or the attractive volatile compounds they produce, may enhance the efficacy and continuity of such interventions. In addition, we propose innovative vector control strategies that target these skin microorganisms on vertebrates. For example, bacteriophage-derived endolysins can provide us with new tools due to their specificity, allowing selective removal of attractive bacterial species from a skin bacterial community [75].

Recent developments in vector biology increasingly take vector-borne microorganisms and their manipulations into account. Vector-borne microorganisms impact the host-location process of their arthropod hosts, by impacting the cues emitted by vertebrates, as well as by triggering several behavioural alterations of the arthropod vector. We argue that the vector-borne microorganisms appear to steer the host preference of arthropod vectors in such ways that they (vector-borne microorganisms) are, indeed, in control of the tripartite interaction. Future efforts will teach us only more about the exciting mechanisms through which these manipulations occur.

Data Availability

No data were used for the research described in the article.

Declaration of Competing Interest

None.

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