

1 Evolution and manipulation of vector host choice

2 Sylvain Gandon

3 CEFE UMR 5175, CNRS - Université de Montpellier - Université Paul-Valéry Montpellier - EPHE

4 1919 route de Mende, 34293 Montpellier, France

5 **Abstract:**

6 **The transmission of many animal and plant diseases relies on the behavior of arthropod vectors. In**
7 **particular, the choice to feed on either infected or uninfected hosts can dramatically affect the**
8 **epidemiology of vector-borne diseases. I develop an epidemiological model to explore the impact**
9 **of host choice behavior on the dynamics of these diseases and to examine selection acting on**
10 **vector behavior, but also on pathogen manipulation of this behavior. This model identifies multiple**
11 **evolutionary conflicts over the control of this behavior and generates testable predictions under**
12 **different scenarios. In general, the vector should evolve the ability to avoid infected hosts.**
13 **However, if the vector behavior is under the control of the pathogen, uninfected vectors should**
14 **prefer infected hosts while infected vectors should seek uninfected hosts. But some mechanistic**
15 **constraints on pathogen manipulation ability may alter these predictions. These theoretical results**
16 **are discussed in the light of observed behavioral patterns obtained on a diverse range of vector-**
17 **borne diseases. These patterns confirm that several pathogens have evolved conditional**
18 **behavioral manipulation strategies of their vector species. Other pathogens, however, seem**
19 **unable to evolve such complex conditional strategies. Contrasting the behavior of infected and**
20 **uninfected vectors may thus help reveal mechanistic constraints acting on the evolution of the**
21 **manipulation of vector behavior.**

22 **Keywords:** vector borne disease, host choice, parasitic manipulation, mosquito behavior, malaria,
23 virus.

24

25 **1. Introduction**

26 Many animal and plant infectious diseases are transmitted by arthropod vectors. In humans, several
27 deadly vector-borne diseases (e.g. malaria, yellow fever, dengue, West Nile virus) are transmitted by
28 mosquitoes or by other insect species (sandflies, fleas, ticks, tsetse flies). In plants, numerous other
29 vector species (e.g. aphids, leafhoppers, whiteflies) are involved in the transmission of viral and
30 bacterial infections. In spite of the diversity of species involved, the epidemiology of vector-borne
31 diseases can be captured by relatively simple mathematical models describing the pathogen life-cycle
32 across the main host (e.g. a vertebrate, a plant) and the vector (usually an insect). These
33 epidemiological models have clarified the impact of several life-history traits of the vector species for
34 pathogen transmission and pointed out that traits acting on the biting behavior of the vector have a
35 dramatic impact on disease dynamics [1]–[4]. But understanding the evolution of this biting behavior
36 depends on who is controlling this behavior. Indeed, many pathogens are able to manipulate
37 different behavioral traits of their vectors [5]–[7]. Interestingly, the ability of the pathogen to pull the
38 strings of its vector may yield a conflict over the evolution of these traits. For instance, the biting rate
39 maximizing pathogen fitness may be very different from the one maximizing vector fitness [8], [9].
40 The resolution of this conflict has been studied in several different vector-borne diseases [5]–[7],
41 [10]–[12].

42 Another important but often overlooked component of transmission involves host choice behavior of
43 the vector. Several experimental studies have demonstrated that some vector species have biased
44 preferences for infected [13]–[16] or uninfected hosts [17]–[19]. Epidemiological models show that
45 vector preference for infected hosts can boost transmission during the early stage of the epidemic
46 [20]–[26]. This suggests that attraction towards infected hosts may result, at least in part, from a
47 manipulation of the vector by the pathogen. Yet, extreme preference for infected (or uninfected)
48 hosts can also limit or even stop pathogen transmission. For instance, if the vectors bite only infected
49 hosts they can never transmit the disease to uninfected hosts. Besides, recent empirical studies in
50 plant pathogens indicate that the host choice behavior may be conditional on the infection status of
51 the vector itself. In particular, uninfected vectors have been found to be attracted towards infected
52 plants but, after being infected, they are attracted towards uninfected plants [27]–[30]. Roosien et al
53 [26] analysed the consequences of these behavioral shifts and demonstrated its dramatic impact for
54 the epidemiology of plant pathogens. Such a conditional modification of vector behavior seems very
55 adaptive for pathogen transmission but this hypothesis remains to be investigated theoretically.

56 Here I develop a theoretical framework to explore the consequences of vector host choice behavior
57 on the epidemiology and evolution of vector-borne diseases. First, I develop a general
58 epidemiological model to study the impact of the behavior of both infected and uninfected vectors
59 on the persistence of the disease. Second, I use this epidemiological model to study the evolution of
60 vector behavior. Scenarios with or without manipulation are contrasted to discuss the adaptive
61 nature of these modifications of host preference for the vector or for the pathogen. Third, I review
62 experimental studies that have examined host choice behavior in arthropod vectors. In particular, I
63 focus on the handful of studies that have monitored the behavior of both infected and uninfected
64 vectors. The fascinating diversity of vector behaviors in animal and plant vector-borne diseases is
65 discussed in the light of this theoretical model.

66

67 2. The epidemiological model

68 Three organisms are interacting in this vector-borne disease model: the host, the vector (usually an
69 insect) and the pathogen (e.g. virus, bacteria, protozoa). The host can either be infected (state I) or
70 uninfected (state S) and, similarly, the vector can either be infected (state V_I) or uninfected (state
71 V_S). The following set of differential equations governs the dynamics of the densities of these
72 different types of individuals (see table 1 for a summary of the main parameters and the
73 Supplementary Information for details of the derivation of this model):

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

74 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
75 uninfected and infected vectors, respectively. The parameter κ measures the intensity of density
76 dependence while f_S and f_I measure the per capita fecundity of uninfected and infected vectors,
77 respectively. The density of the whole population of the vector, $N_V = V_S + V_I$, is allowed to vary with
78 the dynamics of both uninfected and infected vectors. The first phase of the pathogen life cycle is the
79 infection of the vector after feeding on an infected host. The parameter b is the probability that the
80 vector gets infected after biting an infected host. The behavior of the uninfected vectors is governed
81 by the parameters a_S and a_I which refer to the searching efficiency of uninfected and infected hosts,
82 respectively. The parameter τ is the handling time of the host by the vector and includes the time
83 taken to bite after landing on the host but also the time taken to digest before an attempt to bite a
84 new host. When the handling time is very small the number of infected bites varies linearly with the
85 number of susceptible hosts. When this handling time is large, it is the frequency of uninfected hosts
86 that governs the epidemiological dynamics [21], [31]. The derivation of this Holling type II response is
87 detailed in the appendix 1. The pathogen is allowed to affect vector survival with specific mortality
88 rates for uninfected and infected vectors (δ_{V_S} and δ_{V_I} respectively).

89 The second phase of the pathogen life cycle is the infection of the host by infected vectors. For the
90 sake of simplicity I assume that the total density of hosts, $N = S + I$, is a constant. This means that
91 whenever a host dies (this occurs at a constant rate d) it is immediately replaced by a new
92 susceptible host. The parameter β is the probability that the host gets infected after being bitten by
93 an infected vector. The behavior of the infected vectors is governed by the parameters α_S and α_I
94 which refer to the searching efficiency of uninfected and infected hosts, respectively.

95 To determine the ability of a pathogen to invade a disease-free environment I derive the pathogen's
96 basic reproduction ratio R_0 (see appendix 2):

$$R_0 = \sqrt{\frac{b\beta N N_V}{d\delta_{V_I}} \frac{\alpha_S}{1 + \tau\alpha_S N} \frac{a_I}{1 + \tau a_S N}} \quad (2)$$

97 where $N_V = (f_S - \delta_{V_S})/\kappa f_S$ is the equilibrium density of the vector when the pathogen is absent.
98 The pathogen can invade this disease-free equilibrium when $R_0 > 1$. Higher densities of both hosts
99 and vector are always increasing R_0 but the behavior of both uninfected and infected vectors can
100 also affect the basic reproduction ratio of the pathogen. The preference of uninfected vectors for
101 infected hosts (large a_I and low a_S) and the attraction of infected vectors towards susceptible hosts
102 (large α_S) increase R_0 . Note, however, that when τ or N get very large the basic reproduction ratio
103 depends only on the behavior of uninfected vectors. Under the assumption that the sums of
104 searching efficiencies $a = a_S + a_I$ and $\alpha = \alpha_S + \alpha_I$ are fixed in uninfected and infected vectors,
105 respectively, one can focus on the effects of the preference between infected and uninfected hosts.
106 More specifically, I introduce the parameters $p = a_I/(a_S + a_I)$ and $\pi = \alpha_I/(\alpha_S + \alpha_I)$ that control
107 the preference towards infected hosts in uninfected and infected vectors, respectively (Table 1).
108 Figure 1A shows that R_0 is maximized when uninfected vectors prefer biting infected hosts and when
109 infected vectors prefer biting uninfected hosts. The figure also illustrates that extreme choice
110 strategies can lead to parasite extinction (i.e. $R_0 < 1$).

111 After pathogen invasion the system reaches an endemic equilibrium where the host, the vector and
112 the pathogen can coexist (the notation \bar{x} is used to refer to the equilibrium density of the variable x
113 at this endemic equilibrium). These equilibrium densities depend on the behavior of the vectors as
114 well as all the other parameters of the model. I failed to find simple analytic expressions for those
115 densities but they can be readily obtained numerically using (1).

116 Note that the per capita fecundities f_S and f_I were assumed to be fixed quantities in figure 1A. The
117 fecundity of many vector species, however, is likely to be limited by the availability and/or the quality
118 of different types of hosts. Consequently, the fecundity of both infected and uninfected vectors are
119 also going to depend on vector behavior:

$$\begin{aligned} f_S &= F_S \frac{a_S \bar{S} + a_I \phi \bar{I}}{1 + \tau(a_S \bar{S} + a_I \bar{I})} \\ f_I &= F_I \frac{\alpha_S \bar{S} + \alpha_I \phi \bar{I}}{1 + \tau(\alpha_S \bar{S} + \alpha_I \bar{I})} \end{aligned} \quad (3)$$

120 where F_S and F_I are the maximal fecundities of uninfected and infected vectors, respectively. The
121 parameter ϕ measures the intrinsic quality of the infected host relative to the uninfected host. For
122 instance, $\phi < 1$ indicates that infected hosts may provide less nutrients than healthy ones (e.g. in the
123 case of malaria because of anaemia). The influence of vector behavior on vector fecundity can lead
124 to complex epidemiological dynamics. For instance, the dynamical system may exhibit backward
125 bifurcation at $R_0 = 1$. In other words, depending on the initial condition, the pathogen may either go
126 extinct or reach an endemic equilibrium when $R_0 < 1$. In particular, this occurs when preference of
127 uninfected vectors towards infected hosts becomes very pronounced (figure 1B). In the following, for
128 the sake of simplicity, I will focus on situations where $R_0 > 1$.

129 3. Evolution

130 In the following I study the long-term evolutionary dynamics of the above dynamical system. Using
131 the classical formalism of Adaptive Dynamics I assume mutation rate to be low which allows
132 decoupling evolutionary and epidemiological dynamics [32]–[35]. In other words, I study the
133 evolution of vector behavior (i.e. searching efficiency, host choice preference) through the derivation

134 of the invasion of rare mutants (the subscript m refers to the mutant) in a resident system at
135 equilibrium. First I analyze the evolution of vector behavior when this behavior is governed by the
136 vector itself. In a second step I examine a situation where vector behavior is (at least partly)
137 manipulated by the pathogen and evolution takes place in the pathogen population.

138 3.1 Vector evolution

139 The model can first be used to study the evolution of vector behavior in the absence of the pathogen.
140 In this case all the vectors are uninfected but they can adopt different searching efficiency strategies.
141 Higher searching efficiency allows the vector to exploit more hosts and thus to produce more
142 offspring but, on the other hand, searching for hosts may be costly because more energy is allocated
143 into flying. I analyze the evolution of searching efficiency in appendix 3 and I show that the
144 evolutionary stable searching efficiency decreases with the host population size, N , the handling
145 time, τ , or the fecundity cost associated with higher allocation to searching efficiency.

146 When the pathogen is present, the invasion of the mutant vector involves two compartments since
147 the vector can either be infected or not. The invasion of a mutant vector can be analyzed using the
148 per-generation invasion number [36] (appendix 3):

$$R_{Vm} = \frac{f_{Sm}\delta_{V_I} + f_{Im}T_{V_{Sm} \rightarrow V_{Im}}}{\delta_{V_I}(T_{V_{Sm} \rightarrow V_{Im}} + \delta_{V_S})} (1 - \kappa N_V) \quad (4)$$

149 where $T_{V_{Sm} \rightarrow V_{Im}} = b \frac{a_{Im}\bar{I}}{1 + \tau(a_{Sm}\bar{S} + a_{Im}\bar{I})}$.

150 One could use the above invasion condition to study the evolution of searching efficiency but I want
151 to focus on the preference for uninfected or infected hosts. I will thus assume that the searching
152 efficiencies $a = a_S + a_I$ and $\alpha = \alpha_S + \alpha_I$ of uninfected and infected vectors are fixed and I will focus
153 only on the evolution of the preference between infected and uninfected hosts. More specifically, I
154 will study the evolution of parameters p and π that control the preference towards infected hosts in
155 uninfected and infected vectors, respectively (Table 1).

156 The derivation of evolutionarily stable strategies can be obtained by maximizing R_{Vm} when the
157 endemic equilibrium (i.e. \bar{V}_S , \bar{V}_I , \bar{S} and \bar{I}) is set by the resident strategy (i.e. p and π). Factors
158 governing the direction of selection on vector behavior are detailed in appendix 3. In short, the
159 model allows taking into account multiple evolutionary forces: (i) the cost of looking for a rare host,
160 (ii) the cost of feeding on infected hosts, (iii) the potential fitness costs associated with the reduction
161 of the fecundity and/or the survival of infected vectors. In other words, vector evolution is driven by
162 time-limitation (risk of dying before reproducing) and/or egg-limitation (risk of producing a lower
163 number of eggs) as in classical models of life-history evolution of parasitoids [37]. In malaria, for
164 instance, the impact of the infection on vector survival is reduced but it is often associated with a
165 reduced fecundity [38]–[40]. These fitness costs are expected to select vectors that avoid biting
166 infected hosts. But, if the prevalence of infected hosts is very high the opposite may be predicted
167 because the vector cannot afford to lose too much time looking for rare uninfected hosts. For
168 instance figure 2 shows the evolutionary stable strategy of the vector when it is unable to adopt
169 conditional strategies (i.e. $p = \pi$). For a broad range of parameter values the vector prefers to bite
170 uninfected hosts (figure 3A) but when the prevalence in the infection is very high in the host
171 population, the vector may evolve a preference towards infected hosts.

172 Note, that our analysis yields extreme preference strategies that may ultimately lead the pathogen
173 population to extinction (figure 1). This is because the current model assumes that any preference
174 strategy can evolve. Preference, however, requires an ability to discriminate between different types
175 of hosts. In most biological systems this ability is likely to be imperfect or to carry fitness costs. The
176 above model can be readily modified to account for an intrinsic cost associated with strong
177 preference strategies but this would obscure the qualitative understanding of the evolutionary
178 analysis.

179 **3.2 Pathogen evolution**

180 In the above section the vector was allowed to evolve different host preference strategies. But what
181 if these preferences are governed (at least partly) by the pathogen? To answer this question I focus
182 on the dynamics of a mutant pathogen in a resident pathogen population. Using a generalization of
183 classical superinfection models [41], [42] it is assumed that when a vector infected with strain i bites
184 a host infected with strain j the vector has a probability σ_V to lose the strain i and to become
185 infected with strain j , while the host has a probability σ_H to lose the strain j and become infected
186 with strain i . Although this is a very crude approximation of the within-host competition taking place
187 between different pathogens it allows to account for multiple infections in the vector and in the host
188 (e.g. in malaria [43], [44]). The ability of the mutant to outcompete the resident pathogen can be
189 studied using the per-generation invasion number of the mutant (see appendix 4):

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

190 where the notation $T_{X \rightarrow Y}$ refers to the transition between the states X and Y . Importantly, these
191 transitions depend critically on the way the pathogen acts on the behaviour of the vectors. In the
192 following I will consider three different scenarios.

193 **Pathogen manipulates vectors from within infected hosts:**

194 The pathogen may act on vector behaviour through a manipulation of the attractiveness of the
195 infected host. For example, this manipulation could act through the modification of the volatiles
196 emitted by the infected hosts. In this scenario the behaviour of infected and uninfected vectors are
197 undistinguishable (i.e. $p = \pi$) because both types of vectors are attracted by the volatiles released by
198 infected hosts (figure 3B). In this case the pathogen evolves a manipulation strategy that attracts the
199 vector towards infected hosts. In other words selection on the pathogen is driven by the necessity to
200 attract uninfected vectors even if it also attracts infected vectors. Superinfection in the vector, σ_V ,
201 enhances this trend because even already infected vectors can transmit the mutant pathogen
202 currently in the infected host. In contrast, superinfection in the host, σ_H , decreases the magnitude of
203 selection because the mutant currently in the host may be ousted by another strain introduced by
204 infected vectors.

205 **Pathogen manipulates only infected vectors:**

206 Next, I assume that infected vectors are manipulated by the pathogen from within the infected
207 vector. In the absence of host superinfection the pathogen is always evolving manipulation strategies
208 leading higher vector preference towards uninfected hosts. Superinfection in the vector, σ_V ,

209 enhances this trend because the mutant pathogen currently in the vector may be ousted by another
210 pathogen strain if it bites an already infected host. Superinfection in the host, however, may
211 counteract this trend (and may even select preference for infected hosts) because the mutant
212 currently in the vector may outcompete another pathogen strain in an already infected host.
213 Biologically relevant parameter values (i.e. low probability of superinfection, intermediate
214 prevalence) yields preference for uninfected hosts (figure 3C). The behavior of uninfected vectors is
215 driven by selection acting on the vector which yields uninfected vectors to avoid infected hosts. In
216 other words, I recover the prediction obtained when the vector controls its own behavior (compare
217 figure 3A and 3C).

218 **Pathogen manipulates independently the preference of infected and uninfected vectors:**

219 Finally I consider a situation where manipulation is conditional because it can act both from within
220 infected vectors and from within infected hosts. I only consider the case where the manipulation of
221 infected vectors is fully governed by the pathogen in the vector and the pathogen in the infected
222 host can only affect the behaviour of uninfected vectors. In this case selection favors very different
223 conditional strategies in infected and uninfected vectors. The pathogen manipulates uninfected
224 vectors to bite infected hosts and it manipulates infected vectors to bite uninfected hosts and to
225 avoid infected hosts (figure 3D).

226 In conclusion the model clearly shows that different assumptions regarding the control of vector
227 behaviour have major consequences on the evolutionary and coevolutionary outcome (figure 3). In
228 particular, I see that if the vector is fully controlling its behaviour it should generally avoid feeding on
229 infected hosts. When this preference is at least partly manipulated by the pathogen three different
230 evolutionary outcomes are possible depending on the mechanisms of the manipulation. These
231 different evolutionary outcomes reveal the existence of conflicts between the vector and the
232 pathogen over the control of vector behaviour. But they also reveal conflicts between the pathogen
233 in the host (who is trying to attract uninfected vectors) and the pathogen in the vector (who is trying
234 to get access to uninfected hosts).

235 **4. Experimental studies of host choice behavior**

236 It is particularly interesting to contrast the above theoretical predictions with available information
237 on vector preference in different host-parasite systems. Most of the experimental and empirical
238 work investigating the relative preference for infected or uninfected hosts focused only on host-
239 choice behavior of uninfected vectors. I review this work below before discussing the more limited
240 number of studies that monitored the host-choice behavior of both infected and uninfected vectors
241 (figure 4 and Table S1).

242 **4.1 Behavior of uninfected vectors**

243 First, there is evidence that some vector species have evolved the ability to discriminate and avoid
244 infected individuals. For instance, sharpshooter leafhoppers, a vector of the generalist plant
245 pathogen *Xylella fastidiosa*, are more attracted towards healthy grapevines than symptomatic ones
246 [19]. Similarly, chickens infected with *Plasmodium gallinaceum* have been found to be less attractive
247 to the mosquito vector *Aedes aegypti* [17]. This observed preference for uninfected hosts is likely to
248 be an adaptation of the vector who is trying to avoid low quality hosts (figure 3A). In the Anther-smut

249 disease caused by *Ustilago violacea* the transmission of the spores relies on pollinator visits. Several
250 studies report that insect vectors have the ability to avoid infected flowers [18], [45]. This may result
251 from an adaptation of the vector because infected flowers do not produce any pollen ($\phi < 1$). But
252 the fact that infected plants are known to bloom earlier and to produce more flowers may attract
253 pollinators early in the season which is likely to result from an adaptation of the pathogen to
254 maximize its transmission to healthy plants later on in the season [45].

255 Second, several studies found evidence of pathogen manipulation where infected hosts tend to
256 attract uninfected vectors. For instance, hamsters infected with *Leishmania infantum* are more
257 attractive to female sandflies [46]. Humans infected with *Plasmodium falciparum* and mice infected
258 with *Plasmodium chabaudi* are more attractive to their respective mosquito vectors [14], [47].
259 Phytoplasma are bacterial plant pathogens that are known to convert infected plants into more
260 attractive hosts for their leafhopper vectors [48]. The causative agent of mummy berry disease of
261 blueberry is the fungal pathogen *Monilinia vacciniae-corymbosi* which induces the production of
262 pseudoflowers and mimicry of floral volatiles that attract insect vectors towards infected plants [49].

263 **4.2 Behaviour of infected and uninfected vectors**

264 Most of the work on conditional preference in vectors has been carried out in plant pathosystems.
265 One of the first studies testing for such conditional preference has been done with Barley yellow
266 dwarf virus (BYDV). Although the noninfected aphid *Rhopalosiphum padi* prefers to feed on infected
267 wheat plants, the acquisition of the virus dramatically alters the behavior of the infected vector that
268 prefers noninfected plants [27]. A similar reversal of feeding preference has been found in aphids
269 infected by Potato leafroll virus (PLRV) [50]. This preference is mediated by virus-induced changes of
270 potato plants that emit volatile blends enriched in monoterpenes, aldehydes and sesquiterpenes
271 [50]. The Tomato yellow leaf curl virus (TYLCV) can also alter the host preference of its whitefly
272 vector in the same way but, interestingly, this switch is modulated by the genotype of the vector, the
273 genotype of the host and the timing of the infection [51], [52]. In particular the conditional
274 preference of the whitefly was prominent only 6 weeks after infection on susceptible genotypes of
275 plants. The Tomato severe rugose virus (ToSRV) is another virus infecting tomatoes where
276 viruliferous (i.e. infectious) whiteflies are attracted towards volatiles emitted by uninfected plants,
277 while non-viruliferous whiteflies do not show any preference between volatiles emitted by infected
278 or uninfected plants [53]. These four different plant viruses match the above theoretical prediction
279 when pathogen manipulates independently the preference of infected and uninfected vectors (figure
280 3D).

281 Bacterial pathogens have also been found to affect the behavior of insect vectors. For instance,
282 *Candidatus liberibacter asiaticus* (Las) has been found to enhance attraction to both uninfected and
283 infected psyllid vectors [54]. This differential preference appears to be mediated by pathogen-
284 induced emission of methyl salicylate in infected plants. The fact that infected vectors also prefer
285 infected plants is likely to result from the emission of a general signal that attracts all the aphids
286 (uninfected or not infected vectors) as discussed in our theoretical model (figure 3B). Note, that the
287 pathogen has evolved other ways to encounter uninfected plants. First, aphids landing on infected
288 plants are rapidly driven away from these poor quality hosts (lower palatability). Second, infected
289 aphids have been found to increase their propensity to disperse (i.e. higher α in our model) which
290 may also allow the pathogen to settle in new uninfected plant populations. The bacterial pathogen

291 *Erwinia tracheiphilia* [55] was also found to alter the foliar and floral volatile emission of its wild
292 gourd host in ways that attract the beetle vectors towards infected leaves and uninfected flowers.
293 The beetles may thus acquire *E. tracheiphilia* from infected leaves and transmit the pathogen to a
294 new plant because cucumber beetle via attraction of their uninfected flowers. This differential effect
295 on leaves and flowers may be yet another way to promote pathogen transmission between infected
296 and healthy plants even though infection of the beetle does not seem to affect its preference.

297 All the above examples refer to plant pathogens that reside for extended periods in their vectors.
298 These persistently transmitted pathogens (PTP) have therefore more opportunities to act on the
299 preference of their insect vectors. In contrast, some plant pathogens are non-persistent in their
300 vectors (NPTP) and are expected to have lower abilities to act on vector behavior [29]. For instance
301 the *Cucumber mosaic virus* (CMV) bind to specific regions of the mouthparts of the vector and are
302 acquired and inoculated during brief tastes of outer plant cells. CMV has been shown to increase the
303 volatile emissions in infected plants and to attract aphid vectors [29]. But CMV also alters nutrient
304 cues of infected plants and this reduction of palatability encourages aphids to seek new and possibly
305 uninfected plants. This pathogen manipulation is likely to enhance pathogen transmission but the
306 conditional change of vector preference is driven by the poor quality of the infected host which is
307 perceived by the vector after landing and not by a direct effect of the pathogen in the individual
308 vector. The Tomato chlorosis virus (ToCV) is semi-persistent but does not circulate in its whitefly
309 vector and seems to induce maladaptive modifications of its vector. Non-viruliferous whiteflies
310 prefer the volatiles emitted by uninfected plants but viruliferous vectors do not exhibit any
311 preference [53].

312 As far as I know a very limited number of studies have been done on the conditional behavior of
313 infected and uninfected vectors of pathogens of animals. Unlike earlier results obtained with *P.*
314 *gallinaceum* [17], uninfected *Culex pipiens* mosquitoes are attracted by passerine birds infected with
315 *Plasmodium relictum* [15]. In a subsequent study Cornet et al. [56] showed that both infected and
316 uninfected *C. pipiens* mosquitoes are attracted towards infected birds. This result is in line with the
317 above theoretical predictions when the pathogen manipulates vectors from within the infected hosts
318 (figure 3B). This suggests that the manipulation of host-choice behavior by *P. relictum* acts on the
319 quantity and/or the quality of volatiles emitted by infected birds [47] and that both infected and
320 uninfected mosquitoes are attracted by the scent of this infection. Further studies are required to
321 confirm this prediction and to better characterize the underlying mechanism acting on mosquito
322 behaviour in other malaria parasites including human malaria [57].

323 5. Discussion

324 The epidemiology of vector borne disease is very sensitive to the host-choice behavior of the
325 arthropod vector. I developed a general model of vector borne transmission taking into account key
326 features of the ecology of a broad range of different pathosystems. Interestingly, this model allows
327 to escape the classical dichotomy between density and frequency dependent models [31] and may
328 help provide a more realistic description of the transmission process of vector borne diseases. This
329 model shows that extreme choice strategies can have dramatic consequences on the epidemiology
330 of the disease and can even lead to pathogen eradication. However, when the uninfected vectors are
331 more attracted towards infected hosts the dynamical system may exhibit backward bifurcation at
332 $R_0 = 1$. In other words, a stable endemic equilibrium may exist even if $R_0 < 1$. This result implies

333 that vector choice may prevent the eradication of pathogens even if human interventions managed
334 to reduce R_0 below its critical level. Similar bistability has been observed in models of malaria
335 transmission [58], [59] but here I show that the behavior of uninfected mosquitoes is a key driver of
336 this dynamic. Further work is required to better identify conditions promoting this epidemiological
337 bistability.

338 The evolutionary analysis of this model reveals complex conflicts between the vector and the
339 pathogen over host-choice behaviour. Under some scenarios, the evolutionary interests of the vector
340 and the pathogen are aligned which leads to a unique evolutionary outcome. In particular, when the
341 pathogen is only able to manipulate the behaviour of infected vectors, both the vector and the
342 pathogen are generally evolving a preference towards uninfected hosts (figure 3A and 3C). In this
343 situation it is impossible to determine who is controlling the evolution of vector behaviour from
344 observed preference patterns.

345 But pathogen evolution and vector evolution can yield qualitatively very different strategies under
346 other scenarios. This conflict emerges as soon as the parasite in the infected hosts is able to govern
347 host-choice behaviour of the vector. In this case, pathogen selection favours manipulation strategies
348 leading uninfected vectors to prefer infected hosts (figure 3B). Indeed, numerous empirical studies
349 show that pathogens can modify the scent of infected hosts to attract vectors [29]. This manipulation
350 often involves the elevation or exaggeration of existing cues used by vectors to locate hosts. As
351 pointed out by Mauck et al. [60] the evolution of such a “supernormal stimulus” does not involve
352 major qualitative differences between infected and uninfected hosts and it is thus very difficult for
353 the vector to evolve avoidance strategies even if infected vectors suffer from major fitness costs.

354 Finally, when the pathogen is able to adopt a different strategy in the host or in the vector,
355 conditional preference strategies can evolve. Indeed, the transmission of the pathogen is maximised
356 when uninfected vectors are attracted towards infected hosts and when infected vectors are
357 attracted towards uninfected hosts (figure 3D). Interestingly, only plant viruses with a persistent and
358 circulative mode of vector transmission have been shown to evolve such conditional preference
359 strategies (figure 4). This suggests that only pathogens that evolved a persistent and intimate
360 relationship with their vector are able to induce conditional preference strategies. Note, however,
361 that in spite of persistent infection in its mosquito vector, *Plasmodium* does not induce conditional
362 preference strategies [56]. Further studies exploring the host-choice preference of both infected and
363 uninfected vectors of other pathogens are required to confirm that only virus have the ability to
364 evolve such complex conditional manipulation strategies. In addition, it would be interesting to see if
365 some pathogens are able to evolve other forms of conditional manipulation of host preference
366 varying with the age of the infection in the vector. Indeed, one may expect different manipulation
367 strategies in infected but not yet infectious vectors.

368 An interesting extension of this work would be to analyse situations where multiple pathogens share
369 the same host and/or the same vector. It is easy to imagine how these complex epidemiological
370 scenarios could yield new evolutionary conflicts over the manipulation of vector behaviours [61]. In
371 addition, many pathogens can infect multiple host species and the vector preference for different
372 host species can also have massive epidemiological consequences [62]–[64]. Several recent studies
373 indicate that preference for different host species is heritable and could thus evolve as a response to

374 a change of the environment [65], [66]. The above theoretical framework could be used to
375 understand and predict the evolution and the manipulation of this other important behavioural trait.

376 The predictive power of these evolutionary models hinges upon our knowledge of the constraints
377 acting on these behavioural traits. To understand these constraints it is important to study the
378 mechanisms underlying vector preference. Experimental studies on vector preference indicate that
379 host-choice can be mediated by multiple cues like odour, colour and taste [29], [67], [68]. Some
380 pathogens have been shown to modify vector behaviour through the modification of these cues [29],
381 [13], [69]. But in most cases the underlying mechanisms driving these modifications of vector
382 behaviour remain elusive. A better understanding of these underlying mechanisms could also lead to
383 the development of novel public-health strategies to control vector-borne diseases [70]–[73]. The
384 above theoretical analysis provides a framework to understand the evolution and the manipulation
385 of key behavioural traits of vectors (e.g. host choice, biting rate) as well as a guide to structure the
386 exploration of the mechanistic constraints acting on this evolution in a broad range of vector-borne
387 diseases.

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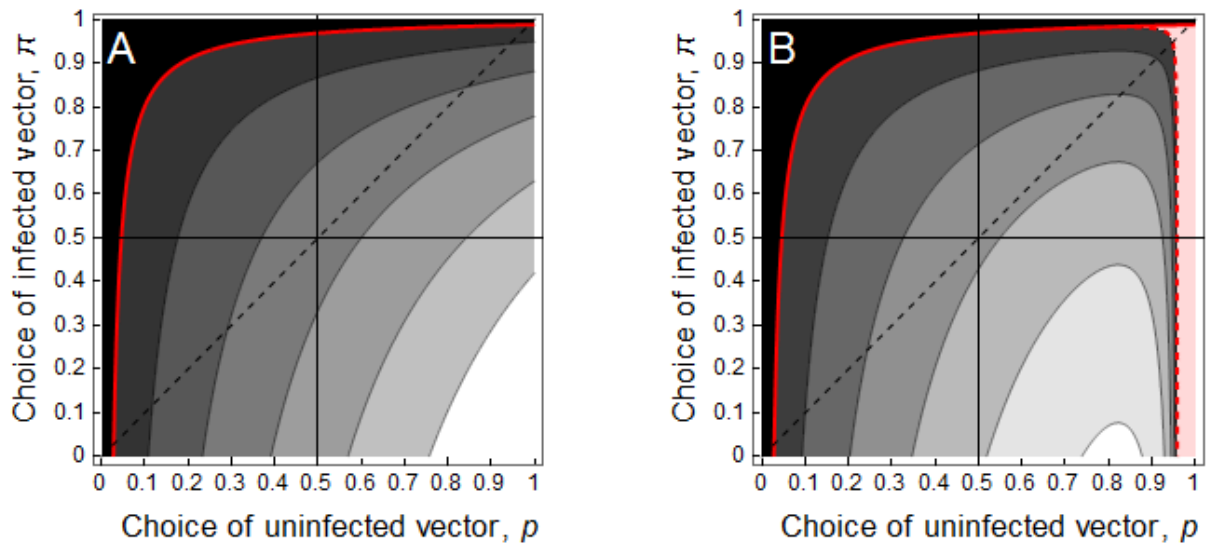
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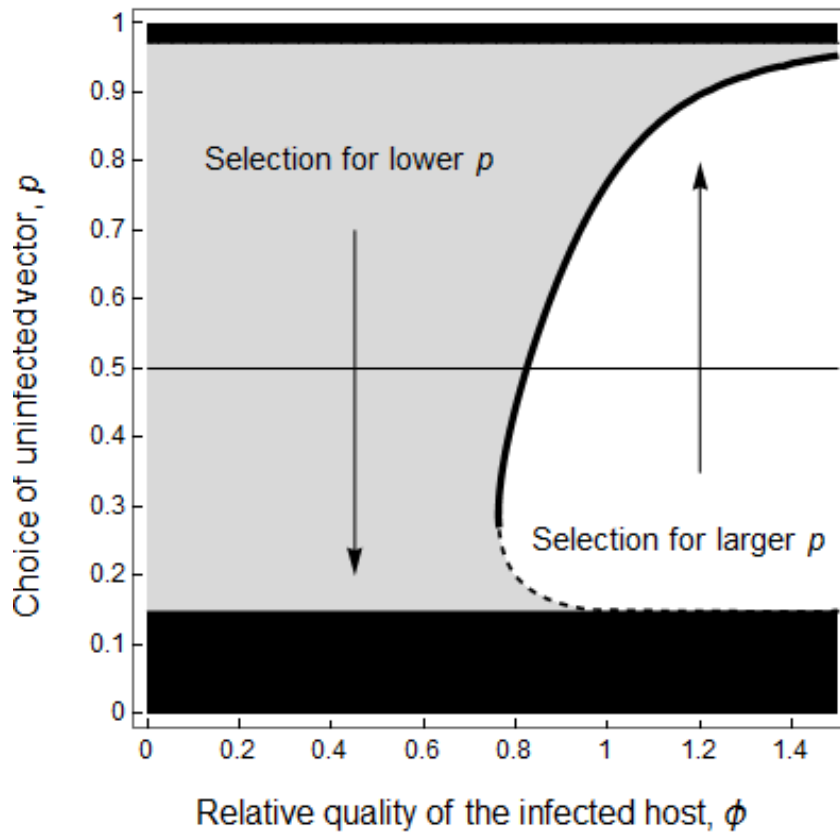
563 **Table1:** Definitions of the main parameters of the model.

Main parameters	Definitions
$N = S + I$	Host density (susceptible + infected)
$N_V = V_S + V_I$	Vector density (susceptible + infected)
a_S, a_I	Searching efficiency of uninfected vectors for uninfected and infected hosts
α_S, α_I	Searching efficiency of infected vectors for uninfected and infected hosts
$p = \frac{a_I}{a_S + a_I}, \pi = \frac{\alpha_I}{\alpha_S + \alpha_I}$	Preference towards infected hosts in uninfected and 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
$\delta_{V_S}, \delta_{V_I}$	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
c	Cost of searching efficiency on vector fecundity
ϕ	Quality (for the fecundity of the vector) of the infected host relative to the uninfected host
σ_H, σ_V	Probability of superinfection of an infected host and an infected vector, respectively

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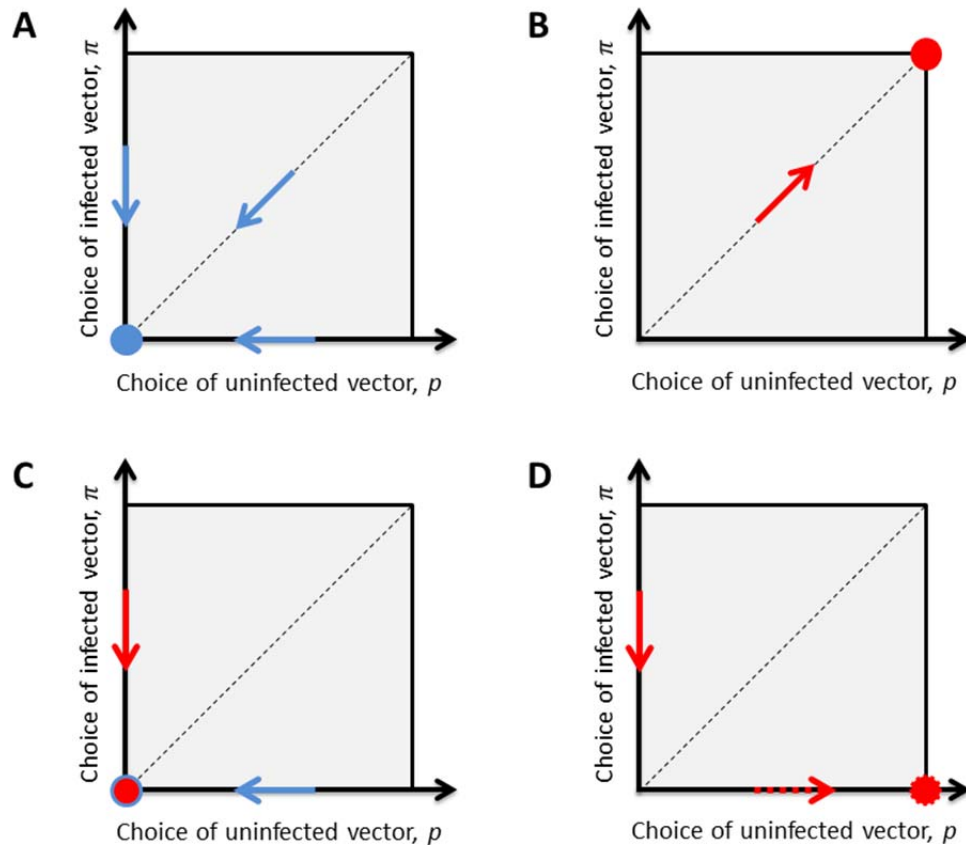


565
 566 **Figure 1:** Effect of vector host choice (preference for the infected host) on the basic reproduction
 567 ratio R_0 of the pathogen given in equation (2). The red line indicates the threshold value where
 568 $R_0 = 1$ and the shades of gray indicate different values of R_0 from 1 to 6 (darkest to lightest). In (A)
 569 the population size of the vector, N_V , before the introduction of the pathogen does not depend on
 570 host choice behavior because vector fecundity is assumed to be constant $f_S = 10$. In (B) the
 571 population size of the vector, N_V , depends on vector behavior because fecundity is assumed to
 572 depend on host preference as indicated in equation (3) with $F_S = 10$. Note that when uninfected
 573 vectors prefer infected hosts, the system exhibits a backward bifurcation at $R_0 = 1$ (dashed red line)
 574 and, depending on the initial conditions of the system, the pathogen may either go extinct or reach
 575 an endemic equilibrium when $R_0 < 1$ (light red region). The full red line and the black area indicate
 576 the parameter region where the pathogen is always driven to extinction. Other parameter values:
 577 $N = 500$, $\kappa = 0.01$, $b = \beta = 1$, $d = 0.05$, $\delta_{V_S} = \delta_{V_I} = 1$, $\tau = 0.1$, $a = \alpha = 0.01$.

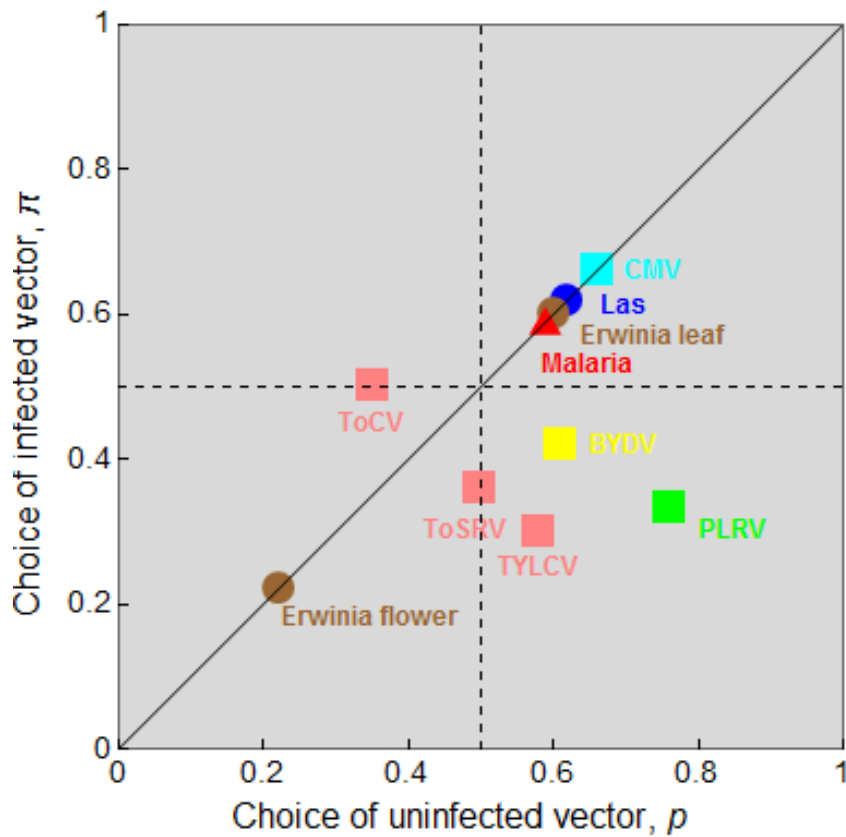


578

579 **Figure 2:** Effect of the relative quality of the infected host, ϕ , on the evolution of unconditional host
580 choice (preference for the infected host) of the vector. The pathogen goes extinct when vector
581 preference reaches extreme values (black region). When the relative quality of the infected host is
582 low vectors evolve preference for uninfected hosts (gray region). But when the quality of infected
583 host is relatively high vectors can evolve preference for infected hosts. The ultimate outcome may
584 either be an intermediate preference strategy (bold black line) or extreme avoidance strategy
585 towards infected hosts and, consequently, pathogen extinction. Other parameter values: $N = 1000$,
586 $\kappa = 0.001$, $b = \beta = 0.5$, $d = 0.1$, $\delta_{V_S} = \delta_{V_I} = 1$, $\tau = 0.5$, $a = \alpha = 0.01$, $F_S = F_I = 5$.



587
588 **Figure 3:** Schematic representation of the evolution of host choice (preference for the infected host)
589 by uninfected and infected vectors under different scenarios. Blue arrows indicate the direction of
590 evolution under vector control and red arrows indicate direction of evolution under pathogen
591 control. In (A) the host choice is only governed by the vector. In (B) the host choice of both infected
592 and uninfected vectors is governed by the pathogen in the infected host (i.e. $p = \pi$). In (C) the host
593 choice of infected vectors is governed by the pathogen while the host choice of uninfected vectors is
594 governed by the vector. In (D) the dashed arrow indicates evolution driven by the pathogen in the
595 infected hosts while the full arrow indicates evolution driven by the pathogen in the infected vector.
596 These four different scenarios yield different ultimate evolutionary outcomes indicated by a large
597 point in each panel. Note that the above panels summarize general evolutionary trends under
598 biologically relevant parameter values but extreme parameter values may yield qualitatively different
599 evolutionary predictions (see main text).



600

601 **Figure 4:** Host choice (preference for the infected host) in uninfected and infected vectors of
602 different pathogens: Tomato yellow leaf curl virus (TYLCV), Tomato severe rugose virus (ToSRV), Tomato
603 chlorosis virus (ToCV), Potato leaf roll virus (PLRV), Cucumber mosaic virus (CMV), *Candidatus liberibacter*
604 *asiaticus* (Las), *Erwinia tracheiphila* (wilt disease), *Plasmodium relictum* (avian malaria). A detailed
605 presentation of the references used to make this figure is presented in Table S1. Different symbols
606 are used to distinguish between viruses (circle), bacteria (square) and protozoan (triangle).