Evolution and Manipulation of Vector Host Choice

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abstract: The transmission of many animal and plant diseases relies on the behavior of arthropod vectors. In particular, the specific preference for infected or uninfected hosts observed in many vector species is expected to affect the circulation of vector-borne diseases. Here I develop a theoretical framework to study the epidemiology and evolution of the manipulation of host choice behavior of vectors. I show that vector preference strategies have dramatic epidemiological consequences. I also explore the evolution of vector host choice under different scenarios regarding control of the vector behavior by the pathogen. This analysis yields multiple evolutionary outcomes and explains the diversity of host choice behaviors observed in a broad range of vector-borne diseases. In particular, this analysis helps us understand why several pathogens have evolved manipulation strategies that vary with the infectious status of their vector species while other pathogens seem unable to evolve such complex conditional strategies. I argue that contrasting the behavior of infected and uninfected vectors is key to revealing the mechanistic constraints acting on the evolution of the manipulation of vector behavior.

Keywords: vector-borne disease, parasite manipulation, vector behavior, evolutionary epidemiology theory.

Introduction

Many animal and plant infectious diseases are transmitted by arthropod vectors. In humans, several deadly vector-borne diseases (e.g., malaria, yellow fever, dengue, West Nile fever) are transmitted by mosquitoes or other insect species (sandflies, fleas, ticks, tsetse flies). In plants, numerous other vector species (e.g., aphids, leafhoppers, whiteflies) are involved in the transmission of viral and bacterial infections. In spite of the diversity of species involved, the epidemiology of vector-borne diseases can be captured by relatively simple mathematical models describing the pathogen life cycle across the main host (e.g., a vertebrate, a plant) and the vector (usually an insect; Ross 1916; Macdonald 1957; Bailey 1975; Koella 1991; Anderson and May 1992; Antonovics et al. 1995). These epidemiological models have clarified the impact of several life-history traits of the vector species for pathogen transmission and pointed out that different components of the biting behavior of the vector have dramatic consequences for disease dynamics. First, the biting rate has a direct impact on pathogen transmission because more frequent biting increases the probability of infecting a new host. Second, host choice behavior (i.e., the preference to bite specific types of hosts) may also have important consequences for pathogen epidemiology. For instance, a preference to bite a host species that is resistant to a specific pathogen is expected to hamper the spread of the disease (Macdonald 1957; Elton 2000; Ostfeld and Keesing 2012). However, even within a single host species the vector may also exhibit a preference between different types of hosts. The choice to bite infected or uninfected hosts is key for pathogen transmission. Several epidemiological models have shown that vector preference for infected hosts can boost transmission during the early stage of the epidemic (Kingsolver 1987; Antonovics et al. 1995; McElhany et al. 1995; Hosack et al. 2008; Sisterson 2008; Chamchod and Britton 2011; Roosien et al. 2013). Yet extreme preference for infected (or uninfected) hosts can also limit or even stop pathogen transmission.

Interestingly, several vector-borne pathogens have been shown to manipulate different behavioral components of their vectors to promote their transmission to new hosts (Moore 2002; Lehane 2005; Lefèvre and Thomas 2008). Previous studies mainly focused on the adaptive manipulation hypothesis, in which the pathogen is expected to increase the biting rate of infected vectors (Koella 1999; Schwartz and Koella 2001; Moore 2002; Lehane 2005; Lefèvre and Thomas 2008; Stafford et al. 2011; Cator et al. 2012, 2013). In contrast, the study of the manipulation of host choice behavior remains relatively unexplored. While many of those studies focused on the host choice behavior of uninfected vectors, a limited (but growing) number of experimental studies have contrasted the

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host choice behavior of infected and uninfected vectors (for a review of these studies, see the supplemental material, available online). Figure 1 summarizes the observed behavioral patterns obtained over a range of pathosystems. Each point on the figure presents the preference of uninfected vectors for infected hosts (*X*-axis) and the preference of infected vectors for infected hosts (*Y*-axis). Preference is a dimensionless number between 0 and 1 that measures the attraction to infected hosts. This preference can be measured experimentally as the proportion of vectors that chose to feed on infected hosts when they are given a choice between uninfected and infected hosts. The absence of preference corresponds to the value 0.5, at the center of the figure (the intersection between dashed lines), and deviations from this point indicate preference or aversion for infected hosts (for more details on each of these studies, see table S1, available online). The graph illustrates a diverse range of host choice behaviors. Note that several points lay on the diagonal (Mauck et al. 2010; Mann et al. 2012; Shapiro et al. 2012; Cornet et al. 2013*a*, 2013*b*), which indicates that uninfected and infected vectors behave similarly. Note also that several points fall below the diagonal, which indicates that uninfected vectors are attracted by infected hosts while infected vectors are attracted by uninfected hosts (Ingwell et al. 2012; Fang et al. 2013; Rajabaskar et al. 2014; Legarrea et al. 2015; Fereres et al. 2016; Mauck et al. 2016). Such a conditional modification of vector behavior is likely to promote pathogen transmission and may thus result from a manipulation of the vector by the pathogen. Yet the analysis of the adaptive nature of these behavioral modifications requires taking into account different scenarios. This behavior may be under the control of (i) the vector itself, (ii) the pathogen infecting the vector, and/or (iii) the pathogen infecting the host (because the pathogen may modify vector behavior through a manipulation of the attractiveness of the infected hosts). The emergence of potential conflicts between these different actors raises a theoretical challenge and thus requires a mathematical analysis of the manipulation hypothesis.

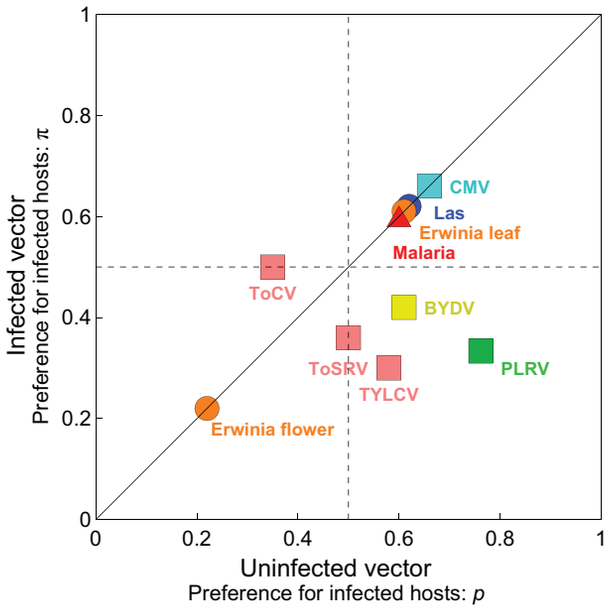

Figure 1: Host choice (preference for the infected host) in uninfected and infected vectors of different pathogens: barley yellow dwarf virus (BYDV), potato leaf roll virus (PLRV), cucumber mosaic virus (CMV), tomato yellow leaf curl virus (TYLCV), tomato severe rugose virus (ToSRV), tomato chlorosis virus (ToCV), *Candidatus liberibacter asiaticus* (Las), *Erwinia tracheiphila* (wilt disease), and *Plasmodium relictum* (avian malaria). A detailed presentation of the studies used to make this figure is available in the supplemental material (table S1). Different symbols are used to distinguish between viruses (circles), bacteria (squares), and protozoa (triangles).

Here I develop a theoretical framework to explore the consequences of vector host choice behavior for the epidemiology and evolution of vector-borne diseases. First, I develop a general epidemiological model to study the impact of the behavior of both infected and uninfected vectors on the epidemiology and persistence of the disease. Second, I use this epidemiological model to study the evolution of vector behavior. Different scenarios, with or without manipulation, are contrasted to discuss the adaptive nature of these modifications of host preference for the vector or for the pathogen. The fascinating diversity of vector behaviors in animal and plant vector-borne diseases is discussed in the light of this theoretical model. In particular, I argue that the observed diversity of behavioral preference of uninfected and infected vectors can be explained by different mechanistic constraints acting on the ability of the pathogen to manipulate its vector.

The Epidemiological Model

Three organisms interact in this vector-borne disease model: the host, the vector (usually an insect), and the pathogen (e.g., viruses, bacteria, protozoa). The host can be either infected (state I) or uninfected (state S), and similarly the vector can be either infected (state V_I) or uninfected (state V_S). The following set of differential equations governs the dynamics of the densities of these different types of individuals (for a summary of the main parameters, see table 1; for details on the derivation of this model, see the supplemental material):

$$\begin{aligned}
\dot{V}_S &= \lambda_S + \lambda_I - V_S b \frac{a_I I}{1 + \tau(a_S S + a_I I)} - \delta_{V_S} V_S, \\
\dot{V}_I &= V_S b \frac{a_I I}{1 + \tau(a_S S + a_I I)} - \delta_{V_I} V_I, \\
\dot{I} &= V_I \beta \frac{\alpha_S S}{1 + \tau(\alpha_S S + \alpha_I I)} - dI,
\end{aligned} \tag{1}$$

Table 1: Definitions of the main parameters of the model

Parameter	Definition
$N_H = S + I$	Host density (susceptible + infected)
$N_V = V_S + V_I$	Vector density (susceptible + infected)
$p = \frac{a_I}{a_S + a_I}$, $\pi = \frac{\alpha_I}{\alpha_S + \alpha_I}$	Preference for infected hosts in uninfected and infected vectors
$a = a_S + a_I$	Searching efficiency of uninfected vectors
$\alpha = \alpha_S + \alpha_I$	Searching efficiency of infected vectors
b	Probability that an uninfected vector gets infected after biting an infected host
β	Probability that an uninfected host gets infected after being bitten by an infected vector
τ	Handling time
$\lambda_S = V_S f_S(1 - \kappa N_V)$	Fecundity of uninfected vectors
$\lambda_I = V_I f_I(1 - \kappa N_V)$	Fecundity of infected vectors
f_S, f_I	Per capita fecundities of uninfected and infected vectors
F_S, F_I	Maximal fecundities of uninfected and infected vectors
κ	Intensity of density dependence on vector fecundity
d	Mortality rate of infected host
δ_{V_S}, δ_{V_I}	Mortality rates of susceptible and infected vectors
R_0	Basic reproduction ratio of the pathogen
R_{Vm}	Per-generation invasion ratio of a mutant vector
R_{Pm}	Per-generation invasion ratio of a mutant pathogen
ϕ	Quality (for the fecundity of the vector) of the infected host relative to the uninfected host
ϕ_H, ϕ_V	Probability of superinfection of an infected host and an infected vector, respectively
ρ	Cost associated with a bias in vector preference

where $\lambda_S = V_S f_S(1 - \kappa N_V)$ and $\lambda_I = V_I f_I(1 - \kappa N_V)$ refer to the density-dependent fecundity of uninfected and infected vectors, respectively. The parameter κ measures the intensity of density dependence, while f_S and f_I measure the per capita fecundity of uninfected and infected vectors, respectively. The density of the whole population of the vector, $N_V = V_S + V_I$, is allowed to vary with the dynamics of both uninfected and infected vectors. The first phase of the pathogen life cycle is the infection of the vector after feeding on an infected host. The parameter b is the probability that the vector gets infected after biting an infected host. The behavior of the uninfected vectors is governed by the parameters a_S and a_I, which refer to the searching efficiency of uninfected and infected hosts, respectively. The parameter τ is the handling time of the host by the vector and includes the time taken to bite after landing on the host but also the time taken to digest before an attempt to bite a new host. For instance, many hematophagous vectors need to digest their blood meal before seeking a new host. When the handling time is very small, the number of infected bites varies linearly with the number of susceptible hosts. When this handling time is large, it is the frequency of uninfected hosts that governs the epidemiological dynamics (Antonovics et al. 1995; McCallum et al. 2001). The derivation of this Holling type II response is detailed in the supplemental material. The pathogen is allowed to affect vector survival with specific mortality rates for uninfected and infected vectors (δ_{V_S} and δ_{V_I}, respectively).

The second phase of the pathogen life cycle is the infection of the host by infected vectors. For the sake of simplicity, I assume, as in classical vector-borne disease models (Ross 1916; Macdonald 1957; Koella 1991; Anderson and May 1992), that the total density of hosts, $N_H = S + I$, is constant. This means that whenever a host dies (this occurs at a constant rate d), it is immediately replaced by a new susceptible host. The parameter β is the probability that the host gets infected after being bitten by an infected vector. The behavior of the infected vectors is governed by the parameters α_S and α_I, which refer to the searching efficiency toward uninfected and infected hosts, respectively.

To determine the ability of a pathogen to invade a disease-free environment, I derive the pathogen's basic reproduction ratio R_0 (see the appendix, available online):

$$R_0 = \sqrt{\frac{b\beta N_H N_V}{d\delta_{V_I}} \frac{\alpha_S}{1 + \tau\alpha_S N_H} \frac{a_I}{1 + \tau a_S N_H}}, \tag{2a}$$

where $N_V = (f_S - \delta_{V_S})/(\kappa f_S)$ is the equilibrium density of the vector when the pathogen is absent. The pathogen can invade this disease-free equilibrium when $R_0 > 1$. Higher vector density is always increasing R_0, but the effect of host density depends critically on the handling time τ. When τ is small (i.e., $\tau \ll 1/(a_S N_H)$ and $\tau \ll 1/(\alpha_S N_H)$), the basic reproduction ratio reduces to

$$R_0 = \sqrt{\frac{b\beta N_H N_V \alpha_S a_I}{d\delta_{V_I}}}. \tag{2b}$$

We recover a classical density-dependent transmission model where R_0 increases with host density (McCallum et al. 2001). In contrast, when τ is high (i.e., $\tau \gg 1/(a_S N_H)$ and $\tau \gg 1/(\alpha_S N_H)$), the basic reproduction ratio reduces to

$$R_0 = \sqrt{\frac{b\beta}{\tau^2 d\delta_{V_I}} \frac{N_V}{N_H} \frac{a_I}{a_S}}. \tag{2c}$$

We recover a classical frequency-dependent transmission model where R_0 decreases with higher host density (McCallum et al. 2001).

The above expressions can be used to show how the behavior of both uninfected and infected vectors affect the basic reproduction ratio of the pathogen. At this stage, it is particularly useful to rewrite searching rates in terms of vector preference for uninfected and infected hosts. More specifically, I introduce the parameters p and π that control the preference for infected hosts in uninfected and infected vectors, respectively. These two dimensionless parameters can be written as ratios of searching rates ($p = a_I/(a_S + a_I)$ and $\pi = \alpha_I/(\alpha_S + \alpha_I)$) and are readily measurable in behavioral assays where the vector has to choose between uninfected or infected hosts (fig. 1). Both the preference of uninfected vectors for infected hosts (large p) and the attraction of infected vectors to susceptible hosts (low π) increase R_0. Note, however, that when τ is high, the basic reproduction ratio depends only on the behavior of uninfected vectors (see eq. [2c]). This latter scenario is particularly relevant because it corresponds to the classical model of malaria transmission (Ross 1916; Macdonald 1957; Koella 1991; Anderson and May 1992). Figure 2 shows that even a modest bias in preference for infected hosts can have an important impact on R_0, in particular when τ is high. More generally, figure 3*A* illustrates that R_0 is maximized when uninfected vectors prefer biting infected hosts and when infected vectors prefer biting uninfected hosts. This figure also illustrates that extreme choice strategies can lead to parasite extinction (i.e., $R_0 < 1$). In particular, when infected vectors avoid uninfected hosts and/or when uninfected vectors avoid infected hosts, the pathogen has difficulties to complete its life cycle between the host and the vector compartments. But when $R_0 > 1$, the pathogen can invade the host population, and the system reaches an endemic equilibrium where the host, the vector, and the pathogen can coexist (the notation $\bar{x}$ is used to refer to the equilibrium density of the variable x at this endemic equilibrium). Numerical exploration of system (1) revealed that this endemic equilibrium was always locally stable.

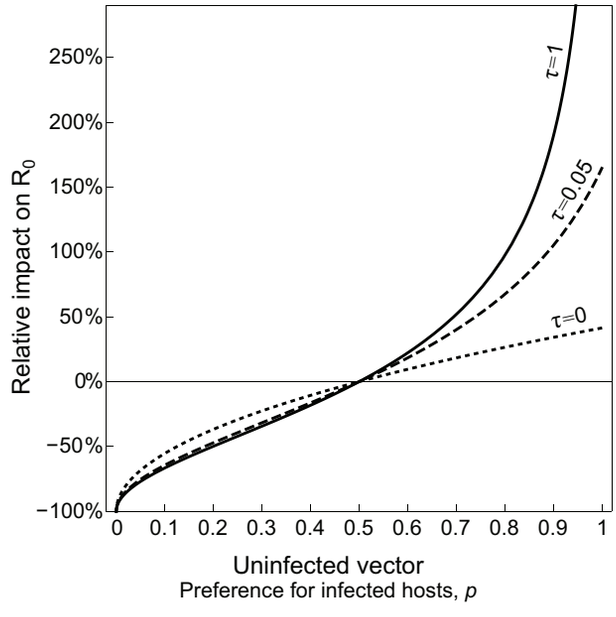

Figure 2: Relative impact of vector host choice (preference for the infected host) on the basic reproduction ratio of the pathogen for different values of handling time: $\tau = 0$ (short-dashed line), $\tau = 0.05$ (long-dashed line), and $\tau = 1$ (full line). This figure plots the ratio $(R_0 - R_0^*)/R_0^*$, where R_0 is given in equation (2) and R_0^* is the value of R_0 in the absence of vector preference (i.e., $p = \pi = 0.5$).

In figure 3*A*, the per capita fecundities f_S and f_I are assumed to be fixed quantities. The fecundity of many vector species, however, is likely to be limited by the availability and/or the quality of different types of hosts. Consequently, in the following I will assume that the fecundity of both infected and uninfected vectors may also depend on vector behavior:

$$f_S = F_S \frac{a_S S + a_I \phi I}{1 + \tau(a_S S + a_I I)},$$
$$f_I = F_I \frac{\alpha_S S + \alpha_I \phi I}{1 + \tau(\alpha_S S + \alpha_I I)}, \tag{3}$$

where F_S and F_I are the maximal fecundities of uninfected and infected vectors, respectively. The parameter ϕ measures the intrinsic quality of the infected host relative to the uninfected host. For instance, $\phi < 1$ indicates that infected hosts may provide fewer nutrients than healthy ones (e.g., in the case of malaria because of anemia). The influence of vector behavior on vector fecundity can lead to complex epidemiological dynamics. For instance, the dynamical system may exhibit backward bifurcation at $R_0 = 1$. In other words, depending on the initial condition, the pathogen may either become extinct or reach an endemic equilibrium when $R_0 < 1$. In particular, this occurs when the preference of uninfected vectors for infected hosts becomes very pronounced (fig. 3*B*). Indeed, when the prevalence of the infection in the host is initially very low and the vector has a strong preference for infected hosts, it is very difficult to find a host to feed on. Many vectors will die before reproducing, and the vector population goes down. This further reduces the prevalence of the infection and ultimately leads to pathogen extinction. But if the prevalence is initially high, the vector with a strong preference for infected hosts has no difficulty finding a suitable host to feed on. Consequently, vector reproduction is abundant and maintains persistence of the vector population. This high vector density promotes

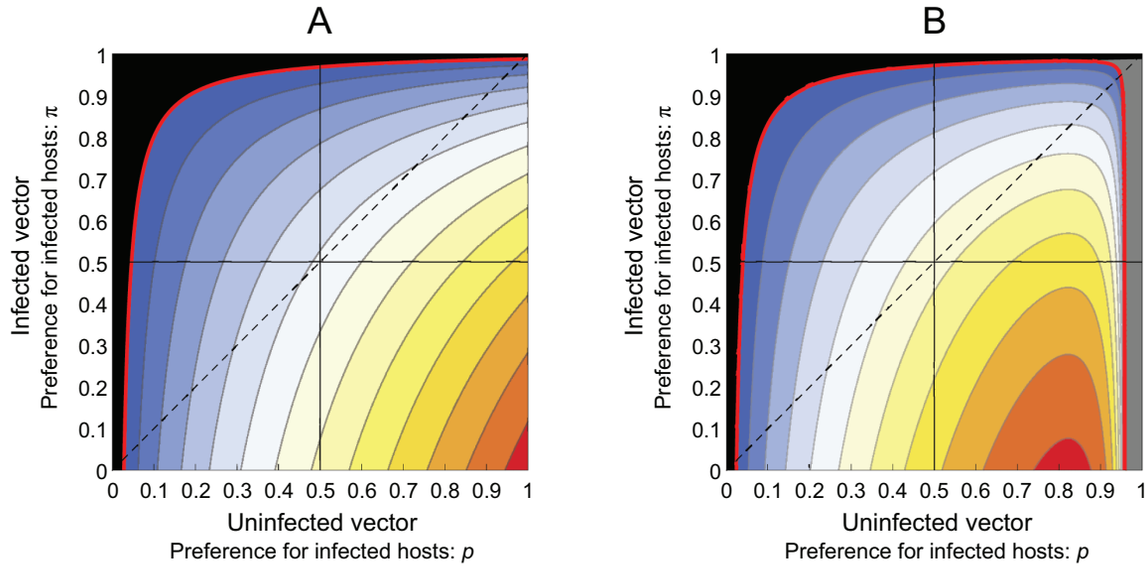

Figure 3: Effect of vector host choice (preference for the infected host) on the basic reproduction ratio R_0 of the pathogen given in equation (2). The red line indicates the threshold value where $R_0 = 1$, and the different colors indicate increasing values of R_0 from 1 to 7, with 0.5 steps (blue to red). In *A*, the density N_V of the vector before the introduction of the pathogen does not depend on host choice behavior because vector fecundity is assumed to be constant $f_S = 5$. In *B*, the density N_V of the vector depends on vector behavior because fecundity is assumed to depend on host preference, as indicated in equation (3), with $F_S = 5$. Note that when uninfected vectors prefer infected hosts, the system exhibits a backward bifurcation at $R_0 = 1$, and, depending on the initial conditions of the system, the pathogen may either become extinct or reach an endemic equilibrium when $R_0 < 1$ (in the gray area). The black area indicates the parameter region where the pathogen is always driven to extinction. Other parameter values are $N_H = 500$, $\kappa = 0.01$, $b = \beta = 1$, $d = 0.05$, $\delta_{V_S} = \delta_{V_I} = 1$, $\tau = 0.1$, and $a = \alpha = 0.01$.

pathogen transmission and allows the pathogen population to escape extinction.

Evolution

In the following, I study the long-term evolutionary dynamics of the above dynamical system. Using the classical formalism of adaptive dynamics, I assume the mutation rate to be low, which allows decoupling evolutionary and epidemiological dynamics (Metz et al. 1992; Geritz et al. 1998; Waxman and Gavrilets 2005; Kisdi and Geritz 2010). In other words, I study the evolution of vector behavior (i.e., searching efficiency, host choice preference) through the derivation of the invasion of rare mutants (the subscript *m* refers to the mutant) in a resident system at equilibrium. First, I analyze the evolution of vector behavior when this behavior is governed by the vector itself. In a second step, I examine a situation where vector behavior is (at least partly) manipulated by the pathogen and evolution takes place in the pathogen population.

Vector Evolution

To study the evolution of vector behavior, I derive the invasion fitness per generation of a mutant vector at the endemic equilibrium set by a resident population of vectors (Hurford et al. 2010; see the appendix):

$$R_{V_m} \propto \underbrace{\frac{f_{S_m}}{T_{V_{S_m}\to V_{I_m}} + \delta_{V_S}}}_{\substack{\text{reproductive output}\\ \text{of uninfected vectors}}} + \underbrace{\frac{T_{V_{S_m}\to V_{I_m}}}{T_{V_{S_m}\to V_{I_m}} + \delta_{V_S}}}_{\substack{\text{probability of transition}\\ \text{between uninfected}\\ \text{and infected states}}} \times \underbrace{\frac{f_{I_m}}{\delta_{V_I}}}_{\substack{\text{reproductive output}\\ \text{of infected vectors}}}, \tag{4}$$

where

$$T_{V_{S_m}\to V_{I_m}} = b\frac{a_{I_m}\bar{I}}{1 + \tau(a_{S_m}\bar{S} + a_{I_m}\bar{I})}$$

measures the rate of transition between uninfected and infected vectors. The above expression allows identification of the contribution of both uninfected and infected vectors, as well as the transition between these two states, to this invasion fitness. The mutant will invade the resident population if $R_{V_m} > 1$, and this invasion fitness can be used to derive the gradient of selection on vector behavior at the endemic equilibrium (i.e., $\bar{V}_S$, $\bar{V}_I$, $\bar{S}$, and $\bar{I}$) set by the resident strategy (see the supplemental material).

The above invasion condition can be used to study the evolution of searching efficiency (see the supplemental material), but I want to focus on the preference for uninfected or infected hosts. In the following I will thus assume that the searching efficiencies a and α of uninfected and

infected vectors are fixed and only the preference between infected and uninfected hosts is allowed to evolve. More specifically, I will study the evolution of parameters p and π that control the preference for infected hosts in uninfected and infected vectors, respectively (table 1).

The analysis of the evolution of these two behavioral traits (p and π) is based on the gradients of selection acting on these two traits (dR_{Vm}/dp_m and $dR_{Vm}/d\pi_m$, evaluated when $p_m = p$ and $\pi_m = \pi$) and is detailed in section 2.2 of the supplemental material. In short, this analysis indicates that selection is governed by two main factors. First, the vector should avoid rare and poor-quality hosts. Avoidance of infected hosts evolves when $\bar{I}(\phi - a\tau(1-\phi)\bar{S}) - \bar{S}$ is low. Second, the vector should avoid infected hosts when vector infection induces fitness costs on fecundity and/or survival. These fitness costs are proportional to $F_S/\delta_{V_S} - F_I/\delta_{V_I}$. In other words, vector evolution is driven by time limitation (risk of dying before reproducing) and/or egg limitation (risk of producing a lower number of eggs), as in classical models of the life-history evolution of parasitoids (Godfray 1994). But it is also governed by the cost of infection. In malaria, for instance, the impact of the infection on vector survival is limited, but it is often associated with a reduced fecundity (Ferguson and Read 2002; Hurd 2003; Vézilier et al. 2012). These fitness costs are expected to select vectors that avoid biting infected hosts. But if the prevalence and quality of infected hosts are high, the vector may evolve the opposite preference strategy. For instance, figure 4 shows the evolutionary stable strategy of the vector when it is unable to adopt conditional strategies (i.e., $p = \pi$). For a broad range of parameter values the vector prefers to bite uninfected hosts, but when the relative quality of infected host increases, the vector may evolve a preference for infected hosts. Interestingly, the evolution of vector preference feeds back on epidemiology and yields an evolutionary bistability between alternative strategies. Indeed, the prevalence of the infection depends on vector preference (fig. 3), and higher densities of infected hosts select for higher values of p. When the cost of the infection is high, vectors generally evolve a preference for uninfected hosts (low p and π; fig. 5*A*), but when the initial state of the population is strongly biased (π lower than p), this epidemiological feedback can maintain this bias (gray area in fig. 5*A*). Such an initial bias in preference is very unlikely, but it is worth noting here that vector evolution has, in principle, the potential to select for conditional preference strategies with high p and low π.

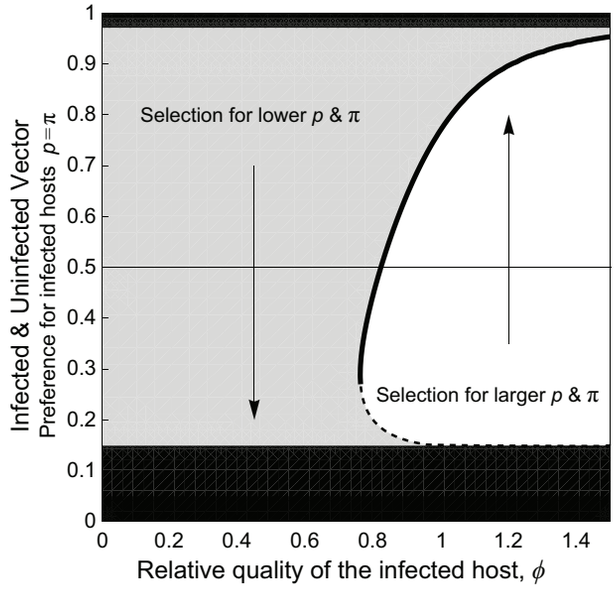

Figure 4: Effect of the relative quality of the infected host, ϕ, on the evolution of unconditional host choice (preference for the infected host) of the vector. The pathogen becomes extinct when vector preference reaches extreme values (black region). When the relative quality of the infected host is low, vectors evolve a preference for uninfected hosts (gray region). But when the quality of the infected host is relatively high, vectors can evolve a preference for infected hosts. The ultimate outcome may be either an intermediate preference strategy (bold black line) or an extreme avoidance strategy toward infected hosts and, consequently, pathogen extinction. The dashed line indicates unstable evolutionary equilibria. Above this dashed line, the vector evolves higher preference for infected hosts. Below this dashed line, the vector evolves lower preference for infected hosts. Other parameter values are $N_H = 1{,}000$, $\kappa = 0.001$, $b = \beta = 0.5$, $d = 0.1$, $\delta_{V_S} = \delta_{V_I} = 1$, $\tau = 0.5$, $a = \alpha = 0.01$, and $F_S = F_I = 5$.

Pathogen Evolution

In the above section, the vector was allowed to evolve different host preference strategies. But what if these preferences are governed (at least partly) by the pathogen? To answer this question, I focus on the dynamics of a mutant pathogen in a resident pathogen population. Using a generalization of classical superinfection models (Nowak and May 1994; Gandon et al. 2001), it is assumed that when a vector infected with strain i bites a host infected with strain j, the vector has probability σ_V to lose strain i and to become infected with strain j, while the host has probability σ_H to lose strain j and become infected with strain i. Although this is a very crude approximation of the within-host competition taking place between different pathogens, it allows accounting for multiple infections in the vector and in the host (e.g., in malaria; de Roode et al. 2005; Pollitt et al. 2015). The ability of the mutant to outcompete the resident pathogen can be studied using the per-generation invasion fitness of the mutant (appendix):

$$R_{P_m} = \sqrt{\frac{b\beta(\bar{V}_S T_{V_S \to V_{I_m}} + \sigma_V \bar{V}_I T_{V_I \to V_{I_m}})(\bar{S} T_{S \to I_m} + \sigma_H \bar{I} T_{I \to I_m})}{(\delta_{V_I} + \sigma_V b \bar{I} T_{V_{I_m} \to V_I})(d + \sigma_H \beta \bar{V}_I T_{I_m \to I})}}, \quad (5)$$

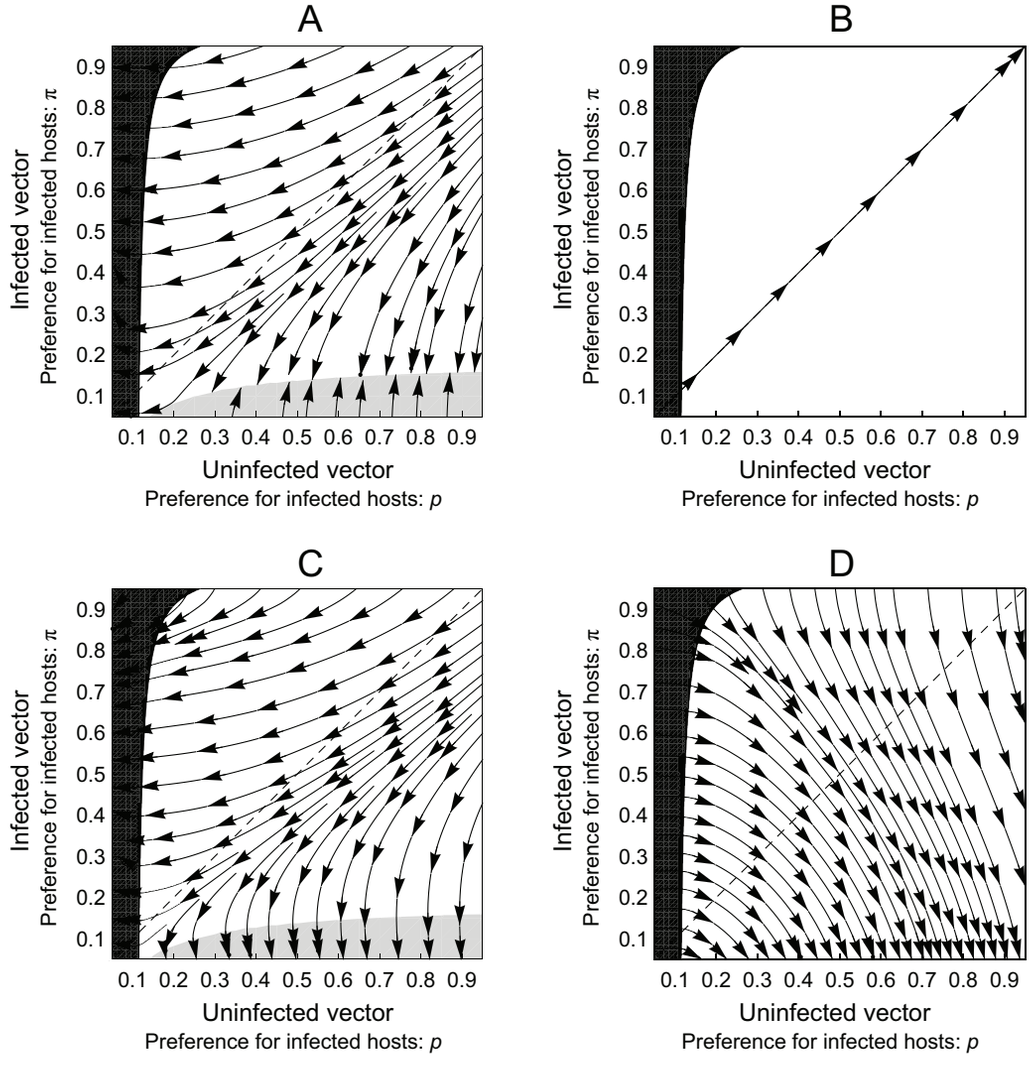

Figure 5: Evolution of host choice (preference for the infected host) by uninfected vectors (p) and infected vectors (π) under different scenarios. The arrows indicate the direction of the gradient of selection on both p and π. The black area indicates the parameter region where the pathogen is always driven to extinction. In *A*, the host choice is governed only by the vector. The gray area in this panel indicates the parameter region where higher values of p and π are selected for. In *B*, the host choices of infected and uninfected vectors are equal and are governed by the pathogen in the infected host (i.e., $p = \pi$). In *C*, the host choice of infected vectors is governed by the pathogen, while the host choice of uninfected vectors is governed by the vector. The gray area in this panel indicates the parameter region where higher values of p are selected for. In *D*, the host choices of both infected and uninfected vectors are governed by the pathogen and are allowed to evolve independently. Parameter values are $N_H = 1{,}000$, $\kappa = 0.001$, $b = \beta = 0.5$, $d = 0.1$, $\delta_{V_S} = \delta_{V_I} = 1$, $\tau = 0.5$, $a = \alpha = 0.02$, $F_S = F_I = 10$, $\phi = 0.5$, and $\sigma_H = \sigma_V = 0$.

where the notation $T_{X \to Y}$ refers to the transition between states X and Y. These transition terms depend on the assumptions regarding the control of vector behavior (see the supplemental material). Note that the per-generation invasion fitness of the pathogen is very different from the basic reproduction ratio R_0. Indeed, R_0 is a measure of the per-generation increase of the pathogen in a naive host population. In contrast, the per-generation invasion fitness depends on the densities of the different types of vectors and hosts at the endemic equilibrium (i.e., $\bar{V}_S$, $\bar{V}_I$, $\bar{S}$, and $\bar{I}$).

The analysis of the evolution of the manipulation of vector behavior (p and π) is based on the gradients of selection acting on these two traits (dR_{Pm}/dp_m and $dR_{Pm}/d\pi_m$, evaluated when $p_m = p$ and $\pi_m = \pi$). An analysis of the direction of selection on these two traits under three biologically relevant scenarios is detailed in the supplemental material.

Pathogen Manipulates Vectors from Within Infected Hosts. The pathogen may act on vector behavior through a manipulation of the attractiveness of the infected host. For ex-

ample, this manipulation could act through the modification of the volatiles emitted by the infected hosts. In this scenario, the behavior of infected and uninfected vectors is undistinguishable (i.e., $p = \pi$) because both types of vectors are attracted by the volatiles released by infected hosts (fig. 5*B*). The selection gradient on the manipulation of vector preference is

$$\left.\frac{dR_{Pm}}{dp_m}\right|_{\substack{p_m\to p\\ \pi_m\to\pi}} \propto \left.\frac{T_{V_S\to V_{I_m}}\bar{V}_S + \sigma_V d T_{I_m\to I}\bar{V}_I}{d + \sigma_H T_{I_m\to I}\beta\bar{V}_I}\right|_{\substack{p_m\to p\\ \pi_m\to\pi}} > 0. \tag{6}$$

This gradient of selection is always positive, which indicates that the pathogen evolves a manipulation strategy that attracts the vector to infected hosts. In other words, selection on the pathogen is driven by the necessity to attract uninfected vectors even if it also attracts infected vectors. Superinfection in the vector, σ_V, enhances this trend because even already-infected vectors can transmit the mutant pathogen currently in the infected host. In contrast, superinfection in the host, σ_H, decreases the magnitude of selection because the mutant currently in the host may be ousted by another strain introduced by infected vectors.

Pathogen Manipulates Only Infected Vectors. Next, I assume that infected vectors are manipulated by the pathogen from within the infected vector. The selection gradient on the manipulation of infected vector preference is

$$\begin{aligned}\left.\frac{dR_{Pm}}{d\pi_m}\right|_{\substack{p_m\to p\\ \pi_m\to\pi}} \propto\ & -\bar{S}\delta_{V_I}(1+\alpha\tau\bar{I}) - \sigma_V\alpha b\bar{S}\bar{I}\\ & + \sigma_H\bar{I}\delta_{V_I}(1+\alpha\tau\bar{S}).\end{aligned} \tag{7}$$

In the absence of host superinfection ($\sigma_H = 0$), this gradient is always negative and the pathogen is always evolving manipulation strategies that lead to higher vector preference for uninfected hosts. Superinfection in the vector, σ_V, enhances this trend because the mutant pathogen currently in the vector may be ousted by another pathogen strain if it bites an already-infected host. Superinfection in the host, however, may counteract this trend (and may even select preference for infected hosts) because the mutant currently in the vector may outcompete another pathogen strain in an already-infected host. Biologically relevant parameter values (i.e., low probability of superinfection, intermediate prevalence) yields preference for uninfected hosts (fig. 5*C*). The behavior of uninfected vectors is driven by selection acting on the vector, and as discussed above the ultimate evolutionary outcome may depend on initial conditions (figs. 4, 5*A*). In general, uninfected vectors evolve preference for uninfected hosts. But an initial bias in vector preference (π lower than p) increases prevalence in the host population and may select for even stronger preference for infected hosts in the uninfected vectors (gray area in fig. 5*C*). It is interesting to note that the predictions under this scenario are very similar to the ones obtained when the behavior of both infected and uninfected individuals is under the control of the vector (compare fig. 5*A* and fig. 5*C*).

Pathogen Manipulates Independently the Preference of Infected and Uninfected Vectors. Finally, I consider a situation where manipulation is conditional because it can act both from within infected vectors and from within infected hosts. I consider only the case where the manipulation of infected vectors is fully governed by the pathogen in the vector and the pathogen in the infected host can affect only the behavior of uninfected vectors. The selection gradient on the manipulation of both uninfected and infected vector preference are

$$\left.\frac{dR_{Pm}}{dp_m}\right|_{\substack{p_m\to p\\ \pi_m\to\pi}} \propto a\bar{V}_S > 0,$$

$$\begin{aligned}\left.\frac{dR_{Pm}}{d\pi_m}\right|_{\substack{p_m\to p\\ \pi_m\to\pi}} \propto\ & (-\bar{S}\delta_{V_I}(1+\alpha\tau\bar{I}) - \sigma_V\alpha b\bar{S}\bar{I}\\ & -\sigma_V\sigma_H b\bar{I}^2(1+\alpha\tau\bar{S})T_{V_{I_m}\to V_I})\Big|_{\substack{p_m\to p\\ \pi_m\to\pi}} < 0.\end{aligned} \tag{8}$$

Selection thus favors very different conditional strategies in infected and uninfected vectors. The pathogen manipulates uninfected vectors to prefer infected hosts, and it manipulates infected vectors to prefer uninfected hosts (fig. 5*D*).

The above evolutionary analysis yields extreme preference strategies that may ultimately lead the pathogen population to extinction (fig. 3). This is because the current model assumes that any preference strategy can freely evolve. Host choice, however, requires an ability to discriminate between different types of hosts. In most biological systems, this ability is likely to be imperfect or to carry fitness costs. Besides, this preference may be a dynamical trait. After some time looking for the best host (e.g., when host density is low), the choosiness may wear out, and the vector may simply feed on whatever host becomes available (Godfray 1994; Wajnberg 2006). The above model can be readily modified to account for extra costs that necessarily select for less extreme strategies. For instance, figure 6 illustrates a scenario where the pathogen manipulates independently the preference of uninfected and infected vectors but deviations from the no-preference strategy (i.e., $p = \pi = 0.5$) are associated with a fitness cost detailed in the legend of figure 6. Under this scenario, intermediate preference strategies can evolve. The evolution of intermediate strategies also allows exploration of the influence of other parameters on the evolutionary outcome. For instance, figure 6 shows that host superinfection selects for a less extreme preference strategy in infected

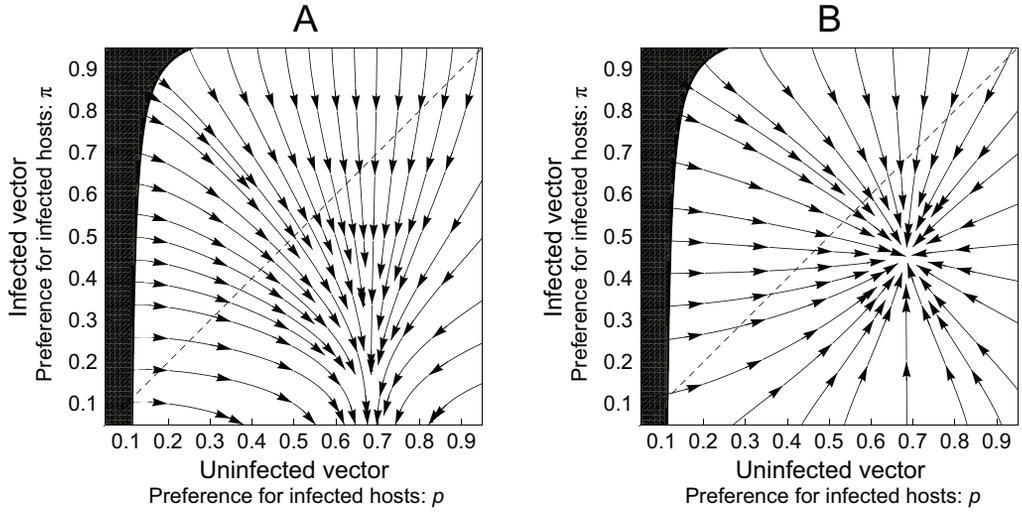

Figure 6: Evolution of host choice (preference for the infected host) by uninfected vectors (p) and infected vectors (π) when vector behavior is under the control of the pathogen. In contrast with figure 5*D*, I assume that a bias in vector preference (i.e., $p \neq 0.5$ and/or $\pi \neq 0.5$) is associated with a fitness cost ρ. More specifically, I assume that the mutant fitness is $R_{Pm}(\rho) = R_{Pm}(0)e^{-\rho(p-0.5)^2}e^{-\rho(\pi-0.5)^2}$, where $R_{Pm}(0)$ is given in equation (5). In *A* there is no superinfection ($\sigma_H = \sigma_V = 0$), and in *B* superinfection is feasible in the host ($\sigma_H = 0.5$ and $\sigma_V = 0$). Parameter values are $N_H = 1{,}000$, $\kappa = 0.001$, $b = \beta = 0.5$, $d = 0.1$, $\delta_{V_S} = \delta_{V_I} = 1$, $\tau = 0.5$, $a = \alpha = 0.02$, $F_S = F_I = 10$, $\phi = 0.5$, and $\rho = 2$.

hosts because pathogen transmission may occur even if the infected mosquito bites an already-infected host.

In conclusion, the model clearly shows that different assumptions regarding the control of vector behavior have major consequences for evolutionary and coevolutionary outcomes (fig. 5). In particular, if the vector is fully controlling its behavior, it should generally avoid feeding on infected hosts. When this preference is at least partly manipulated by the pathogen, three main evolutionary outcomes are possible depending on the mechanisms of the manipulation. These different evolutionary outcomes reveal the existence of conflicts between the vector and the pathogen over the control of vector behavior. They also reveal conflicts between the pathogen in the host (which is trying to attract uninfected vectors) and the pathogen in the vector (which is trying to gain access to uninfected hosts).

Discussion

The epidemiology of vector-borne disease is very sensitive to the host choice behavior of the arthropod vector (Macdonald 1957; Koella 1991; Anderson and May 1992). I developed a general model of vector-borne transmission, taking into account key features of the ecology in a broad range of different pathosystems. This model shows that extreme choice strategies can have dramatic consequences for the epidemiology of the disease and can even lead to pathogen eradication. Interestingly, on the verge of extinction the dynamical system may exhibit backward bifurcation at $R_0 = 1$, when the uninfected vectors are more attracted to infected hosts. In other words, a stable endemic equilibrium may exist even if $R_0 < 1$. This result implies that vector choice may prevent the eradication of pathogens even if human interventions managed to reduce R_0 below its critical level. Similar bistability has been observed in models of malaria transmission (Chitnis et al. 2006; Buonomo and Vargas-De-León 2013), but here I show that the behavior of uninfected mosquitoes is a key driver of this dynamic. Further work is required to better identify conditions promoting this epidemiological bistability. In particular, it is unclear whether such bistability can emerge for the less extreme preference strategies that have been observed in different pathosystems (fig. 1).

What is the adaptive nature of the specific preference of the vector for infected or uninfected hosts? The evolutionary analysis detailed above clarifies the different forces acting on the evolution of the manipulation of vector behavior. I have shown how epidemiological dynamics and in particular the densities of infected and uninfected hosts feed back on the selection gradient. These feedbacks can yield evolutionary bistability, which means that the evolutionary outcome may depend critically on the initial state of the system. This evolutionary analysis also helps us understand how the different mechanistic constraints acting on the vector and the pathogen could generate the diversity of vector preference observed in a broad range of vector-borne diseases (compare fig. 1 and fig. 5). In particular, it is important to distinguish between pathogens that can act on vector behavior only via a modification of host attractiveness

(fig. 5*B*) and pathogens that also have the ability to manipulate the host choice of infected vectors (fig. 5*D*). In the first case, the pathogen evolves manipulation strategies that lead both uninfected and infected vectors to prefer infected hosts. Indeed, numerous empirical studies show that pathogens can modify the scent of infected hosts to attract vectors (Mauck et al. 2016). This manipulation often involves the elevation or exaggeration of existing cues used by vectors to locate hosts. As pointed out by Mauck et al. (2010), the evolution of such a "supernormal stimulus" does not involve qualitative differences between infected and uninfected hosts, and it is thus very difficult for the vector to evolve avoidance strategies even if infected vectors suffer from major fitness costs. All of the points located on the diagonal in figure 1 are likely to fit in this category. *Erwinia tracheiphila* and its fascinating ability to alter conditionally the scent of leaves and flowers of infected plants may represent an exception that challenges the simplicity of the present theoretical framework.

When the pathogen is able to act independently on the host choice behavior of infected and uninfected vectors, conditional preference strategies can evolve. Indeed, the transmission of the pathogen is maximized when uninfected vectors are attracted to infected hosts and when infected vectors are attracted to uninfected hosts (fig. 5*D*). Interestingly, only plant viruses with a persistent and circulative mode of vector transmission have been shown to evolve such conditional preference strategies (fig. 1). This suggests that only pathogens that have evolved a persistent and intimate relationship with their vector are able to induce conditional preference strategies. This may explain the seemingly maladaptive behavior of tomato chlorosis virus (ToCV), which is the only point falling above the diagonal in figure 1 (Fereres et al. 2016). ToCV does not circulate in its *Bemisia tabaci* vector and, in contrast to tomato severe rugose virus, has a much less intimate relationship with its vector. Besides, the preference indicated in figure 1 is based on an experiment where the vectors had to choose between volatiles emitted by infected and uninfected plants. Fereres et al. (2016) have shown that visual cues are particularly important in this system, where both infected and uninfected vectors are attracted by the yellowing symptoms of infected plants. Further experimental work is thus required to explore the manipulation of vector preference by ToCV under more realistic conditions. But even some nonpersistent infections have found ways to promote a switch in vector behavior after a viral infection. For example, after landing on plants infected by cucumber mosaic virus, the aphid vectors quickly fly away because infected plants are less palatable (Mauck et al. 2010). Hence, even if infected plants are more attractive to the vector (fig. 1), infected aphids will spend more time feeding on uninfected plants. This type of behavioral modification is not allowed in the above model but is likely to promote the spread of the virus. In contrast to this fascinating ability of viruses to manipulate their vectors, some pathogens seem to be able to induce conditional switch in vector behavior. For instance, despite persistent infection in its mosquito vector, *Plasmodium* does not induce conditional preference strategies (Cornet et al. 2013*a*). Further studies exploring the host choice preference of both infected and uninfected vectors of other pathogens are required to confirm whether only viruses have the ability to evolve such complex conditional manipulation strategies. In addition, it would be interesting to see whether some pathogens are able to evolve other forms of conditional manipulation of host preference varying with the age of the infection in the vector. Indeed, one may expect different manipulation strategies in infected but not yet infectious vectors.

An interesting extension of this work would be to analyze situations where multiple pathogens share the same host and/or the same vector. It is easy to imagine how these complex epidemiological scenarios could yield new evolutionary conflicts over the manipulation of vector behaviors (Peñaflor et al. 2016). In addition, many arthropod vectors can feed on multiple host species (or multiple genotypes within the same species), which may or may not be suitable for the pathogen. In these situations, the vector preference for different host species (or different host genotypes) can also have massive epidemiological consequences (Kilpatrick et al. 2006; Lyimo and Ferguson 2009; Takken and Verhulst 2013). For instance, vector preference can directly affect the emergence of a "dilution effect," which states that disease risk is expected to decrease with higher host diversity (Keesing et al. 2006; Ostfeld and Keesing 2012). The above theoretical framework could be used to understand and predict the evolution and manipulation of vector preference for different host species (McBride et al. 2014; Main et al. 2016).

The predictive power of these evolutionary models hinges on our knowledge of the constraints acting on these behavioral traits. To understand these constraints, it is important to study the mechanisms underlying vector preference. Experimental studies of vector preference indicate that host choice can be mediated by multiple cues, such as odor, color, and taste (Gutiérrez et al. 2013; Dietzgen et al. 2016; Mauck et al. 2016). Some pathogens have been shown to modify vector behavior through modification of these cues (Eigenbrode et al. 2002; Mauck et al. 2016; Emami et al. 2017). But in most cases the underlying mechanisms driving these modifications of vector behavior remain elusive. A better understanding of these underlying mechanisms could also lead to the development of novel public health strategies to control vector-borne diseases (Grieco et al. 2007; Achee et al. 2012; Busula et al. 2015; Lynch and Boots 2016). The above theoretical analysis provides a framework for understanding the evolution and manipulation of key behavioral traits of vectors (e.g., host choice, biting rate) as well as a guide to structuring exploration of the mechanistic constraints acting on this evolution in a broad range of vector-borne diseases.

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