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► To cite this version:

Julien D Lombard, François Massol, Sébastien Lion. Double Trouble: Multiple infections and the coevolution of virulence-resistance in structured host-parasite populations. 2024. hal-04732148

HAL Id: hal-04732148

<https://hal.science/hal-04732148v1>

Preprint submitted on 11 Oct 2024

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1 Double Trouble : Multiple infections and the coevolution of virulence-resistance in structured host-parasite populations.

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DOI not yet assigned

Abstract

Parasite evolution is expected to modulate selective pressures acting upon host, and alter its response to infection. In such a context, parasite competition seems to be a key variable for the evolutionary dynamics and epidemic features. We develop a nested coevolutionary model of host resistance and parasite virulence. From individual-based traits, we define a within-host model and derive from the within-host equilibrium the main epidemiological features of interest -transmission, virulence, recovery-. We use this first model to build an adaptive dynamics model in order to assess the joint evolution of the parasite virulence and host resistance. We compared the coevolutionarily stable states predicted by the model under different competition regimes, including single infections (preemption), superinfection (dominance) and coinfections (mixed). We find that parasite virulence under coinfections evolved towards higher values than under superinfections, while the opposite trend was observed for host resistance. The local coexistence of parasites enables kin selection effects that reduce both virulence and the subsequent host response. We showed that the magnitude of multiple infections effects varies with the ecological context, and that the coevolutionary outcomes deviate from simple optimization of persistence depending on the degree of spatial coupling of hosts.

Keywords: multiple infections, virulence, resistance, epidemiology, kin selection, metapopulation

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Introduction

2

3 The study of host-parasite coevolution is of major interest in a wide variety of scientific
4 fields including agronomy, conservation biology and human or animal health. The antagonis-
5 tic interaction between parasites and their hosts leads to complex eco-evolutionary feedback
6 loops. Assessing how evolutionary forces shape and are shaped by environmental or physiolog-
7 ical mechanisms is thus a difficult task. Since the seminal work of May and Anderson, 1979,
8 there has been numerous tentatives of drawing a mathematical picture of the evolution of host-
9 parasite interactions. Particularly, a strong effort has been dedicated to the study of coevolution
10 in attack-defense traits. There is increasing theoretical and empirical support showing that the
11 coevolution of parasite virulence and host resistance are crucial determinants of the ecology and
12 evolution of infectious diseases (Best et al., 2009, Restif and Koella, 2003, Carval and Ferriere,
13 2010, Kada and Lion, 2015 for the theory; Webster et al., 2004, Lefèvre et al., 2007, Frickel et al.,
14 2016 for the empirical part). One important feature of infections is that hosts are often infected
15 with multiple parasite strains that -at least transiently- coexist in the host (e.g. Susi et al., 2015).
16 Multiple infections, and more specifically within-host competition, are known to shape evolu-
17 tionary dynamics De Roode et al., 2005 and can therefore induce conflicting levels of selection
18 (reviewed in Mideo et al., 2008, Cressler et al., 2016). However, such phenomena remain poorly
19 accounted for in theoretical studies, especially in a coevolutionary framework.

20 Amongst epidemiological models analyzing the evolution of virulence, most -if not all- rely
21 on phenomenological assumptions to resolve within-host competition dynamics. From our lit-
22 erature survey, three main approaches are traditionally used. The first is to neglect multiple
23 infections altogether: infected hosts are prevented from being infected by new strains. Thus,
24 competition is assumed to be ruled exclusively by the colonization of new susceptible individ-
25 uals at the between-host scale. A second approach relies on the superinfection assumption, in
26 which competition between two coinfecting strains is instantaneously resolved by the exclusion
27 of the less competitive one Kada and Lion, 2015, Nowak and May, 1994. The underlying hypoth-
28 esis is that parasite strains respect a strict competitive hierarchy. While this hypothesis may hold
29 when competitive differences are strong, it is however unlikely for multiple infections with ge-
30 netically close strains. A third approach is to explicitly allow strains to coexist within a host May
31 and Nowak, 1995, Mosquera and Adler, 1998. Alizon & Van Baalen Alizon and Baalen, 2008 pre-
32 sented a multiple-infection model in which coinfections emerge as an outcome of within-host
33 dynamics. Their model include mixed regimes of competition because a strain with a compet-
34 itive advantage will slowly displace its competitor, but might not succeed to fully replace the
35 other during the infectious time. One of their main findings was that allowing for transient co-
36 existence of competing strains promotes evolutionary branching of virulence when coinfections
37 are frequent. This result comes from the induction of heterogeneity in hosts to be infected and
38 an emerging sort of competition-colonization trade-off.

39 Multiple infections in epidemiology share conceptual similarities with community ecology,
40 the host-parasite system being considered as a two-species community. Competition for new
41 susceptibles in single-infection models acts in a very similar way to preemptive competition in
42 metapopulations models (i.e the resident status of a strain preclude further competitive replace-
43 ment by another, e.g. Levins and Culver, 1971). Superinfection models, on the other hand, de-
44 scribe competitive rules that are very similar to the ones defining the competition-colonization
45 trade-off model Hastings, 1980 Tilman, 1994 from Levins seminal formalism Levins, 1969. In

46 such cases, better competitors instantaneously displace the poor ones, such that competition
47 acts through strict dominance. More recently, it has been shown that allowing for mixed regimes
48 of competition has several implications for eco-evolutionary dynamics, for example by altering
49 the likelihood of species coexistence at a regional scale Calcagno et al., 2006. In particular, coexis-
50 tence of species or strains at the regional scale should be favored when fitness is not completely
51 determined by the colonization process -i.e. the transmission to susceptible hosts, in an epidemi-
52 ological context-. The integration of mixed regimes of competition in multiple infections thus
53 appears to be a relevant feature to include in coevolutionary studies.

54 The importance of multiple infections may not be without consequences for the way hosts
55 respond to parasite infections. In particular, the host resistance to infections appears to be a
56 good candidate for driving parasite evolution in the context of multiple infections. When seen
57 as an avoidance mechanism, resistance reduces the transmission rate, and thus the likelihood of
58 multiple infections Boots and Haraguchi, 1999. When seen as a clearance mechanism, it reduces
59 the infectious period Baalen, 1998. These phenomena are expected to determine the nature of
60 competition between strains during multiple infections, due to a shift in the balance between
61 preemptive and dominance effects. There is thus a need to incorporate multiple infections and
62 detailed within-host interactions processes in a coevolutionary framework. However, despite no-
63 table theoretical advances in host-parasite evolution, such mechanisms remain poorly included.
64 Particularly, the potential feedback of multiple infections in host response to parasite evolution
65 remains to our knowledge, unexplored.

66 Here, we build on the existing theory of metapopulation ecology to build a nested model
67 to study the coevolution of host resistance and parasite virulence. From individual-based traits,
68 we define a within-host model including parasite growth and host-induced parasite attrition.
69 Then, using a time-scale separation argument, we derive from the within-host equilibrium the
70 main epidemiological features of interest (transmission, virulence, recovery) and use them to
71 construct a between-host epidemiological model. Our results are derived assuming trade-offs
72 between parasite replication and virulence, and the host resistance and fecundity. Using the
73 now classical toolbox of adaptive dynamics Geritz et al., 1998, we first provide an overview of
74 the evolutionary outcomes resulting from the evolution of either the host or the parasite. Then
75 we consider the coevolution of both partners, and determine how strain competition and host
76 response drive selection upon host resistance, and parasite virulence.

77

The model

SIS epidemiological model

79 Our starting point is the classic susceptible-infected-susceptible (SIS) model Kermack and
80 McKendrick, 1927. We first clarify the link between the SIS model and metapopulation models.
81 Because parasites view the host population as a well-mixed metapopulation of fully connected
82 patches, we follow the usual approach from metapopulation ecology and track the dynamics of
83 the fractions of patch states. Here, each patch can be empty (0) or occupied by a single suscepti-
84 ble (S) or infected host (I). Assuming no density dependence on mortality and a constant number
85 of usable "patches" for hosts (which enforces a negative density-dependence on birth rate), the
86 demographic and epidemiological dynamics of the host is given as:

$$(1) \quad \begin{aligned} \frac{dp_S}{dt} &= [b_S p_S + b_I p_I] p_0 - dp_S - \beta p_I p_S + \tau p_I \\ \frac{dp_I}{dt} &= [\beta p_S - (d + \alpha + \tau)] p_I \end{aligned}$$

87 where p_x is the fraction of patches in state x . Note that our model reduces to two equations
 88 because the patch frequencies sum to 1 ($p_S + p_I + p_0 = 1$). Susceptible (resp. infected) hosts
 89 reproduce at rate b_S (resp. b_I), and give birth to susceptible newborns, which can only develop
 90 into adults if they find an empty patch p_0 . Both susceptible and infected hosts have a background
 91 mortality rate d . Infected hosts have an additional mortality rate (virulence) α , and can recover
 92 at rate τ . Finally, transmission occurs at rate β .

93 The model has two non-trivial equilibria: a disease-free equilibrium in the form ($\tilde{p}_0 = \frac{d}{b_S}$, $\tilde{p}_S =$
 94 $1 - \frac{d}{b_S}$, $\tilde{p}_I = 0$), and an endemic equilibrium (p_0^* , p_S^* , p_I^*). For the endemic equilibrium to exist, the
 95 following condition is required:

$$(2) \quad R_0 = \frac{\beta \tilde{p}_S}{d + \alpha + \tau} > 1$$

96 where R_0 is the basic reproduction number of the parasite Diekmann et al., 1990. It is useful to
 97 notice that R_0 is here equivalent to the number of successful dispersers produced by an initial
 98 parasite infecting a host " R_m " Ajar, 2003, Metz and Gyllenberg, 2001, Massol et al., 2009 in the
 99 absence of evolution.

100 Within-host model

101 Following Alizon and Baalen, 2005, we derive the epidemic traits from within-host interac-
 102 tions. We introduce a model of within-host parasite growth which tracks the dynamics of within-
 103 host parasite density, X :

$$(3) \quad \frac{dX}{dt} = (r_0 \theta - r_1 X) X - (\mu + m + \gamma \sigma) X$$

104 Parasites replicate at rate $r_0 \theta$, where r_0 is the maximum replication rate and θ the parasite strategy
 105 of host exploitation, which takes values between 0 and 1. We assume that within-host replication
 106 is density-dependent, with strength r_1 . Parasite emigrate from their host at rate m and die at rate
 107 $\mu + \gamma \sigma$, where μ refers to background parasite mortality and $\gamma \sigma$ is the host resistance level. γ is
 108 a theoretical maximum for resistance, and σ is the investment trait, with values between 0 and
 109 1. The within-host dynamics have two possible outcomes: either the parasite becomes extinct
 110 ($\tilde{X} = 0$), or its density stabilises at an equilibrium parasite load :

$$(4) \quad X^*(\theta, \sigma) = \frac{r_0 \theta - \mu - m - \gamma \sigma}{r_1}$$

111 Bridging the scales

112 System (1) describes a well-mixed population. However, from the parasite perspective, the
 113 host population can be seen as a set of discrete patches linked through the dispersal of parasite
 114 propagules. Our SIS model can therefore describe the colonization-extinction dynamics of local
 115 parasite populations Levins, 1969, the metapopulation dynamics of which are given by eqn.(3).
 116 For system (1) to remain consistent, we assume that within-host dynamics is fast compared to the
 117 processes that put an end to infection (*i.e.* host mortality, recovery and virulence). This requires

118 that the rate at which eq.(3) shifts from equilibrium \tilde{X} to $X^*(\theta, \sigma)$ exceeds the inverse of the total
119 infectious period, which can be mathematically translated into :

$$(5) \quad r_0\theta - (\mu + m + \gamma\sigma) \gg d + \alpha + \tau$$

120 Epidemiological traits

121 We assume that the fecundity of infected hosts, b_I , the transmission rate β , the recovery rate
122 τ and the virulence α depend on two underlying traits: (1) the host's investment into defence σ ,
123 and (2) the parasite's investment in host exploitation θ . Specifically, we assume that the epidemic
124 traits expressed in infected hosts are under the shared control of both partners, and note :

$$\beta = \beta(X^*)$$

$$\alpha = \alpha(X^*)$$

$$\tau = \tau(X^*)$$

125 We assume that the dependance of epidemic features to host and parasite individual traits
126 occurs through the within-host equilibrium load. Assuming that transmission is a linear increasing
127 function of the equilibrium load, we define :

$$(6) \quad \beta(X^*) = cX^*(\theta, \sigma)$$

128 where $c = m(1 - \rho)$ is the rate of successful dispersal of parasite propagule, with m the rate at
129 which propagules leave their host, and ρ a dispersal cost that represents the fraction of emigrat-
130 ing propagules lost during dispersal.

131 We also assume virulence and recovery to be functions of traits through equilibrium load.
132 We generically define the functions $\alpha(\theta, \sigma)$ and $\tau(\theta, \sigma)$ in the following way:

$$(7) \quad u(\theta, \sigma) = u_0 f_u(\tilde{X}(\theta, \sigma))$$

133 where $u \in \{\alpha, \tau\}$, and u_0 is a theoretical maximum for the epidemiological trait α (resp. τ). The
134 trade-off function f_α (resp. f_τ) is assumed to be an increasing (resp. decreasing) function of the
135 parasite load. A complete description of the functions used is given in appendix C. In addition, a
136 table summarising parameter notations and interpretations is provided in appendix A.

137 Furthermore, we assume that host defense is costly and leads to a reduced fecundity of
138 infected hosts, that is :

$$b_S = b(0) = b_0$$

$$b_I = b(\sigma)$$

139 where $b(\sigma)$ is a decreasing function of σ . Note that this implicitly assumes that the constitutive
140 costs of resistance are negligible, but its induced costs are not.

141 Resistance in our model acts in two ways: as an avoidance mechanism (*i.e.* causing a reduc-
142 tion in disease transmission), and as a clearance mechanism (*i.e.* causing an increase in host
143 recovery, and/or a decrease in virulence). Both transmission and virulence are assumed to be
144 increasing functions of the within-host replication rate, which has received strong empirical sup-
145 port Acevedo et al., 2019. Because both traits depend on the parasite's strategy θ , our model
146 also incorporates the classic virulence-transmission trade-off: an increase in transmission can
147 only be bought at the expense of a reduced infectious period Alizon et al., 2009.

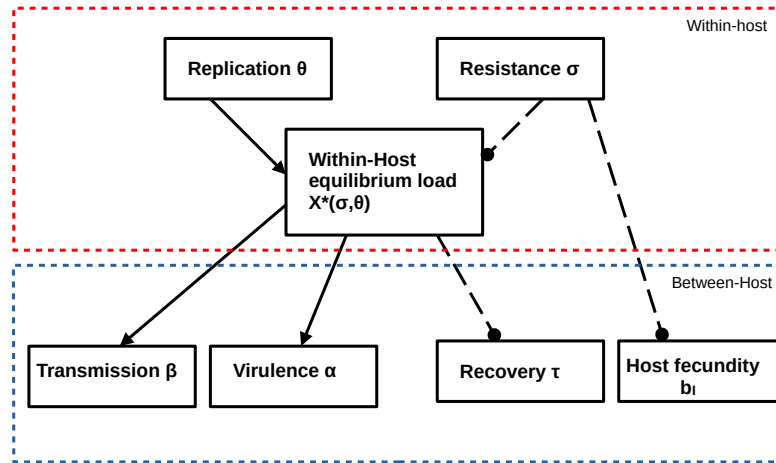


Figure 1 – Schematic view of interactions between resistance and exploitation traits, and their consequences on equilibrium density $X^*(\theta, \sigma)$ and associated epidemiological parameters. Solid arrows refers to up-regulation links (when the origin quantity increases, it induces an increase in the terminal quantity). Dashed lines with black circles refers to inhibition links (when the origin quantity increases, it induces a decrease in the terminal quantity). The red square delimits processes acting at the within-host level, while the blue square delimits between-host processes.

Host evolution

148

149 We first describe the outcome of host resistance evolution. In this section, we assume that
150 parasite investment in replication θ is fixed, and write $X^*(\theta, \sigma) = X^*(\sigma)$.

151 Host and parasite coexistence.

152 For an endemic equilibrium of the disease to exist, we require that the equilibrium of system
153 (3) also exists and is positive, which holds if :

$$(8) \quad \frac{\mu + m + \gamma\sigma}{r_0} < \theta \text{ or equivalently } \sigma \leq \frac{r_0\theta - (\mu + m)}{\gamma}$$

154 In addition, we also require that the number of secondary infections following the initial
155 invasion of the disease-free equilibrium by a single parasite (the epidemiological R_0) is above
156 one. Note that this implies that the within-host equilibrium load exists and is positive.

157 From (8), it follows that in absence of host response, parasite growth is only determined by
158 $r_0\theta - (\mu + m)$. It also ensues that a parasite that do not sufficiently invest in virulence is unviable,
159 as shown in figure (2a). For σ constrained on $[0,1]$, the host is able to drive its parasite towards
160 local extinction when :

$$(9) \quad \frac{r_0\theta - (\mu + m)}{\gamma} \leq \sigma \leq 1$$

161 From (9), it appears that only a sufficiently slow-growing parasite can be driven to extinction
162 by the host. It also means that setting $\frac{r_0\theta - (\mu + m)}{\gamma} \geq 1$ ensures that no host-driven extinction is
163 achievable. From now, we will restrict our analysis to the set of cases in which the host is always
164 unable to eradicate its parasite, whatever its level of resistance. However, an overview of cases
165 where the host evolution can drive the parasite towards extinction is presented in appendix (B).

166 Invasion Fitness.

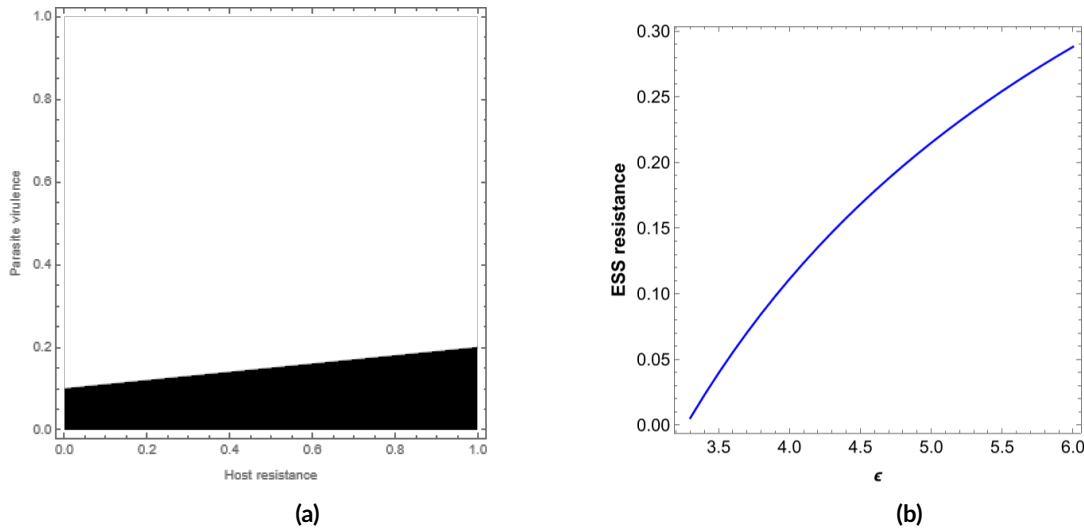


Figure 2 – (a) Phase diagram describing the parasite domain of existence. White areas represent the cases where the hosts and parasite always coexist, while black areas represent the set of cases where the host can drive its parasite towards extinction. (b) CSS strategy of host investment in resistance according to the shape of the trade-off functions between hosts resistance and fecundity. Fixed parameter values for figures a-d were set to : $b_0 = 0.8$, $b_1 = 0.5$, $\alpha_0 = 1$, $r_0 = 10$, $\theta = 0.8$, $r_1 = 0.04$, $\rho = 0.9$, $\gamma_0 = 1$, $d_0 = 0.05$, $\tau_0 = 1$, $\delta = 3$, $\kappa = 1$, $d = 0.5$

167 We consider the fate of a rare mutant host with investment σ_m invading a resident host pop-
 168 ulation with investment σ at its endemic equilibrium. We define the invasion fitness as the initial
 169 growth rate of the mutant in the equilibrium resident population Geritz et al., 1998. For struc-
 170 tured populations, a proxy for the invasion growth rate is obtained using the next-generation
 171 theorem Diekmann et al., 1990; Hurford et al., 2010; Otto and Day, 2007. Denoting quantities
 172 that depends on the mutant trait by a subscript m , this yields (see appendix D for the complete
 173 derivation) :

$$(10) \quad W_h = \frac{b_0 \Psi_m + b_m \beta p_j^*}{d \Psi_m + (d + \alpha_m) \beta p_j^*} p_0^*$$

174 where $\Psi_m = d + \alpha_m + \tau_m$, such that $1/\Psi_m$ is the average infectious period of a mutant host.
 175 Eq.(10) is similar to eq.(A7) in Kada & Lion (2015) Kada and Lion, 2015 or eq.(6) in Restiff
 176 & Koella (2003) Restif and Koella, 2003, with some noticeable differences. First, mutant fitness
 177 relies on the infectious period not only through the recovery rate, but also parasite virulence.
 178 Second, the force of infection βp_j^* also depends on the host trait. Third, the birth rate of suscep-
 179 tible individuals does not depend on the investment in resistance, as we assume its costs come
 180 by mounting an immune response. It is then straightforward to see that in the absence of the
 181 parasite (*i.e.* in a disease-free population or when the host can drive its parasite to extinction),
 182 resistance becomes a neutral trait (see appendix B). As only infected individuals pay the costs of
 183 resistance, parasite presence is needed for resistance to be under selection.

184 Singular strategies.

185 Let our parameters be constrained to always verify condition (2). Setting $r_0 \theta - (\mu + m) > \gamma$
 186 ensures that no infected host can get rid of the parasite, whatever its level of resistance. We
 187 study the fixed points of the adaptive dynamics by solving for σ values for which $\left. \frac{\partial W_h}{\partial \sigma_m} \right|_{\sigma_m = \sigma} = 0$.

188 Evolutionary stability is studied through the second derivatives of the fitness function. A strat-
189 egy is said *evolutionarily stable* (ESS) if the second partial derivative of the fitness function with
190 respect to the mutant trait is negative Geritz et al., 1998. In addition, if the derivative of the fit-
191 ness gradient evaluated at the singular strategy is negative, the strategy is said to be *convergence*
192 *stable*, which ensures that it is a locally attracting point. A strategy that is both evolutionarily sta-
193 ble and convergence stable is thus an endpoint of the evolutionary dynamics and is termed as a
194 *continuously stable strategy* (CSS). A strategy that is neither evolutionarily stable nor convergence
195 stable is therefore an evolutionary repeller.

196 We analyzed how the shape of the trade-off function between resistance and fecundity af-
197 fects the existence of singular states. Figure (2b) shows that our model allows us to recover some
198 results from Best et al., 2009, Boots and Haraguchi, 1999. That is, a CSS is found for a sufficiently
199 concave trade-off function between σ and $b(\sigma)$. Biologically, this means that an evolutionarily
200 stable investment in resistance occurs only when the subsequent physiological costs are acceler-
201 ating. When the costs are moderately decelerating, the evolutionarily singular point is a repeller
202 that lies outside of the parameters region that is biologically relevant. In such a case, selection
203 drives resistance towards zero investment. When the costs are strongly decelerating, the repeller
204 then appears and selection drives resistance towards an all-or-nothing strategy, depending on
205 the initial conditions. Pairwise invasibility plots for decelerating costs are presented in appendix
206 A.

207 When a CSS level of investment exists, it increases with the acceleration of cost (Fig.2b).
208 In such a case, higher investment levels can be reached without paying an excessive cost, as
209 $b'(\sigma)$ decreases for low σ . Unlike previously cited studies, we found no evidence for evolution-
210 ary branching depending on the shape of the trade-off function. This is easily explained by the
211 assumption made on the distribution of resistance costs. Indeed, host fitness is determined by
212 a single environmental variable (p_I), which prevents branching Lion and Metz, 2018. This con-
213 trasts with the work of Best et al., 2009, Boots and Haraguchi, 1999, where the consideration
214 of constitutive costs of immunity leads the host fitness to be affected by the densities of both
215 susceptible and infected individuals.

216 Parasite evolution

217 We analyse the evolutionary dynamics of parasite investment. We assume that the host in-
218 vestment in resistance is not subject to selection, such that σ is arbitrarily fixed and we write
219 $X^*(\theta, \sigma) = X^*(\theta)$.

220 Due to the metapopulation structure of the parasite, it is not possible anymore to define
221 fitness as the initial growth rate of a mutant invader in a given patch. We therefore use as a
222 fitness measure the average lifetime population success R_m , Metz and Gyllenberg, 2001, Ajar,
223 2003, following the methods initially described in Jansen and Vitalis, 2007 and Pillai et al., 2012.
224 Competition dynamics in coinfecting hosts.

225 We consider the fate of a mutant parasite with trait θ_m and load X_m^* during its early stage
226 of invasion. This implies considering reinvasion dynamics of strains. These reinvasions can occur
227 when the mutant invades a patch already occupied by the resident parasite, or conversely when
228 it is invaded by the resident while alone in a host.

229 The dynamics of the mutant frequency in a shared patch is described by (see appendix E for
230 details on the derivation)

$$(11) \quad \frac{df}{dt} = \Delta_s f(1 - f)$$

231 with competition acting through the differential replication of the two strains, *i.e.* through
232 the quantity $\Delta_s = r_0(\theta' - \theta)$. After reinvasion, each strain will produce dispersers until extinc-
233 tion or competitive exclusion occurs. When extinction is likely to occur before exclusion, even
234 a less competitive strain will benefit from having been the first to colonize a new host, which
235 enables preemptive effects in competition. We thus have to explicitly account for the transient
236 replacement dynamics of the strains. Equation (11) can be solved in closed form and yields :

$$(12) \quad f^\phi(t) = \frac{\phi}{\phi + (1 - \phi) \exp^{-t\Delta_s}}$$

237 where ϕ refers to the initial frequency of the mutant in a particular coinfection scenario. Note
238 that by definition, $f^\phi(t) = \phi$ when $\Delta_s = 0$. We define two initial conditions of interest: $\phi_{rm} =$
239 $\frac{1}{X_m^* + 1}$, the initial mutant frequency after it re-invades a resident host and $\phi_{mr} = \frac{X_m^*}{X_m^* + 1}$ the initial
240 mutant frequency after being re-invaded by a resident.

241 By definition, a strain at its own equilibrium has a null net growth rate. As our model assume
242 density-dependence acting on natality, an invading mutant whose replication is close to the
243 resident has a low birth rate. Competitive exclusion should therefore be a slow process. We thus
244 assume that the total density of parasite in a coinfecting host reaches a quasi-equilibrium value,
245 that is slowly changing through the frequency dynamics of strains, given by:

$$(13) \quad Y^\phi(t) = X_m^* f^\phi(t) + X^*(1 - f^\phi(t))$$

246 Doing so, virulence and recovery in coinfecting hosts now depends on the quasi-equilibrium
247 parasite load. It allows us to define the inverse of the average infectious period during coinfec-
248 tions as :

$$(14) \quad \psi^\phi(t) = d + \alpha^\phi(t) + \tau^\phi(t)$$

249 where $\alpha^\phi(t)$ and $\tau^\phi(t)$ are now functions of of the quasi-equilibrium load Y^ϕ (eq.13). Study-
250 ing the dynamics of coinfection leads us to look at the number of strains received by the host
251 at equilibrium. A host can theoretically be reinvaded without limitations. However, in order to
252 keep the model analytically tractable, we assume that during its lifespan hosts suffer at most
253 two infections events. This assumption has already been used in the context of virulence evolu-
254 tion Baalen and Sabelis, 1995, or dispersal evolution Jansen and Vitis, 2007. Disentangling the
255 number of infections at one strain equilibrium is achieved by extending system (1) into :

$$(15) \quad \begin{aligned} \frac{dp_S}{dt} &= [b_S p_S + b_I(p_1 + p_2)] p_0 - dp_S - \beta(p_1 + p_2) p_S + \tau(p_1 + p_2) \\ \frac{dp_1}{dt} &= \beta(p_1 + p_2) p_S - [\beta(p_1 + p_2) - (d + \alpha + \tau)] p_1 \\ \frac{dp_2}{dt} &= \beta(p_1 + p_2) p_1 - (d + \alpha + \tau) p_2 \end{aligned}$$

256 where p_1 and p_2 refer to the number of hosts that have received one or two parasite invasions,
257 respectively. Setting $p_1 + p_2 = p_I$ allows us to recover system (1). Solving system (15) equilibria

258 now allows to break down the endemic equilibrium in the form $p_0 = p_0^*$, $p_s = p_s^*$, $p_1 = p_1^*$, $p_2 = p_2^*$,
 259 with $p_1^* + p_2^* = p_I^*$.

260 Invasion fitness.

261 We follow the number of successful emigrants produced by a rare focal mutant landing in a
 262 given host. This number is equal to the sum of emigrants produced in each of the different hosts
 263 states (susceptible or infected) in which the mutant can appear, weighted by the time spent in
 264 each of those states Massol et al., 2009. We consider the set of fates a mutant invader can expe-
 265 rience. If the mutant lands in a susceptible host p_s^* , it will produce $\beta_m = cX_m^*$ dispersers per unit
 266 of time until the infection ends or the host is reinvaded. Such reinvasion will happen with prob-
 267 ability $\frac{\beta p_I^*}{\beta p_I^* + \Psi_m}$. Subsequently, the mutant will produce additional dispersers until competitive
 268 exclusion occurs or infection ends.

269 Noting $F^\phi(t)$ the amount of dispersers produced after a given reinvasion, we have :

$$(16) \quad F^\phi(t) = cY^\phi(t)f^\phi(t) \exp^{-\int_0^t \psi_\phi(s)ds}$$

270 Here $cY^\phi(t)f^\phi(t)$ denotes the number of mutants dispersers produced at time t , and $\exp^{-\int_0^t \psi_\phi(s)ds}$
 271 is a survival function that describes the probability that the infection has not ended until t . Thus,
 272 $\int_0^\infty F^{\phi mr}(t)dt$ dispersers are produced when the mutant is reinvaded by the resident. Similarly,
 273 a mutant landing in an already infected host p_I^* will produce $\int_0^\infty F^{\phi rm}(t)dt$ dispersers over the
 274 lifespan of its host. Dropping the dependency on the resident trait for notational convenience,
 275 and denoting dependencies on the mutant by a subscript m , we put all scenarii together and
 276 obtain the parasite fitness function :

$$(17) \quad W_p = cp_s^* \left[\frac{X_m^*}{\beta p_I^* + \Psi_m} + \frac{\beta p_I^*}{\beta p_I^* + \Psi_m} \int_0^\infty F_m^{\phi mr}(t)dt \right] + cp_I^* \int_0^\infty F_m^{\phi rm}(t)dt$$

277 In the absence of multiple infections (i.e. with $cp_I^* = cp_1^* = 0$), parasite fitness reduces to :

$$(18) \quad W_p = \frac{\beta p_s^*}{\Psi_m} = \frac{R_{0m}}{R_0}$$

278 which is the classic expression for parasite fitness in the SIR model. The evolutionary be-
 279 haviour of this model has been extensively studied. In this case, selection drives parasite viru-
 280 lence towards R_0 maximization.

281 Fitness gradient.

282 The complete derivation of the fitness gradient is described in appendix (F). Dropping the
 283 dependency on traits to avoid notational clutter, it leads to the following expression :

$$(19) \quad \begin{aligned} \frac{\partial W_p}{\partial \theta_m} \Big|_{\theta_m=\theta} &= \frac{\Psi}{\beta p_I^* + \Psi} \left[\frac{1}{X^*} \frac{dX_m^*}{d\theta_m} \Big|_{\theta_m=\theta} - \frac{1}{\beta p_I^* + \Psi} \frac{d\Psi_m}{d\theta_m} \Big|_{\theta_m=\theta} \right] \\ &+ \frac{\beta p_I^*}{\beta p_I^* + \Psi} \left[-\frac{1}{\beta p_I^* + \Psi} \phi^{mr} \frac{d\Psi_m}{d\theta_m} \Big|_{\theta_m=\theta} \right. \\ &\left. + \left(\frac{1}{X^*} \frac{\partial X_m^*}{\partial \theta_m} \Big|_{\theta_m=\theta} - \frac{1}{\Psi} \frac{d\Psi_m}{d\theta_m} \Big|_{\theta_m=\theta} \right) \left(R - \frac{p_1^*}{p_2^*} \bar{R} \right) + r_0 \frac{p_I^*}{p_2^*} \bar{R} \frac{1}{\Psi} \right] \end{aligned}$$

284 Where R and \bar{R} are the relatedness and unrelatedness measures in metapopulation, the
 285 derivation of which is described in appendix (F).

286 In the absence of multiple infections (*i.e.* when putting $cp_j^* = 0$), eq. (19) reduces to a simpler
287 form :

$$(20) \quad \frac{\partial W_p}{\partial \theta_m} \Big|_{\theta_m=\theta} = \frac{\frac{d\beta_m}{d\theta_m} p_s^*}{\Psi} - \frac{\beta p_s^* \frac{d\Psi_m}{d\theta_m}}{\Psi^2} \\ = \frac{1}{R_0} \frac{\partial R_0(\theta_m)}{\partial \theta_m} \Big|_{\theta_m=\theta}$$

288 Note that this is, as expected, equal to the selection gradient obtained from differentiating
289 eq.(18). Without multiple infections, competition is only driven by preemption (*i.e.* the competi-
290 tion for new susceptibles). We then retrieve classic results from the single-population epidemi-
291 ology, such that selection obeys the R_0 optimization principle Lion and Metz, 2018.

292 Eq. (19) can be partially understood in such terms. Terms on the first line have an interpreta-
293 tion analogous to eq. (20), and correspond to changes in R_0 considering reinvasions can occur.
294 The first term between brackets describes the fitness gain of a higher replication when coloniz-
295 ing a susceptible host. The second term reflects the change in fitness due to an alteration of the
296 infectious period. These terms are weighted by the probability that the infection ends before a
297 secondary infection has occurred. On the second line, the term in factor denotes the probability
298 of occurrence of a secondary infection. The first term between brackets is the fitness change due
299 to the alteration of the infectious period followed by the introduction of a second strain.

300 Terms in the third line reflect the additional selective pressures induced by the consideration
301 of within-host dynamics. Interestingly, the within-host component can be interpreted in terms
302 of kin structure. The first term in \bar{R} shows the fitness loss through competition with the other
303 strain. This term is accompanied by a term in R that is always of opposite sign and reflect how
304 a change in within-host density or duration of infection would also benefit to the production of
305 dispersed relatives. Thus, if selection favors higher levels of virulence due to the competitive ad-
306 vantage conferred by a higher replication rate, this effect should be dampened by a kin selection
307 effect. The last term between brackets that depends on \bar{R} is always positive, such that increased
308 virulence has always an advantage when multiple infections are allowed for. Our model also con-
309 siders that any invasion is successful but that less competitive strains are slowly excluded. Thus,
310 there is always an advantage -even small- for any strain to be able to invade an already infected
311 host.

312 The limit case of pure dominance competition (*i.e.* close or equal to a superinfection frame-
313 work) is a bit more difficult to mimic on the basis of equation (19). In order to adress it, preemptive
314 effects in infected hosts must become negligible. This would correspond to infinitely long
315 infectious periods, or strong competitive differences between strains. The first case would force
316 crucial epidemiological parameters (virulence and recovery) to also become negligible, which
317 would compromise the evolutionary analysis. The second case would interfere with the quasi-
318 equilibrium assumption used to derive our fitness equation. Consequently, the derivation of pure
319 dominance competition from (19) require additional assumptions. If one assumes that within-
320 host competitive exclusion occurs instantaneously, restricting the number of invasions is not
321 necessary anymore. Then, eq.(17) drastically simplifies and gives the parasite invasion fitness
322 under the superinfection framework :

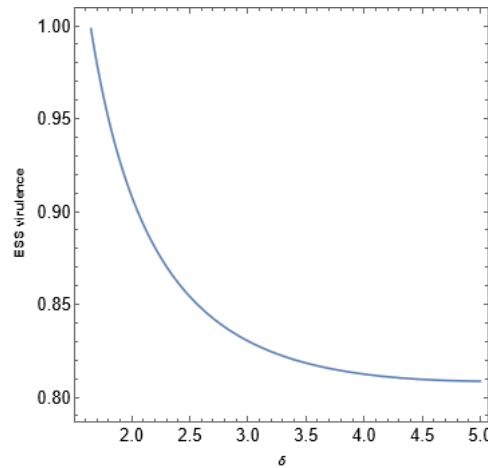


Figure 3 – CSS Parasite virulence as a function of trade-off shape between virulence and replication, with θ left as a variable and σ set to 0.5. Other parameters were fixed to $b_0 = 0.8, \mu = 0.5, \alpha = 1, r_0 = 10, r_1 = 0.04, \rho = 0.9, \gamma_0 = 1, d_0 = 0.05, \tau = 0.5, \delta = 0.8, \kappa = 1, d = 0.5$

$$(21) \quad W_p^s = \frac{\beta_m p_I^*}{\Psi_m + \beta p_I^*} + \frac{\beta_m p_S^*}{\Psi_m + \beta p_I^*}$$

323 which, in the absence of the shared control of epidemiological traits, is equivalent to eq.(A3)
 324 in [Kada & Lion] with their superinfection efficiency parameter equal to one. In such a case, the
 325 fitness gradient becomes

$$(22) \quad \left. \frac{\partial W_p^s}{\partial \theta_m} \right|_{\theta_m = \theta} = [p_S^* + p_I^*] \left[\frac{1}{\Psi + \beta p_I^*} \frac{d\beta_m}{d\theta_m} - \frac{\beta_m}{(\Psi + \beta p_I^*)^2} \frac{d\Psi_m}{d\theta_m} \right]$$

326 Regardless of the framework considered (*i.e.* superinfection or coinfection), the fitness of a
 327 mutant parasite is always determined by both its R_0 and its within-host competitive ability. This
 328 has already been found in several theoretical works Kada and Lion, 2015, Baalen, 1998, Nowak
 329 and May, 1994, Alizon et al., 2013, Alizon and Baalen, 2008 and has been shown to generally
 330 select for higher virulence. We find that the same effect occurs in our model, as competition is
 331 determined by the growth rate, which is an increasing function of virulence.

332 Existence of singular strategies.

333 Evolutionarily singular strategies are given by studying the set of θ that cause equation (19) to
 334 vanish. Figure (3) shows that we found that an evolutionarily stable investment in virulence exists
 335 *iff* the trade-off between replication and virulence is sufficiently convex. Otherwise, investment
 336 in virulence is always pushed towards its maximal value. Biologically speaking, this means that
 337 an intermediate evolutionarily stable investment is possible only when the costs of virulence are
 338 accelerating.

339 Coevolution

340 We now extend our framework to coevolutionary dynamics. We first constrain the trade-
 341 off curvatures such that an evolutionarily stable strategy exists for both species when evolving
 342 alone. The potential endpoints of host and parasite coevolutionary dynamics (co-CSS strategies)
 343 are found by studying values that cause both host and parasite gradients to vanish. ESS-stability

344 and convergence stability were assessed using criteria detailed in Best et al., 2009, Appendix
345 I.

346 The standalone evolutionary analysis of host resistance and parasite virulence (see eqs. (10),
347 (19)) revealed that the force of infection and the infectious period are important drivers of within-
348 host competition. The force of infection determines the prevalences in the host population, and
349 thus the likelihood of multiple infections. The infectious period determines the time allowed
350 to strain competition when multiple infections occurs. Shortened infectious period should thus
351 enhance the part of preemption in parasite fitness, while long infectious period should elicit
352 dominance competition. We therefore choose to focus our coevolutionary analysis on model
353 parameters that are the more susceptible to affect those epidemiological features, and compared
354 the coevolutionary outcomes under the coinfection and superinfection models.

355 Dominance competition strengthens selection towards virulent parasites and well-defended
356 hosts.

357 Figures (4, 6, 7) shows that the coevolutionary dynamics exhibits one single co-CSS.

358 Our first result is that both host resistance and parasite virulence are selected towards higher
359 levels in the superinfection model than in the coinfection model. This can easily be explained by
360 the absence of preemption effects in superinfections. As dominance competition takes a larger
361 place in parasite fitness under superinfections, higher virulence levels are selected for. Allow-
362 ing for preemptive effects by considering the local coexistence of strains (*i.e.* coinfections) leads
363 to lower levels of investment in virulence. In addition, we have also shown (see section 4) that
364 coinfections induce the emergence of a relatedness effect that is expected to counteract com-
365 petition effects, thus dampening selection towards high virulence. The host generally respond
366 to the higher parasite investment observed in superinfections by investing more in resistance, in
367 order to counteract the deleterious consequences of infection.

368 Inducible defense creates an epidemiological feedback that determines host resistance.

369 The force of infection in our model is mainly driven by the parasite dispersal rate m . When
370 parasite dispersal is close to the population viability boundaries (respectively low or high enough),
371 the force of infection is weak. While parasite levels of investment remain high across a wide
372 range of dispersal values, host investment is more variable (fig 4). As a general result, we find
373 that the host investment in resistance and the force of infection follow an inverse pattern. When
374 the parasite dispersal is low, the host then shows relatively high investment in resistance. In
375 such a case, the disease is rare in the population and hosts are infected at high loads. As the
376 damages induced by the parasite are consequent, but the costs of resistance only paid by a few
377 individuals, investment in resistance is favored. In addition, when the parasite dispersal is low,
378 the opportunities of multiple infections are scarce, and both the coinfection and superinfection
379 models tend to be close to the single-infection model and give similar results.

380 When dispersal is driven towards the upper viability boundary, the force of infection is low
381 due to the cost of dispersal. Few hosts are infected, with small within-host parasite densities.
382 The host investment in resistance is then favored as a way to control the effects of infection,
383 resulting in even higher recovery rates and lesser mortality risks.

384 When parasite dispersal is intermediate, the force of infection is maximal. In such a case,
385 the opportunities of multiple infections are common, and increase the competition for infected
386 hosts. As a large fraction of the host population is infected, the demographic costs of resistance
387 are widely incurred, which selects for lower investment. This is a consequence of our assumption

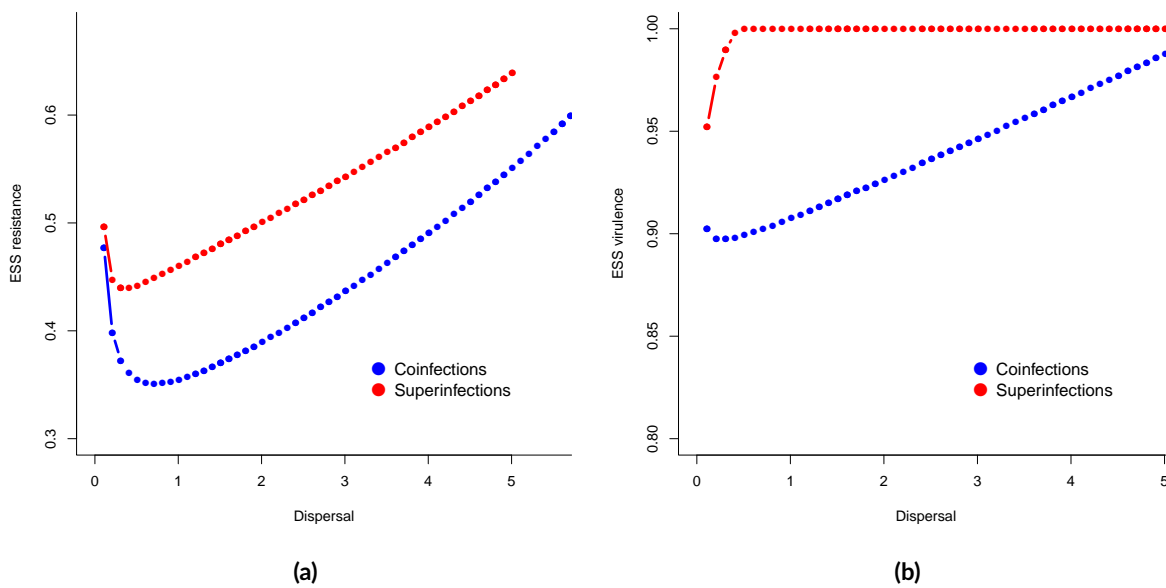


Figure 4 – Coevolutionary singular points as a function of parasite dispersal rate for a) the host resistance and b) the parasite virulence. Red dots refers to results derived from the superinfection model, while blue refers to results derived from the coinfection model. Fixed parameters were set to $\epsilon = 5$, $b_0 = 0.8$, $\mu = 0.5$, $\alpha_0 = 0.5$, $r_0 = 10$, $r_1 = 0.04$, $\rho = 0.9$, $\gamma_0 = 1$, $d_0 = 0.05$, $\tau = 1$, $\delta = 5$, $\kappa = 1$

388 made on the distribution of resistance costs. We assumed that only infected individuals pay the
389 costs of resistance, and considered that the cost acts on host fecundity. Doing so, the infection
390 prevalence creates a negative demographic feedback on host population. Selection on resistance
391 therefore generally leads the host towards less investment when the disease is widespread and
392 sufficiently lethal.

393 Our assumption on the induced nature of resistance costs also partly conditions the way host
394 and parasite investment respond to changes in the recovery rate. Figure (6) shows that increased
395 recovery select for both higher virulence and resistance, the effect being more important in the
396 superinfection case. This result is fairly common for the parasite (*i.e.* increased recovery has been
397 shown to favor exploitation, *e.g.* Baalen, 1998). Recovery induces a positive demographic feed-
398 back on the host population, because individuals returning to the susceptible state do not suffer
399 from virulence and counterparts of resistance. Increasing the baseline recovery mechanically
400 shortens the infection duration, and thus the time during which resistance costs are paid. In-
401 creased investment in host resistance is thus selected for, as it results in even shorter infectious
402 period, together with a mitigation of the effects of virulence. A previous study on the nature
403 of immune costs Cressler et al., 2015 showed that investment in inducible defenses should be
404 elicited when the associated costs are cheap, or when the probability of infection is low. Our re-
405 sults thus corroborate previous theory, showing that hosts invest in resistance when the disease
406 is globally rare.

407 Deviation from R_0 optimization emerges from a competition-colonization trade-off.

408 The host investment in resistance according to the host background mortality (fig. 7a) shows
409 a quite intuitive pattern. As the host lifespan diminishes, so does the investment in resistance.
410 An intuitive explanation is that the host fecundity is favored over resistance to infectious agents

411 in short-lived species Miller et al., 2007. However, the parasite investment seems, at first glance,
412 more counter-intuitive (fig. 7b). While virulence seems favored when the host lifespan is short in
413 the case of coinfections, superinfections show the opposite tendency. Such a result can however
414 be understood in terms of optimization principles.

415 Simple models of parasite evolution state that virulence should be selected towards values
416 that maximizes the basic reproductive ratio R_0 Lion and Metz, 2018. The addition of complex-
417 ity (*i.e.* multiple infections and host evolution) is expected to cause deviation from the R_0 opti-
418 mization principle, as it increases the dimensionality of the environmental feedback loop. We
419 have shown in section (4) that when the parasite evolves alone, virulence should evolve towards
420 higher levels in multiple infection than expected under the single infection scenario, as a result
421 of the accountance of strain competition. Host evolution does not change this expectation (fig
422 5). However, we also find that the R_0 optimization principle holds in our model when the host
423 or the parasite are driven towards their viability limit. This can be explained by the reduction of
424 the environmental feedback loop, which can be seen as a consequence of a scenario in which
425 trait evolution is driven by ecological persistence. Near to the viability boundary, the occurrence
426 of multiple infection tends to be drastically reduced because when infections are scarce, double
427 infections are scarcer. Thus the environmental feedback loop acting on the parasite should tend
428 to be only determined by the number of susceptible individuals.

429 On the contrary, when both partner exists far from their viability boundary, we have shown
430 that dominance competition has a larger contribution in parasite fitness. Competitive ability in
431 our model is acquired at the cost of an increased virulence, which decreases the within-host
432 persistence time. This particular feature induces the emergence of a competition - colonization
433 trade-off Messinger and Ostling, 2009. Not surprisingly, this trade-off is more intense in the
434 superinfection model than in the coinfection model. As superinfections assumes no preemptive
435 effects in strain competition, this enables a stricter competitive hierarchy in parasite, because
436 competitive exclusion always occurs in infected hosts.

437 Allowing for some preemption through coinfections only leads to a slight deviation from the
438 R_0 optimization. The addition of preemption implies the local coexistence of strains, because ex-
439 clusion may have not occurred at the end of infection. The weak deviation from single-infection
440 models is thus explained by two features that stem from our coinfection framework : (i) the
441 assumption of weak competitive differences, that mechanically dampen the intensity of domi-
442 nance competition and (ii) the induction of a kin selection effect which always drives selection
443 on virulence in the opposite direction to competition.

444

Discussion

445 Our work aims to bridge the gap existing between the ecology of subdivided populations,
446 and theoretical epidemiology assessing coevolution in "attack-defense" traits when multiple in-
447 fections are possible. Following an approach initiated by Restif et Koella Restif and Koella, 2003,
448 we built an epidemiological model under a shared control of transmission, virulence and recov-
449 ery, with parasite load as the main driver of control. In addition, we used a modelling framework
450 anchored in metapopulation ecology to assess parasite evolution in the context of multiple in-
451 fections, under different regimes of competition.

452 Our broader result is that parasite competition strongly affects the evolution of host resis-
453 tance, and determines the host response to the selective pressures induced by the ecological

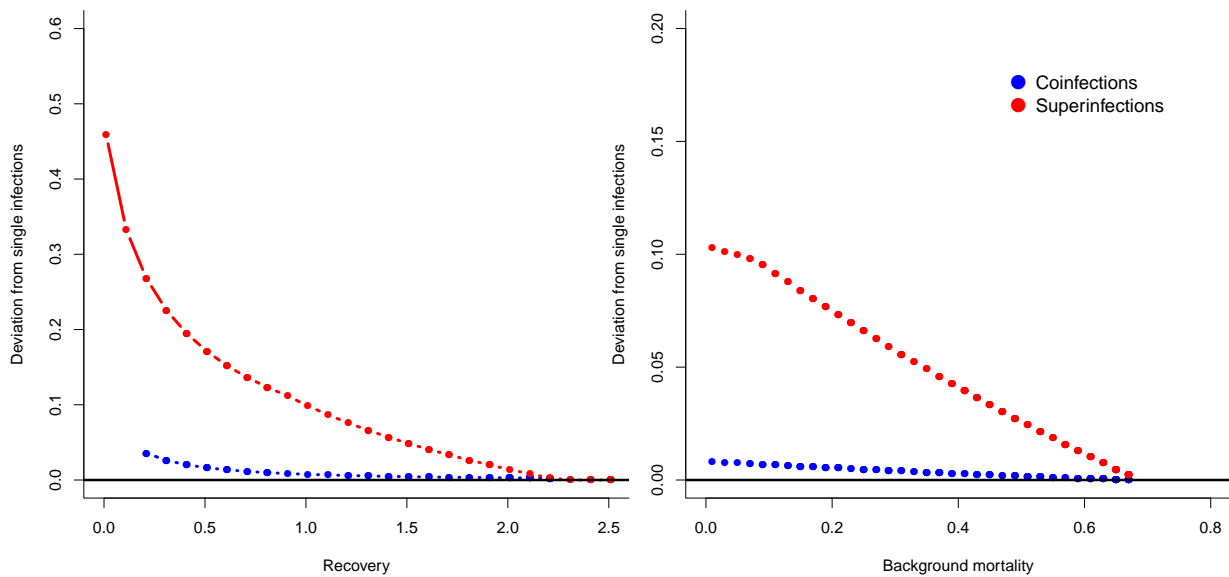


Figure 5 – Deviation between the coevolved R_0 in the coinfection model (blue curve) and superinfection model (red curve) and the R_0 obtained from maximization knowing the host co-singular strategy. Constant parameters were set to $b_0 = 1$, $\mu = 0.5$, $r_0 = 10$, $r_1 = 0.04$, $\rho = 0.9$, $d_0 = 0.05$, $\tau = 1$, $d_0 = 0.05$, $\epsilon = 5$, $\alpha = 1$, $\gamma_0 = 1$, $\delta = 5$, $\kappa = 1$. (a) Deviation is plotted according to the baseline recovery rate τ_0 . (b) Deviation is plotted according to the host background mortality d_0

454 conditions. When strain competition acts mainly through dominance, virulence evolves towards
455 the highest values, and host generally respond by an increased investment in resistance. How-
456 ever, adding preemptive effects in strain competition reduces the overall harm caused by the
457 parasite. Such results are the consequence of two major properties arising from our modelling
458 framework.

459 First, a competition-colonization (hereafter CC) trade-off emerges from the conflictual selec-
460 tive pressures between the colonization of new susceptibles and the within-host competitive-
461 ness Mideo, 2009. The first is expected to maximize the epidemiological R_0 , while the second
462 is maximized with replication, at the cost of a reduction in local persistence time Messinger and
463 Ostling, 2009. Such a trade-off is representative of spatially structured populations Tilman, 1994,
464 and emerge in our model from limited dispersal between discrete host patches.

465 Second, a kin selection effect is induced by the local coexistence of strains, and acts in an
466 opposite sense to competition. Relatedness in coinfecting parasite have been shown to lead
467 to various outcomes according to the nature of exploitation behaviour of individuals Brown et
468 al., 2002 Buckling and Brockhurst, 2008. In our model, virulence is a consequence of collective
469 exploitation of the host patch by the parasite population(s), and depends on both individual
470 traits and the total parasite load. Our work provides consistent results with the idea that when
471 exploitation is limited by the collective action of individuals, relatedness should favor prudent
472 strategies (although it may also depend on the determinism of epidemiological traits and within-
473 host interactions Alizon and Lion, 2011).

474 A corollary result is that both the CC trade-off and the kin selection effect vary depending on
475 the ecological context. In particular, we have shown that both the parasite transmission success

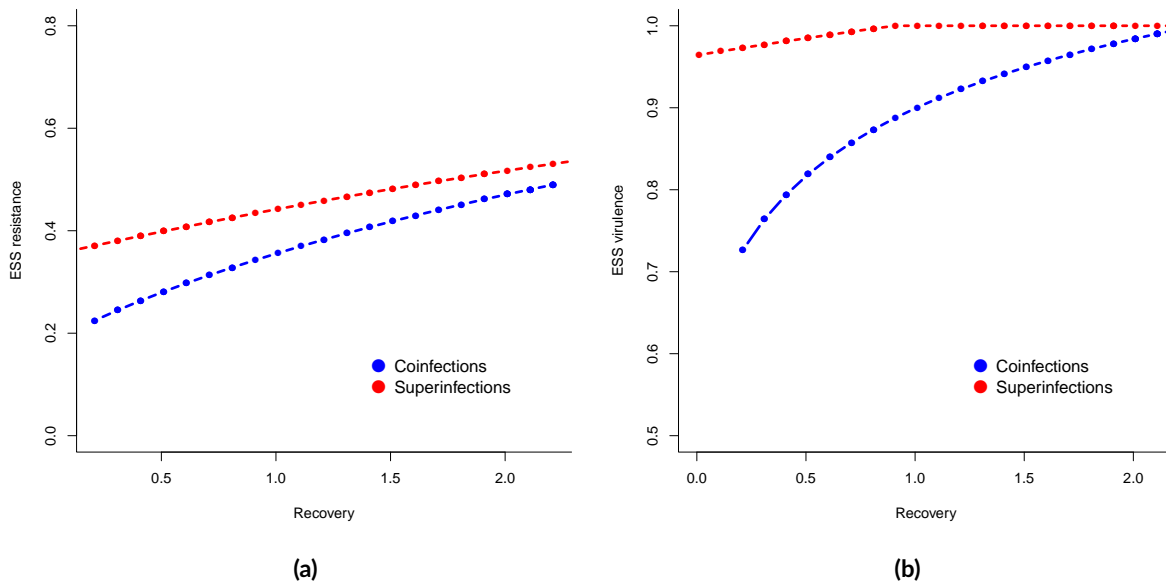


Figure 6 – Coevolutionary singular points as a function of host baseline recovery rate for a) the host resistance and b) the parasite virulence. Red lines refers to results derived from the superinfection model, while blue lines refers to results derived from the coinfection model. Fixed parameters were set to : $\epsilon = 5$, $b_0 = 0.8$, $\mu = 0.5$, $\alpha = 1$, $r_0 = 10$, $r_1 = 0.04$, $\rho = 0.9$, $\gamma_0 = 1$, $d_0 = 0.05$, $\delta = 5$, $\kappa = 1$, $d = 0.5$

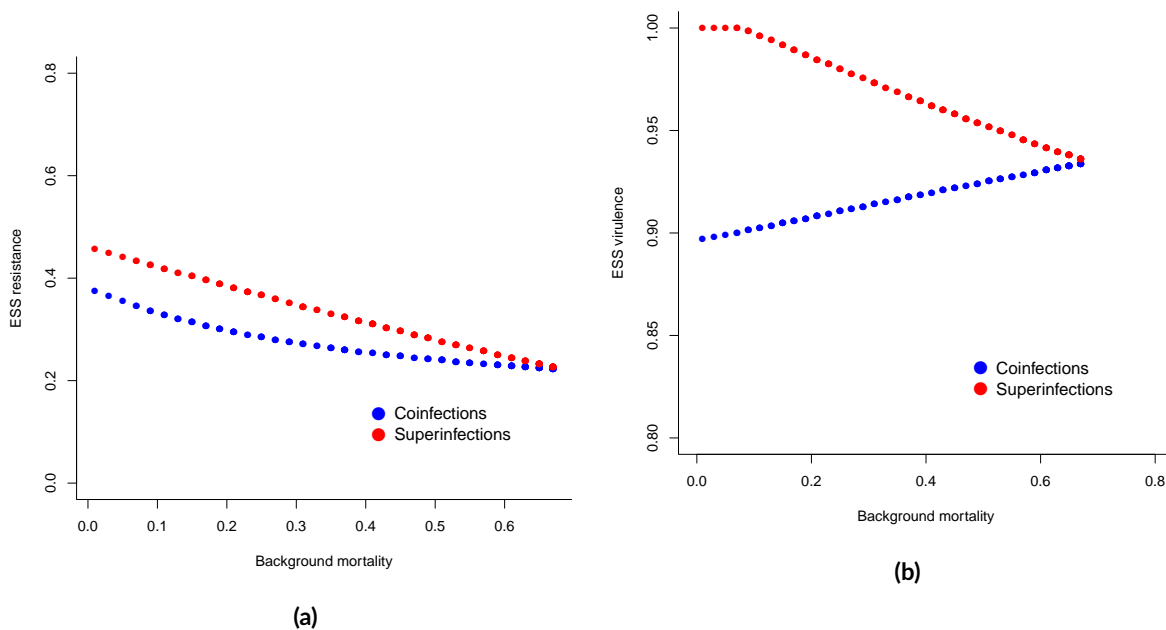


Figure 7 – Coevolutionary singular points as a function of host background mortality for a) the host resistance and b) the parasite virulence. Red lines refers to results derived from the superinfection model, while blue lines refers to results derived from the coinfection model. Fixed parameters were set to : $\epsilon = 5$, $b_0 = 0.8$, $\mu = 0.5$, $\alpha = 1$, $r_0 = 10$, $r_1 = 0.04$, $\rho = 0.9$, $\gamma_0 = 1$, $\tau_0 = 1$, $\delta = 5$, $\kappa = 1$, $d = 0.5$

476 and host demography determine the existence of the CC trade-off. Successful dispersal of par-
 477 asite propagules can be seen as the degree of coupling between host patches, and reflects the

478 contact intensity of the host population. Such coupling determines the dimensions of the eco-
479 evolutionary feedback loop acting on the parasite. When the infection is rare, the (eco-to-evo)
480 feedback drives selection towards maximized persistence because transmission occurs mostly
481 from infected to susceptible. Conversely, widespread parasites cause infected individuals to act
482 as a supplementary ecological niche. This causes deviation from the simple optimization of per-
483 sistence through the epidemiological R_0 , which is a classic result obtained from the study of
484 multiple infections Mosquera and Adler, 1998 Alizon and Baalen, 2008 .

485 We have shown that when coevolution leads to reduced levels of virulence, the host gen-
486 erally responds by a lesser investment in resistance. This can intuitively be explained by the
487 reduction of the damages induced by the parasite. While not exactly surprising, the resulting
488 qualitative patterns of investment put in perspective what is obtained from the single-infection
489 model when the epidemiological traits are under shared control. In the absence of multiple infec-
490 tions, host investment in resistance is expected to reach its maximum for intermediate parasite
491 virulence Restif and Koella, 2003. We did not retrieve this behaviour, and moreover found that
492 both host resistance and parasite virulence decreased in response to increased host mortality,
493 which also contradicts the study conducted by Restif and Koella, 2003. We argue this may result
494 from epidemiological and demographic feedbacks arising from the force of infection $\beta(\sigma, \theta)p_i^*$
495 and the infectious period $\psi(\sigma, \theta)$, which depends on the distribution of costs.

496 The force of infection in our model determines prevalences, and thus the magnitude of resis-
497 tance costs at the host population scale (because only infected individuals suffer from reduced
498 fecundity). Our model predicts that when dominance competition is increased through an in-
499 crease in the force of infection, both superinfection and coinfection hypotheses state that selec-
500 tion should favor higher virulence and lower resistance. Conversely, we also predict that when
501 preemption increases through the reduction of the infectious period, the parasite virulence is
502 selected to optimize of parasite persistence, while host resistance exhibits contrasted dynamics,
503 depending on the resulting demographic feedback.

504 When a reduced infectious period has a positive demographic feedback on the host popula-
505 tion (e.g. by an increase in recovery, which increase the density of susceptible individuals), only
506 the parasite is pushed towards its viability limit. We predict that selection should favor high vir-
507 ulence and resistance. This results from both the shared control of epidemic features, and our
508 assumption on the induced nature of resistance. High resistance allows the host to dampen the
509 deleterious effects of the parasite by reducing both transmission and mortality risks, which is a
510 consequence of the shared control. At the same time, increased resistance enhances the increase
511 of recovery, which has twofold benefits, because a recovered host suffers neither from parasite
512 effects, nor from the costs the resistance. The cost of resistance is thus sufficiently cheap to
513 favor investment Cressler et al., 2015.

514 When the demographic feedback of a reduced infectious period is negative (i.e. by an increase
515 in host mortality), both the host and the parasite are driven towards their viability limit. Selection
516 here leads the traits evolution towards persistence. In the coinfection case, this corresponds to
517 an increase in parasite replication and low (but non-zero) resistance, while in the superinfection
518 case, it leads the parasite to reduce its virulence, because most of the competitive advantage is
519 lost with the opportunities of superinfections. Both behaviors, however, correspond to conver-
520 gence towards the R_0 optimization principle. High virulence is always counter-selected in these
521 cases, because it induces a direct negative demographic feedback on parasite fitness.

522 We can hypothesize that the host metapopulation structure also leads to an indirect demo-
523 graphic feedback that can enable selection towards increased resistance and reduced virulence.
524 We considered the host population as a set of patches, some of which are unavailable for the
525 parasite. While neither parasite nor host fitness are sensitive to this assumption in evolution
526 alone (see eqs. 10, 17), this is not the case when coevolving. By increasing its resistance rate,
527 the host induces a demographic pressure due to the costs on its own birth rate. This decreases
528 the amount of patches available for parasite dispersal. Parasites thus experiment virtually en-
529 hanced costs of transmission, because ending in a dead-end with higher probability would have
530 an indirect beneficial effect on host fitness. Such a feedback induced by the spatial structure is
531 known to favor lower exploitation levels under a wide range of conditions Boots and Haraguchi,
532 1999, Lion and Boots, 2010, Messinger and Ostling, 2009. This effect may explain why hosts
533 does not always give up on resisting, and corroborates empirical studies suggesting that a di-
534 minished reproductive effort following infection can result from host adaptive strategy Hurd,
535 2001.

536 We would like to draw attention on some interesting features of our framework. The fitness
537 equation we derived for the parasite evolution (eq. 17) enables a straightforward link between
538 several theoretical approaches. By considering a well-mixed host population as a set of discrete
539 patches coupled through parasite dispersal, we showed that the measure of the lifetime popula-
540 tion success R_m Metz and Gyllenberg, 2001 is equivalent to the reproductive numbers tradition-
541 ally used in theoretical epidemiology in the absence of multiple infections Lion and Metz, 2018
542 Almcera et al., 2018. Our nested approach also emphasises the now recognized links between
543 fitness in subdivided populations and inclusive fitness theory Ajar, 2003, as well as the vision of
544 the altruistic nature of virulence-related traits Griffin et al., 2004. Moreover, it provides a nat-
545 ural framework for multiscale modelling and accounting for a variety of local interactions. The
546 links between the different interaction scales, as well as the evolving individual traits, are de-
547 fined through quantities that are commonly measured in life sciences (e.g. parasite load, division
548 rate or clearance rate following phagocytosis by macrophages). We believe our methodological
549 framework could thus help empiricists and theoreticians to design system-specific models and
550 experiments to refine our mechanistic understanding of host-parasite interactions.

551 Another strength of our model is that the emergence of multi-scale selection as well as de-
552 mographic feedback are blind to the assumptions made on the cost profile between host and
553 parasite traits (i.e. it does not depend on particular trade-off shapes). However, some of our
554 results are expected to be sensitive to several assumptions of our framework.

555 It is now well-recognized that the choice of the 'take-over' function in multiple infection
556 models can have significant effects on the qualitative outcome of the coevolutionary dynamics,
557 especially relative to the emergence of stable polymorphism Boldin and Diekmann, 2008 Mos-
558 quera and Adler, 1998. Our work assumes that any secondary invasion of a host is by definition
559 successful, in the sense where even an invading uncompetitive mutant will be able to produce
560 propagules for a certain time. Such a deterministic behaviour is quite unlikely to occur in natural
561 systems. A natural expansion of our model would account for the early stochastic dynamics of
562 invasion (e.g. by defining the probability of multiple infections as a function of competitive traits
563 (see Kada and Lion, 2015, Boldin and Diekmann, 2008 for examples).

564 Another caveat of our model relies on the assumptions made on the interaction between
565 host defense and parasite growth. We choose a simple model of parasite growth that account

566 for parasite clearance and derive several mechanisms of avoidance and infection clearance at
567 the host population scale. No possibility of tolerance mechanisms are accounted for. This may
568 have important implications for host and parasite coevolution Carval and Ferriere, 2010, Best
569 et al., 2010 especially in the case of multiple infections. Tolerance is defined in theoretical works
570 as having a positive effect on parasite fitness Carval and Ferriere, 2010, and has been shown
571 to be traded-off with resistance in several systems Salgado-Luarte et al., 2023 Råberg et al.,
572 2007. Recent studies have shown this particular trade-off may strongly affect modes of selection
573 (directional or fluctuating) and alter the possibility of stable coevolutionary coexistence Singh,
574 2023. We expect such considerations to greatly affect our results.

575 The within-host dynamics chosen in our study does not capture the whole diversity of par-
576 asite interactions occurring in natural systems, such as production of public goods, or spiteful
577 behaviours Leinweber et al., 2018, Niehus et al., 2017, Bucci et al., 2011, Bashey et al., 2012.
578 Strain competition in our model acts through (i) exploitation competition for the exact same
579 host resources and (ii) apparent competition against the host's immune system, that can be
580 seen as acting like a generalist predator. However, parasite evolution in our work only account
581 for differences in the intensity of exploitation competition with no possibility to avoid apparent
582 competition. In natural systems, this is achieved through adaptation towards shifts in antigenic
583 determinants that allows new mutant to escape from host immune response Fryer et al., 2010.
584 In spite of these obvious imperfections, we think that the framework used along this paper is
585 readily adaptable to various within-host dynamics.

586 Most models, ours in first line, use the assumption of equilibrium quantities to derive the main
587 results. The coinfection framework slightly relaxes this assumption by using a quasi-equilibrium
588 to describe variation in parasite density during competition. However, many features of real sys-
589 tems remains hidden by such assumptions. Events of co-transmission, or time heterogeneity in
590 the sequence of invasions by multiple parasites for exemple, would certainly lead to different
591 outcome in competition, subsequently reflecting in the coevolutionary dynamics and associated
592 feedbacks. Empirical evidence for such alterations have been reviewed in Dutt et al., 2022, and
593 can also be suggested by contradictory results obtained by clinical studies Sullivan et al., 2015,
594 Fry et al., 2019. One of the crucial challenges for future theoretical studies assessing how para-
595 site competition would alter coevolutionary dynamics will rely on our ability to adress how the
596 'age at secondary invasion' affects the outcome of parasite competition.

597 Fundings

598 This study is part of the FEEDME project coordinated by O. Kaltz, and has been funded by a
599 grant from the Agence Nationale de la Recherche (NO : ANR-20-CE02-0023) to F. Massol and
600 S. Lion.

601 Conflict of interest disclosure

602 The authors declare that they comply with the PCI rule of having no financial conflicts of
603 interest in relation to the content of the article.

604 Data, script, code, and supplementary information availability

605 Datas, script, codes and supplementary information are available online ([https://doi.org/](https://doi.org/10.5281/zenodo.12755175)
606 [10.5281/zenodo.12755175](https://doi.org/10.5281/zenodo.12755175)).

References

607

- 608 Acevedo MA, Dilleuth FP, Flick AJ, Faldyn MJ, Elder BD (2019). *Virulence-driven trade-offs in*
609 *disease transmission: A meta-analysis. Evolution* **73**, 636–647. [https://doi.org/10.1111/](https://doi.org/10.1111/evo.13692)
610 [evo.13692](https://doi.org/10.1111/evo.13692).
- 611 Ajar É (2003). *Analysis of disruptive selection in subdivided populations. BMC Evolutionary Biology*
612 **3**, 1–12. <https://doi.org/10.1186/1471-2148-3-22>.
- 613 Alizon S, Baalen M (2005). *Emergence of a convex trade-off between transmission and virulence. The*
614 *American Naturalist* **165**, E155–E167. <https://doi.org/10.1086/430053>.
- 615 Alizon S, Baalen M (2008). *Multiple infections, immune dynamics, and the evolution of virulence. The*
616 *American Naturalist* **172**, E150–E168. <https://doi.org/10.1086/590958>.
- 617 Alizon S, De Roode JC, Michalakis Y (2013). *Multiple infections and the evolution of virulence. Ecol-*
618 *ogy letters* **16**, 556–567. <https://doi.org/10.1111/ele.12076>.
- 619 Alizon S, Hurford A, Mideo N, Van Baalen M (2009). *Virulence evolution and the trade-off hypoth-*
620 *esis: history, current state of affairs and the future. Journal of evolutionary biology* **22**, 245–259.
621 <https://doi.org/10.1111/j.1420-9101.2008.01658.x>.
- 622 Alizon S, Lion S (2011). *Within-host parasite cooperation and the evolution of virulence. Proceedings*
623 *of the Royal Society B: Biological Sciences* **278**, 3738–3747. [https://doi.org/10.1098/rspb.](https://doi.org/10.1098/rspb.2011.0471)
624 [2011.0471](https://doi.org/10.1098/rspb.2011.0471).
- 625 Almocera AES, Nguyen VK, Hernandez-Vargas EA (2018). *Multiscale model within-host and between-*
626 *host for viral infectious diseases. Journal of Mathematical Biology* **77**, 1035–1057. [https://doi.](https://doi.org/10.1007/s00285-018-1241-y)
627 [org/10.1007/s00285-018-1241-y](https://doi.org/10.1007/s00285-018-1241-y).
- 628 Baalen MV (1998). *Coevolution of recovery ability and virulence. Proceedings of the Royal Society of*
629 *London. Series B: Biological Sciences* **265**, 317–325. [https://doi.org/10.1098/rspb.1998.](https://doi.org/10.1098/rspb.1998.0298)
630 [0298](https://doi.org/10.1098/rspb.1998.0298).
- 631 Baalen M, Sabelis MW (1995). *The dynamics of multiple infection and the evolution of virulence.*
632 *The American Naturalist* **146**, 881–910. <https://doi.org/10.1086/590958>.
- 633 Bashey F, Young S, Hawlena H, Lively C (2012). *Spiteful interactions between sympatric natural*
634 *isolates of Xenorhabdus bovienii benefit kin and reduce virulence. Journal of evolutionary biology*
635 **25**, 431–437. <https://doi.org/10.1111/j.1420-9101.2011.02441.x>.
- 636 Best A, White A, Boots M (2009). *The implications of coevolutionary dynamics to host-parasite*
637 *interactions. The American Naturalist* **173**, 779–791. <https://doi.org/10.1086/598494>.
- 638 Best A, White A, Boots M (2010). *Resistance is futile but tolerance can explain why parasites do*
639 *not always castrate their hosts. Evolution* **64**, 348–357. [https://doi.org/10.1111/j.1558-](https://doi.org/10.1111/j.1558-5646.2009.00819.x)
640 [5646.2009.00819.x](https://doi.org/10.1111/j.1558-5646.2009.00819.x).
- 641 Boldin B, Diekmann O (2008). *Superinfections can induce evolutionarily stable coexistence of pathogens.*
642 *Journal of mathematical biology* **56**, 635–672. [https://doi.org/10.1007/s00285-007-](https://doi.org/10.1007/s00285-007-0135-1)
643 [0135-1](https://doi.org/10.1007/s00285-007-0135-1).
- 644 Boots M, Haraguchi Y (1999). *The evolution of costly resistance in host-parasite systems. The amer-*
645 *ican naturalist* **153**, 359–370. <https://doi.org/10.1086/303181>.
- 646 Brown SP, Hochberg ME, Grenfell BT (2002). *Does multiple infection select for raised virulence?*
647 *Trends in microbiology* **10**, 401–405. [https://doi.org/10.1016/s0966-842x\(02\)02413-7](https://doi.org/10.1016/s0966-842x(02)02413-7).
- 648 Bucci V, Nadell CD, Xavier JB (2011). *The evolution of bacteriocin production in bacterial biofilms.*
649 *The American Naturalist* **178**, E162–E173. <https://doi.org/10.1086/662668>.

- 650 Buckling A, Brockhurst M (2008). *Kin selection and the evolution of virulence*. *Heredity* **100**, 484–
651 488. <https://doi.org/10.1038/sj.hdy.6801093>.
- 652 Calcagno V, Mouquet N, Jarne P, David P (2006). *Coexistence in a metacommunity: the competition–*
653 *colonization trade-off is not dead*. *Ecology letters* **9**, 897–907. <https://doi.org/10.1111/j.1461-0248.2006.00930.x>.
- 654
655 Carval D, Ferriere R (2010). *A unified model for the coevolution of resistance, tolerance, and virulence*.
656 *Evolution* **64**, 2988–3009. <https://doi.org/10.1111/j.1558-5646.2010.01035.x>.
- 657 Cressler CE, Graham AL, Day T (2015). *Evolution of hosts paying manifold costs of defence*. *Pro-*
658 *ceedings of the Royal Society B: Biological Sciences* **282**, 20150065. <https://doi.org/10.1098/rspb.2015.0065>.
- 659
660 Cressler CE, McLeod DV, Rozins C, Van Den Hoogen J, Day T (2016). *The adaptive evolution*
661 *of virulence: a review of theoretical predictions and empirical tests*. *Parasitology* **143**, 915–930.
662 <https://doi.org/10.1017/S003118201500092X>.
- 663 De Roode JC, Helinski ME, Anwar MA, Read AF (2005). *Dynamics of multiple infection and within-*
664 *host competition in genetically diverse malaria infections*. *The American Naturalist* **166**, 531–542.
665 <https://doi.org/10.1086/491659>.
- 666 Diekmann O, Heesterbeek JAP, Metz JA (1990). *On the definition and the computation of the basic*
667 *reproduction ratio R_0 in models for infectious diseases in heterogeneous populations*. *Journal of*
668 *mathematical biology* **28**, 365–382. <https://doi.org/10.1007/BF00178324>.
- 669 Dutt A, Andrivon D, Le May C (2022). *Multi-infections, competitive interactions, and pathogen co-*
670 *existence*. *Plant Pathology* **71**, 5–22. <https://doi.org/10.1111/ppa.13469>.
- 671 Frickel J, Sieber M, Becks L (2016). *Eco-evolutionary dynamics in a coevolving host–virus system*.
672 *Ecology letters* **19**, 450–459. <https://doi.org/10.1111/ele.12580>.
- 673 Fry SHL, Barnabas SL, Cotton MF (2019). *Tuberculosis and HIV—An Update on the “cursed duet” in*
674 *children*. *Frontiers in pediatrics* **7**, 159. <https://doi.org/10.3389/fped.2019.00159>.
- 675 Fryer HR, Frater J, Duda A, Roberts MG, Investigators ST, Phillips RE, McLean AR (2010). *Mod-*
676 *elling the evolution and spread of HIV immune escape mutants*. *PLoS pathogens* **6**, e1001196.
677 <https://doi.org/10.1371/journal.ppat.1001196>.
- 678 Geritz SA, Kisdi E, Mesze
679 NA G, Metz JA (1998). *Evolutionarily singular strategies and the adaptive growth and branch-*
680 *ing of the evolutionary tree*. *Evolutionary ecology* **12**, 35–57. <https://doi.org/10.1023/A:1006554906681>.
- 681
682 Griffin AS, West SA, Buckling A (2004). *Cooperation and competition in pathogenic bacteria*. *Nature*
683 **430**, 1024–1027. <https://doi.org/10.1038/nature02744>.
- 684 Hastings A (1980). *Disturbance, coexistence, history, and competition for space*. *Theoretical popula-*
685 *tion biology* **18**, 363–373. [https://doi.org/10.1016/0040-5809\(80\)90059-3](https://doi.org/10.1016/0040-5809(80)90059-3).
- 686 Hurd H (2001). *Host fecundity reduction: a strategy for damage limitation?* *Trends in parasitology*
687 **17**, 363–368. [https://doi.org/10.1016/s1471-4922\(01\)01927-4](https://doi.org/10.1016/s1471-4922(01)01927-4).
- 688 Hurford A, Cownden D, Day T (2010). *Next-generation tools for evolutionary invasion analyses*.
689 *Journal of the Royal Society Interface* **7**, 561–571. <https://doi.org/10.1098/rsif.2009.0448>.
- 690
691 Jansen VA, Vitalis R (2007). *THE EVOLUTION OF DISPERSAL IN A LEVINS’TYPE METAPOPULA-*
692 *TION MODEL*. *Evolution* **61**, 2386–2397. <https://doi.org/10.1111/j.1558-5646.2007.00201.x>.
- 693

- 694 Kada S, Lion S (2015). *Superinfection and the coevolution of parasite virulence and host recovery*.
695 *Journal of evolutionary Biology* **28**, 2285–2299. <https://doi.org/10.1111/jeb.12753>.
- 696 Kermack WO, McKendrick AG (1927). *A contribution to the mathematical theory of epidemics*.
697 *Proceedings of the royal society of london. Series A, Containing papers of a mathematical and*
698 *physical character* **115**, 700–721. <https://doi.org/10.1098/rspa.1927.0118>.
- 699 Lefèvre T, Sanchez M, Ponton F, Hughes D, Thomas F (2007). *Virulence and resistance in malaria:*
700 *who drives the outcome of the infection?* *Trends in parasitology* **23**, 299–302. <https://doi.org/10.1016/j.pt.2007.04.012>.
- 701
- 702 Leinweber A, Weigert M, Kümmerli R (2018). *The bacterium Pseudomonas aeruginosa senses and*
703 *gradually responds to interspecific competition for iron*. *Evolution* **72**, 1515–1528. <https://doi.org/10.1111/evo.13491>.
- 704
- 705 Levins R (1969). *Some demographic and genetic consequences of environmental heterogeneity for*
706 *biological control*. *Bulletin of the ESA* **15**, 237–240. [https://doi.org/10.1093/besa/15.3.](https://doi.org/10.1093/besa/15.3.237)
707 [237](https://doi.org/10.1093/besa/15.3.237).
- 708 Levins R, Culver D (1971). *Regional coexistence of species and competition between rare species*.
709 *Proceedings of the National Academy of Sciences* **68**, 1246–1248. [https://doi.org/10.](https://doi.org/10.1073/pnas.68.6.1246)
710 [1073/pnas.68.6.1246](https://doi.org/10.1073/pnas.68.6.1246).
- 711 Lion S, Boots M (2010). *Are parasites “prudent” in space?* *Ecology letters* **13**, 1245–1255. <https://doi.org/10.1111/j.1461-0248.2010.01516.x>.
- 712
- 713 Lion S, Metz JA (2018). *Beyond R0 maximisation: on pathogen evolution and environmental dimen-*
714 *sions*. *Trends in ecology & evolution* **33**, 458–473. [https://doi.org/10.1016/j.tree.2018.](https://doi.org/10.1016/j.tree.2018.02.004)
715 [02.004](https://doi.org/10.1016/j.tree.2018.02.004).
- 716 Massol F, Calcagno V, Massol J (2009). *The metapopulation fitness criterion: proof and perspectives*.
717 *Theoretical population biology* **75**, 183–200. [https://doi.org/10.1016/j.tpb.2009.02.](https://doi.org/10.1016/j.tpb.2009.02.005)
718 [005](https://doi.org/10.1016/j.tpb.2009.02.005).
- 719 May RM, Anderson RM (1979). *Population biology of infectious diseases: Part II*. *Nature* **280**, 455–
720 [461](https://doi.org/10.1038/280455a0). <https://doi.org/10.1038/280455a0>.
- 721 May RM, Nowak MA (1995). *Coinfection and the evolution of parasite virulence*. *Proceedings of the*
722 *Royal Society of London. Series B: Biological Sciences* **261**, 209–215. [https://doi.org/10.](https://doi.org/10.1098/rspb.1995.0138)
723 [1098/rspb.1995.0138](https://doi.org/10.1098/rspb.1995.0138).
- 724 Messinger SM, Ostling A (2009). *The consequences of spatial structure for the evolution of pathogen*
725 *transmission rate and virulence*. *The American Naturalist* **174**, 441–454. [https://doi.org/10.](https://doi.org/10.1086/605375)
726 [1086/605375](https://doi.org/10.1086/605375).
- 727 Metz J, Gyllenberg M (2001). *How should we define fitness in structured metapopulation models?*
728 *Including an application to the calculation of evolutionarily stable dispersal strategies*. *Proceedings*
729 *of the Royal Society of London. Series B: Biological Sciences* **268**, 499–508. [https://doi.org/10.](https://doi.org/10.1098/rspb.2000.1373)
730 [1098/rspb.2000.1373](https://doi.org/10.1098/rspb.2000.1373).
- 731 Mideo N (2009). *Parasite adaptations to within-host competition*. *Trends in parasitology* **25**, 261–
732 [268](https://doi.org/10.1016/j.pt.2009.03.001). <https://doi.org/10.1016/j.pt.2009.03.001>.
- 733 Mideo N, Alizon S, Day T (2008). *Linking within-and between-host dynamics in the evolutionary*
734 *epidemiology of infectious diseases*. *Trends in ecology & evolution* **23**, 511–517. [https://doi.org/10.](https://doi.org/10.1016/j.tree.2008.05.009)
735 [1016/j.tree.2008.05.009](https://doi.org/10.1016/j.tree.2008.05.009).
- 736 Miller MR, White A, Boots M (2007). *Host life span and the evolution of resistance characteristics*.
737 *Evolution* **61**, 2–14. <https://doi.org/10.1111/j.1558-5646.2007.00001.x>.

- 738 Mosquera J, Adler FR (1998). *Evolution of virulence: a unified framework for coinfection and super-*
739 *infection. Journal of Theoretical Biology* **195**, 293–313. [https://doi.org/10.1006/jtbi.](https://doi.org/10.1006/jtbi.1998.0793)
740 [1998.0793](https://doi.org/10.1006/jtbi.1998.0793).
- 741 Niehus R, Picot A, Oliveira NM, Mitri S, Foster KR (2017). *The evolution of siderophore production*
742 *as a competitive trait. Evolution* **71**, 1443–1455. <https://doi.org/10.1111/evo.13230>.
- 743 Nowak MA, May RM (1994). *Superinfection and the evolution of parasite virulence. Proceedings of*
744 *the Royal Society of London. Series B: Biological Sciences* **255**, 81–89. [https://doi.org/10.](https://doi.org/10.1098/rspb.1994.0012)
745 [1098/rspb.1994.0012](https://doi.org/10.1098/rspb.1994.0012).
- 746 Otto SP, Day T (2007). *A biologist's guide to mathematical modeling in ecology and evolution*. Prince-
747 *ton University Press*.
- 748 Pillai P, Gonzalez A, Loreau M (2012). *Evolution of dispersal in a predator-prey metacommunity. The*
749 *American Naturalist* **179**, 204–216. <https://doi.org/10.1086/663674>.
- 750 Råberg L, Sim D, Read AF (2007). *Disentangling genetic variation for resistance and tolerance to*
751 *infectious diseases in animals. Science* **318**, 812–814. [https://doi.org/10.1126/science.](https://doi.org/10.1126/science.1148526)
752 [1148526](https://doi.org/10.1126/science.1148526).
- 753 Restif O, Koella JC (2003). *Shared control of epidemiological traits in a coevolutionary model of host-*
754 *parasite interactions. The American Naturalist* **161**, 827–836. [https://doi.org/10.1086/](https://doi.org/10.1086/375171)
755 [375171](https://doi.org/10.1086/375171).
- 756 Salgado-Luarte C, González-Teuber M, Madriaza K, Gianoli E (2023). *Trade-off between plant re-*
757 *sistance and tolerance to herbivory: Mechanical defenses outweigh chemical defenses.* [https :](https://doi.org/10.1002/ecy.3860)
758 [//doi.org/10.1002/ecy.3860](https://doi.org/10.1002/ecy.3860).
- 759 Singh P (2023). *Trade-offs between host defense mechanisms: impacts on evolutionary and coevolu-*
760 *tionary dynamics of host-parasite interactions*. PhD thesis. University of Sheffield.
- 761 Sullivan ZA, Wong EB, Ndung'u T, Kasprowicz VO, Bishai WR (2015). *Latent and active tuber-*
762 *culosis infection increase immune activation in individuals co-infected with HIV. EBioMedicine* **2**,
763 **334–340**. <https://doi.org/10.1016/j.ebiom.2015.03.005>.
- 764 Susi H, Vale PF, Laine AL (2015). *Host genotype and coinfection modify the relationship of within*
765 *and between host transmission. The American Naturalist* **186**, 252–263. [https://doi.org/10.](https://doi.org/10.1086/682069)
766 [1086/682069](https://doi.org/10.1086/682069).
- 767 Tilman D (1994). *Competition and biodiversity in spatially structured habitats. Ecology* **75**, 2–16.
768 <https://doi.org/10.2307/1939377>.
- 769 Webster J, Gower C, Blair L (2004). *Do hosts and parasites coevolve? Empirical support from the*
770 *Schistosoma system. the american naturalist* **164**, S33–S51. [https://doi.org/10.1086/](https://doi.org/10.1086/424607)
771 [424607](https://doi.org/10.1086/424607).