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The paradox of tolerance: parasite extinction due to the evolution of host defence

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Abstract

Host defence against parasite infection can rely on two broad strategies: resistance and tolerance. The spread of resistance traits usually lowers parasite prevalence and decreases selection for higher defence. Conversely, tolerance mechanisms increase parasite prevalence and foster selection for more tolerance. Here we examine the potential for the host to drive parasites to extinction through the evolution of one or other defence mechanism. We analysed theoretical models of resistance and tolerance evolution in both the absence and the presence of a trade-off between defence and reproduction. In the absence of costs, resistance evolves towards maximisation and, consequently, parasite extinction. Tolerance also evolves towards maximisation but the positive feedback between tolerance and disease prevents the disappearance of the parasite. On the contrary, when defence comes with costs it is impossible for the host to eliminate the infection through resistance, because costly resistance is selected against when parasites are at low prevalence. We uncover that the only path to disease clearance in the presence of costs is through tolerance. Paradoxically, however, it is by lowering tolerance -and hence increasing disease-induced mortality- that extinction can occur. We also show that such extinction can occur even in the case of parasite counter-adaptation. Our results emphasise the importance of tolerance as a defence strategy, and identify key questions for future research.

Keywords: adaptive dynamics, tolerance evolution.

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1. Introduction

While facing a parasite infection, hosts can defend them-selves by reducing parasite fitness through mechanisms that lower transmission or clear the parasite, namely *resistance* strategies (Bowers et al., 1994; Malo and Skamene, 1994; Boots and Haraguchi, 1999; Boots et al., 2009; Hoyle et al., 2012). However, a second category of strategies has recently gained the attention of both experimental and theoretical studies. Hosts can develop *tolerance* to the detrimental effects of infection without any negative impact on parasite fitness (Boots and Bowers, 1999; Roy and Kirchner, 2000; Miller et al., 2007; Best et al., 2008; Boots, 2008; Best et al., 2009, 2014). Particularly, we consider tolerance strategies that reduce parasite-induced mortality under infection. This kind of defence was observed firstly in plant studies (Caldwell et al., 1958; Clarke, 1986; Simms and Triplett, 1994), where tolerance has been defined as the reaction norm between plant fitness and an environmental gradient (Simms, 2000). Råberg et al. (2007) adapted this definition to show genetic variation of tolerance in mice, opening the way for several empirical studies focused on animal systems (Råberg et al., 2009; Little et al., 2010; Medzhitov et al., 2012; Råberg, 2014; Kutzer and Armitage, 2016; Adelman and Hawley, 2017). Among them, recent empirical works have addressed the question on how tolerance might play a role in ameliorating the effects of immunopathology (Sears et al., 2011; Soares et al., 2017) or other severe diseases like HIV (Chahroudi et al., 2012; Regoes et al., 2014).

The importance of a distinction between tolerance and resistance traits is most clearly understood in the context of their evolution and its impact on the ecological feedback in host-parasite systems (Boots and Bowers, 1999; Roy and Kirchner, 2000; Miller et al., 2005, 2007; Best et al., 2008; Boots et al., 2009; Best et al., 2009, 2014). Both mechanisms positively affect host fitness but resistance lowers parasite fitness while tolerance is either neutral or increases it. Therefore, there exists a negative feedback between selection for resistance and parasite prevalence, which allows evolutionary branching to coexistence (Antonovics and Thrall, 1994). On the contrary, tolerance evolves towards fixation (Boots and Bowers, 1999; Miller et al., 2007) under general hypotheses (Best et al., 2008) because the spread of a tolerant trait in a population increases disease prevalence and thereby generates an environment not suitable for less tolerant strains. Generally, these studies focused on how quantitative

31 investment in costly defence varies across ecological and epidemiological gradients, and on
32 the potential for evolutionary branching. Here, we consider a different question: can the
33 host drive parasites to extinction through evolving defence?

34 Host-driven parasite extinction is not just a theoretical possibility, but has been observed
35 in experimental studies of host-parasite co-evolution. Co-evolution of host resistance and
36 parasite virulence can result in antagonistic dynamics (Woolhouse et al., 2002). Moreover,
37 environmental factors like temperature gradient (Zhang and Buckling, 2011), host popula-
38 tion bottleneck (Hesse and Buckling, 2016), alterations of resources availability (Zhang and
39 Buckling, 2016; Wright et al., 2016; Gómez et al., 2015) or population mixing (Wright et al.,
40 2016) have been shown to slow down parasite counter-adaptation to the extreme point where
41 they can not keep pace with host defence evolution and extinction results. In these cases,
42 the extinction therefore occurs due to external perturbations of the system. However, we
43 do not have a general understanding of whether parasite extinction is possible due to host
44 evolution in the absence of such environmental factors.

45 A key assumption in almost all theoretical evolution studies is that defence is costly
46 in terms of fitness in the absence of infection, given both theoretical arguments (Stearns,
47 1992; Hoyle et al., 2008) and experimental support (Boots and Begon, 1993; Kraaijeveld and
48 Godfray, 1997; Meador and Boots, 2006). The underlying idea is that mounting a defence
49 response is demanding and it limits the development of other life history traits. An important
50 example is the well-documented trade-off between resistance and growth rate in a moth-
51 virus system (Boots and Begon, 1993; Bartlett et al., 2018). If there were no costs to evolving
52 defence, we would expect resistant or tolerant strains to have always higher fitness than
53 other strategies and defence to reach maximization. In this case, we might expect parasite
54 extinction to be a common outcome. The presence of costs, however, is likely to offset the
55 benefit of evolving to high levels of defence. In this scenario, resistant and tolerant strains
56 have lower fitness than non-defensive ones in the absence of the parasite. Under infection,
57 selection promotes higher defence when the benefits against infection overcome the costs of
58 reduced reproduction. Costs are also necessary to the generation of diversity when either
59 avoidance (Antonovics and Thrall, 1994; Boots and Haraguchi, 1999) or increased recovery
60 (Boots and Bowers, 1999) evolves. In fact, resistance traits are predicted to evolve toward

Parameter	Definition	Default value
a	Host birth rate	2
b	Host mortality rate	0.1
q	Impact of crowding on host birth rate	0.2
β	Infection transmission coefficient	0.3
r	Host avoidance	0
γ	Recovery rate	0.3
α	Disease-induced mortality rate, virulence	varies
τ	Host tolerance	0

Table 1: Summary of model parameters

61 polymorphism rather than fixation (Roy and Kirchner, 2000) as at low parasite prevalence
62 the costs outweigh the benefits. The question remains, therefore, as to whether the presence
63 of costs can prevent host defence evolving to the point where extinction would occur.

64 Using a classic Susceptible-Infected-Susceptible model framework, we analyse the evo-
65 lution of both resistance and tolerance with and without costs. To model the long-term
66 evolutionary dynamics, we adopted an evolutionary invasion analysis (adaptive dynamics)
67 framework (Dieckmann and Law, 1996; Marrow et al., 1996; Geritz et al., 1998). In this
68 context, evolution is modelled as a sequence of steps of trait invasion and substitution under
69 the assumptions of finitely small and rare mutational events and clonal reproduction. These
70 assumptions and the absence of permanent recovery from infection make our model more
71 suitable for microbial systems, e.g. bacteria-phage systems. Our main focus is host defence
72 evolution, therefore, we assume that the impact on host mortality while infected caused
73 by the parasite (virulence) does not change during the evolutionary process. Thus, we do
74 not address theoretically the case of host-parasite co-evolution. Nevertheless, we relax this
75 assumption in the numerical simulations, to address whether parasite extinction can occur
76 despite parasite co-evolution of virulence. We assume also that the parasite sterilises infected
77 individuals to facilitate mathematical tractability. However, we show in Appendix B that
78 the occurrence of parasite extinction due to tolerance evolution does not depend upon the
79 assumption of sterility under infection.

80 **2. Model**

81 We use a classic host-parasite model (Anderson and May, 1981) to study the evolutionary
82 outcomes of host defence, given by

$$\begin{aligned} \frac{dX}{dt} &= (a - b)X - q(X + Y)X - (\beta - r)XY + \gamma Y \\ \frac{dY}{dt} &= (\beta - r)XY - ((\alpha - \tau) + b + \gamma)Y. \end{aligned} \tag{1}$$

83 Model parameters are listed in Table 1. Variables X and Y represent respectively the
84 densities of susceptible and infected individuals. The parameter a is the host birth rate and
85 b is the host natural death rate, while q models the effect of crowding on births. The disease
86 spreads with a transmission coefficient β . As an effect of infection, the infected hosts suffer
87 from an increased death rate by α , namely the parasite virulence. In addition, infected
88 individuals are infertile and do not contribute to reproduction. Moreover, hosts can recover
89 at rate γ and be susceptible to infection again.

90 Following previous studies (Boots and Bowers, 1999; Roy and Kirchner, 2000), we consider
91 two different types of resistance strategies. The first one includes those mechanisms that
92 prevent infection by limiting the possibilities of contagion, for example through barriers or
93 by reducing interactions with other hosts. This category is called avoidance and we model it
94 as a decrease r of the transmission coefficient β . The second category involves mechanisms
95 that help the clearance of the parasite inside the host and reduce the time under infection
96 and increase the possibility of recovery. Thus, we model it as an increase in the recovery
97 rate γ . Tolerance is modelled as a reduction τ in the disease-induced mortality rate α .
98 This choice is in accordance with the definition that tolerance has a non negative impact on
99 parasite fitness, as infected individuals experience lower additional mortality without effects
100 on other parasite traits as reproductive rate or transmission.

101 In the absence of disease, the susceptible population reaches the equilibrium $\bar{X}_0 = (a -$
102 $b)/q$. The disease can spread under the condition

$$R_0 = \frac{(\beta - r)\bar{X}_0}{\Gamma} = \frac{(\beta - r)(a - b)}{(\alpha - \tau + b + \gamma)q} > 1, \tag{2}$$

103 with $\Gamma = \alpha - \tau + b + \gamma$. System (1) shows a unique endemic equilibrium where the disease

104 persists

$$\begin{aligned}\bar{X} &= \frac{\Gamma}{\beta - r} \\ \bar{Y} &= \frac{a - b - q\bar{X}}{q + (\beta - r)\left(1 - \frac{\gamma}{\Gamma}\right)},\end{aligned}\tag{3}$$

105 that is positive and stable, provided (2) is satisfied.

106 We analyse the evolution of both defence strategies under the assumptions of either cost-
107 free or costly defence. To include the costs, trade-off functions have been introduced between
108 defence and birth rate a .

109 According to adaptive dynamics theory, when a resident population has reached its equi-
110 librium, in this case (3), a new mutant strain can invade if its invasion fitness in the en-
111 vironment set by the resident strategy is positive. Specifically, mutant invasion fitness is
112 defined as "the long-term exponential growth rate of a rare mutant in an environment set by
113 the resident" and in a structured population it is calculated as the leading eigenvalue of the
114 mutant invasion matrix (Metz et al., 1992). When the direct computation of the invasion
115 fitness is difficult, it is possible to adopt a fitness proxy instead. As defined in Parvinen
116 and Dieckmann (2018), a fitness proxy is a function that is, up to a constant, sign equiva-
117 lent to the invasion fitness. Adapting Hoyle et al. (2012) proof, we use the negative of the
118 determinants of the mutant invasion matrices as proxies for the sign of the invasion fitness
119 (Appendix A). We name the fitness proxy for resistance as s_r , this is a function of both the
120 resident trait r and the mutant trait r_m . Using a similar notation for recovery and tolerance,
121 we get

$$s_r(r, r_m) = (b + \alpha - \tau + \gamma) (a(r_m) - b - q(\bar{X} + \bar{Y}) - (\beta - r_m)\bar{Y}) + \gamma(\beta - r_m)\bar{Y},\tag{4}$$

$$s_\gamma(\gamma, \gamma_m) = (b + \alpha - \tau + \gamma_m) (a(\gamma_m) - b - q(\bar{X} + \bar{Y}) - (\beta - r)\bar{Y}) + \gamma_m(\beta - r)\bar{Y},\tag{5}$$

$$s_\tau(\tau, \tau_m) = (b + \alpha - \tau_m + \gamma) (a(\tau_m) - b - q(\bar{X} + \bar{Y}) - (\beta - r)\bar{Y}) + \gamma(\beta - r)\bar{Y}.\tag{6}$$

122 In (4)-(6) the dependence from the resident strategies lies in \bar{X} and \bar{Y} , as can be seen in (3).

123 The evolutionary dynamics of one trait stops when it reaches either a singular strategy or
124 the extinction boundary of one species. Singular strategies are characterised by the condition
125 that the derivative of the invasion fitness with respect to the mutant strain, namely the

126 selection gradient, is equal to zero. In this model the selection gradients are

$$\frac{\partial s_r}{\partial r_m} \Big|_{r_m=r} = \Gamma a'(r) + (\alpha - \tau + b) \bar{Y}, \quad (7)$$

$$\frac{\partial s_\gamma}{\partial \gamma_m} \Big|_{\gamma_m=\gamma} = \Gamma a'(\gamma) + (\beta - r) \left(1 - \frac{\gamma}{\Gamma}\right) \bar{Y}, \quad (8)$$

$$\frac{\partial s_\tau}{\partial \tau_m} \Big|_{\tau_m=\tau} = \Gamma a'(\tau) + \frac{\beta - r}{\Gamma} \gamma \bar{Y}. \quad (9)$$

127 Moreover, the selection gradient indicates in which direction the evolutionary path is moving.
 128 In fact, at the slow time-scale of evolution T we can approximate the change in the resident
 129 strategy, e.g. avoidance, as

$$\frac{dr}{dT} \approx \mu \frac{\partial s_r}{\partial r_m} \Big|_{r_m=r} \quad (10)$$

130 where $\mu > 0$ is a coefficient that takes into account rate and variance of the mutation
 131 process. Therefore, a positive selection gradient implies that evolution is moving towards
 132 higher values of r and a negative selection gradient that selection favours lower values of r .
 133 When the evolutionary path leads towards a singular strategy r^* , the singular strategy is
 134 called convergence stable (Geritz et al., 1998). This happens when the following condition
 135 is satisfied

$$\frac{\partial^2 s_{r_m}}{\partial r_m^2} \Big|_{r_m=r=r^*} > \frac{\partial^2 s_{r_m}}{\partial r^2} \Big|_{r_m=r=r^*} \quad (11)$$

136 The same holds for tolerance and recovery.

137 3. Results

138 3.1. Evolution of resistance

139 We firstly consider the case of evolving avoidance without costs, i.e. when the birth rate
 140 $a(r)$ is equal to a positive constant \bar{a} for every resistance strategy r . Under this assumption,
 141 the selection gradient

$$\frac{\partial s_r}{\partial r_m} \Big|_{r_m=r} = (\alpha - \tau + b) \bar{Y} > 0 \quad (12)$$

142 and it is equal to 0 when $\bar{Y} = 0$. Therefore, evolution leads towards higher value of r to the
 143 point where $R_0 = 1$ and the disease can not spread enough to survive. A similar conclusion

144 can be drawn when increased recovery evolves without cost. We choose $a(\gamma) = a_m(\gamma) = \bar{a}$
 145 positive constant such that (2) is satisfied for some γ . Consequently, the selection gradient

$$\frac{\partial s_\gamma}{\partial \gamma_m} \Big|_{\gamma_m=\gamma} = (\beta - r) \left(1 - \frac{\gamma}{\Gamma}\right) \bar{Y} > 0 \quad (13)$$

146 for every γ such that $\bar{Y} > 0$ and equal to zero at $\bar{Y} = 0$, since $\gamma < \Gamma$. Thus, the evolutionary
 147 dynamics reaches the extinction boundary, where the recovery rate is too high for the infec-
 148 tion to persist. The reason for this is that an increase in γ means a decrease in the length
 149 of the infectious period and, consequently, in R_0 .

150 We use the graphical tool of pairwise invasibility plot (PIP) (van Tienderen and de Jong,
 151 1986; Geritz et al., 1998) to show the evolutionary dynamics. In the PIPs, the sign of the
 152 invasion fitness is plotted in the plane spanned by the resident and the mutant strategies.
 153 When the positive region (positive regions are shaded and negative regions are white) is
 154 above the diagonal the evolutionary dynamics moves to the right, while it moves to the left
 155 when the positive region is below the diagonal. In both cases of Fig.1 the absence of costs
 156 allows defence to be favoured even at low values of disease prevalence, where selection for
 157 resistance is weaker.

158 This result does not hold when resistance comes with costs. In line with previous theo-
 159 retical models and experimental studies (Hart, 1990; Stearns, 1992; Hoyle et al., 2008) we
 160 assume a monotonically increasing trade-off $a = a(r)$ between avoidance and birth rate. To
 161 understand if parasite extinction is possible for some value of r , we analyse the selection
 162 gradient when $\bar{Y} \approx 0$ such that we are nearby the point of extinction. Since $a'(r) < 0$, at
 163 the limit for low values of infected population the selection gradient

$$\lim_{\bar{Y} \rightarrow 0^+} \frac{\partial s_r}{\partial r_m} \Big|_{r_m=r} = \Gamma a'(r) < 0 \quad (14)$$

164 Resistance reduces the infection prevalence and, as consequence, lowers the risk of infection
 165 under the level where the costs of resistance exceed the benefits. Therefore, when \bar{Y} is close
 166 to zero, selection promotes lower resistance and the parasite avoids extinction.

167 Similarly, we consider a trade-off $a = a(\gamma)$ that is monotonically decreasing with respect
 168 to γ and satisfies (2) for some γ . Close to the extinction boundary the limit of the selection

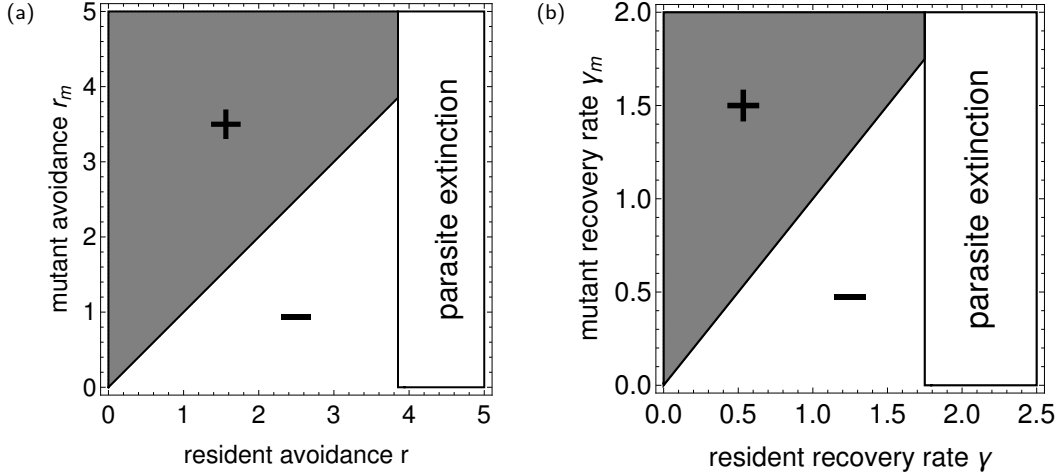


Figure 1: Pairwise invasibility plot for resistance evolution without costs. In (a) the sign of $s_r(r, r_m)$ is plotted in the r - r_m plane under the hypothesis that $a'(r) = 0$. Analogously, (b) shows the sign of $s_\gamma(\gamma, \gamma_m)$ as function of γ and γ_m . In both panels the gray region marks where the sign is positive. Parameter values are summarised in Tab 1, $\alpha = 1$.

169 gradient is

$$\lim_{\bar{Y} \rightarrow 0^+} \frac{\partial s_\gamma}{\partial \gamma_m} \Big|_{\gamma_m = \gamma} = \Gamma a'(\gamma) < 0 \quad (15)$$

170 and mutants with lower values of resistance will invade.

171 It can be shown that R_0 and disease prevalence $\bar{Y}/(\bar{X} + \bar{Y})$, with \bar{X} and \bar{Y} defined in
 172 (3), are monotonically increasing for decreasing resistance, therefore, the host cannot clear
 173 the disease by lowering defence. Notice also that we proved that extinction cannot occur in
 174 the deterministic model under the assumption of small mutations. When \bar{Y} is close to 0,
 175 extinction could be possible if stochastic effects are taken into account.

176 In order to represent graphically the previous results, we define the trade-off function
 177 explicitly

$$a(r) = a^* - \frac{a'(r^*)^2}{a''(r^*)} \left(1 - e^{\frac{a''(r^*)}{a'(r^*)}(r-r^*)} \right) \quad (16)$$

$$a(\gamma) = a^* - \frac{a'(\gamma^*)^2}{a''(\gamma^*)} \left(1 - e^{\frac{a''(\gamma^*)}{a'(\gamma^*)}(\gamma-\gamma^*)} \right). \quad (17)$$

178 This choice allows to easily determine the local shape close to a chosen point (r^*, a^*) or
 179 (γ^*, a^*) and consequently, by absolute monotonicity, a wide range of global behaviours, e.g.

180 different steepness or concavity. Specifically, $a'(r^*)$ and $a'(\gamma^*)$ are chosen such that r^* and γ^*
 181 are a singular strategy, i.e. the selection gradients in (4)-(5) are equal to zero. Notice that
 182 this choice respects the assumption of monotonically increasing costs. We derive the intervals
 183 for $a''(r^*)$ and $a''(\gamma^*)$ such that the singular strategies are convergence stable from (11). If
 184 r^* and γ^* are convergence stable, parasite extinction is trivially avoided (Fig.2a and Fig.2c).
 185 More interestingly, when r^* and γ^* are convergence unstable a second singular strategy close
 186 to the boundary necessarily emerges and prevents the disease dying out (Fig.2b and Fig.2d).

187

188 3.2. Evolution of tolerance

189 In the absence of costs, the selection gradient (6) for tolerance is

$$\frac{\partial s_\tau}{\partial \tau_m} \Big|_{\tau_m=\tau} = \frac{(\beta - r)\gamma \bar{Y}}{\Gamma} > 0 \quad (18)$$

190 when the infection is present and null at the extinction boundary. Therefore, the evolutionary
 191 dynamics moves towards tolerance maximisation and balance the effect of parasite virulence
 192 α . Contrary to the case of resistance, disease prevalence increases when tolerance is selected
 193 and parasite extinction does not occur. This can be observed in the simulation in Fig.3,
 194 implemented as in Appendix C.

195 We consider now the case of costly tolerance. In line with what stated for resistance, we
 196 assume that investing in tolerant strategies limits the allocation of resources for reproduction.
 197 A field study on voles showed evidence for such a trade-off (Jackson et al., 2014; Kutzer
 198 and Armitage, 2016) but our general understanding on the mechanisms behind tolerance
 199 is still limited. When we consider the costs of tolerance, the trade-off $a(\tau)$ is assumed to
 200 be monotonically decreasing with respect to τ . Under this assumption, near the extinction
 201 boundary the selection gradient (6) is

$$\lim_{\bar{Y} \rightarrow 0^+} \frac{\partial s_\tau}{\partial \tau_m} \Big|_{\tau_m} = \tau = \Gamma a'(\tau) < 0, \quad (19)$$

202 meaning that selection for *lower* tolerance can lead to parasite extinction. Such situations
 203 are illustrated in Fig.4a and Fig.4b, in which the sign of $s_\tau(\tau, \tau_m)$ is plotted for different
 204 values of both mutant and resident strategies. Compared to the case without costs, the zero

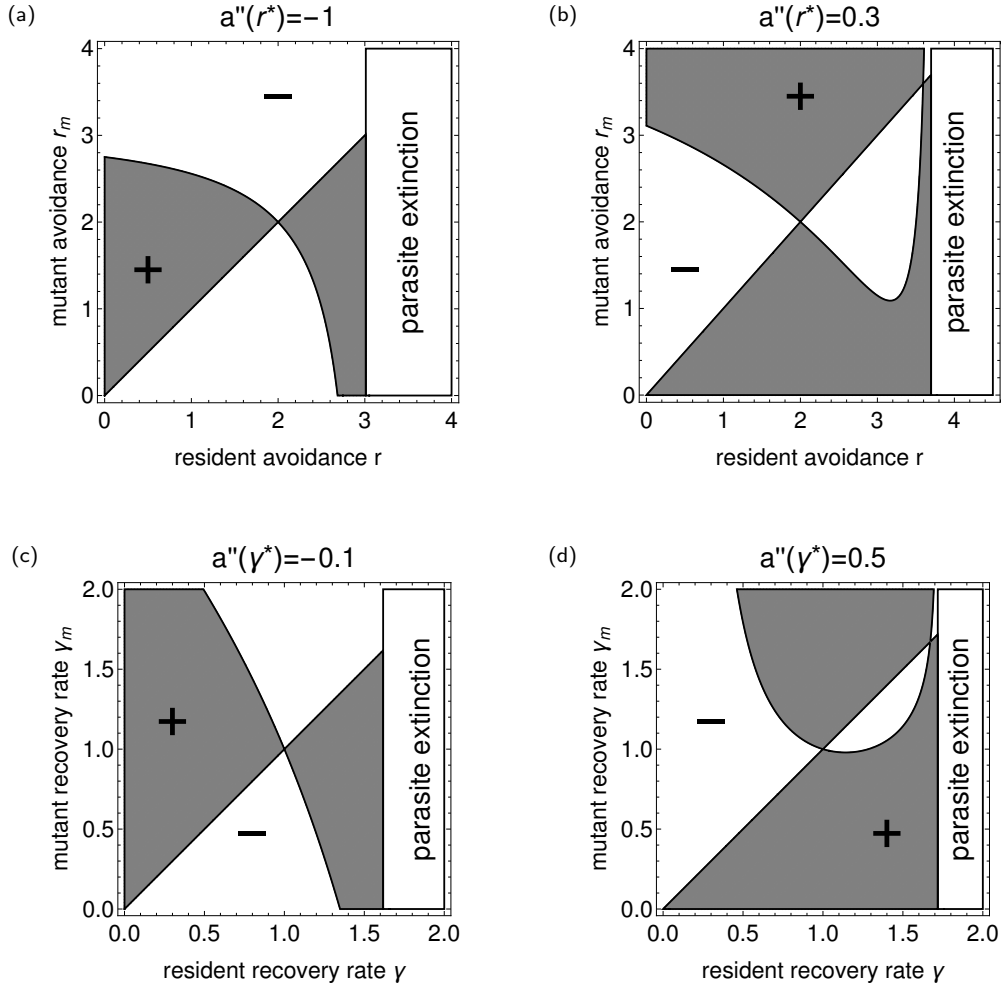


Figure 2: Pairwise invasibility plots for resistance evolution with costs. In (a) and (b) the sign of $s_r(r, r_m)$ is plotted in the r - r_m plane for two different values of the second derivative of the trade-off function $a(r)$ at the singular strategy $r^* = 2$. Similarly, in (c) and (d) the sign of $s_\gamma(\gamma, \gamma_m)$ is plotted for two different values of $a''(\gamma^*)$. In the gray regions the invasion fitness is positive. $\alpha = 1$. In (a) and (b) $\beta^* = 2$; $a(\beta^*) = 2$; $a'(\beta^*) = 0.78$. In (c) and (d) $\gamma^* = 1$; $a(\gamma^*) = 2$; $a'(\gamma^*) = -0.1$.

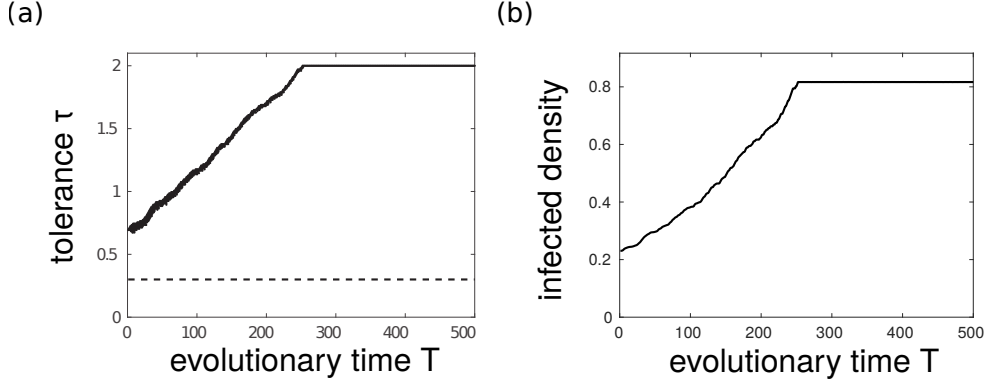


Figure 3: Simulation of the evolution of tolerance in absence of costs (for details see Appendix C). In the left panel, the black region represents the values of τ of the strains present at each iteration and the dashed line the parasite extinction boundary. In the right panel, the continuous curve represents the disease prevalence. $\alpha = 2$.

205 of the selection gradient that was on the extinction boundary has now entered the region of
 206 parasite viability, changing the direction of selection for low \bar{Y} .

207 We investigate now under which conditions on the trade-off function host evolution drives
 208 the parasite to extinction by lowering tolerance. As a first condition, we need the parasite
 209 to be present in the system, meaning $R_0 > 1$. By rearranging condition (2), we found that
 210 it holds when

$$a(\tau) > b + \frac{q(\gamma + b + \alpha)}{\beta - r} - \frac{q}{\beta - r}\tau \quad (20)$$

211 for some values of τ . Secondly, we need parasite extinction to be possible in the system, i.e.

$$a(\tau) = b + \frac{q(\gamma + b + \alpha)}{\beta - r} - \frac{q}{\beta - r}\tau \quad (21)$$

212 has to have a least one real and positive root for some parameter sets otherwise the parasite is
 213 viable for every value of τ . To derive the last condition, we notice that, under the assumption
 214 of a decreasing trade-off $a(\tau)$, R_0 can be non monotonous with respect to τ and the parasite
 215 can be not viable for both low and high values of tolerance (e.g. in Fig.4a). The selection
 216 gradient close to extinction boundary is given in (19) and is negative, therefore, parasite
 217 extinction can occur only for lower values of tolerance. Notice that extinction can happen
 218 only when parasite prevalence is locally monotonically increasing with respect of τ , so it

219 decreases as τ decreases. Infection prevalence P is defined as

$$P = \frac{\bar{Y}}{\bar{X} + \bar{Y}} = \frac{q(\bar{X}_0 - \bar{X})}{a + \alpha - \tau}. \quad (22)$$

220 Consequently, the derivative of P with respect of τ is

$$\frac{dP}{d\tau} = \frac{\left(a'(\tau) - q\frac{d\bar{X}}{d\tau}\right)(a(\tau) + \alpha - \tau) - q(a'(\tau) - 1)(\bar{X}_0 - \bar{X})}{(a + \alpha - \tau)^2}, \quad (23)$$

221 which it is positive when

$$a'(\tau) > -\frac{(\beta - r)(a(\tau) - b) + q(a(\tau) - b - \gamma)}{(\beta - r)(\alpha - \tau + b) + q\Gamma}. \quad (24)$$

222 When we evaluate the right-hand side of (24) at (21), we get that the slope of the trade-off
 223 evaluated at the boundary has to be more than $-q/\beta$, which is minus the ratio between host
 224 internal competition and the parasite transmission coefficient. To summarise, considering a
 225 trade-off that satisfies (20) for some τ , parasite extinction is possible when (21) has at least
 226 one real and positive root where the slope of the trade-off function is more than $-q/\beta$.

227 Notice that another consequence of the non-monotony of disease prevalence is that (21)
 228 may not have any real and positive roots and the disease does not die out for any values of
 229 τ . Due to the trade-off between birth rate and tolerance, if the increase in reproduction is
 230 considerable the large susceptible inflow compensates the shortening of the infectious period
 231 and the disease persists despite tolerance decreasing.

232 We can give a graphical representation to the conditions for parasite extinction by plotting
 233 the right-hand side of (21), i.e. the thick line in Fig.5. Condition (20) is satisfied if a trade-off
 234 function is above the line for some value of τ and condition (21) holds when the trade-off
 235 intersects it. Moreover, the slope of the line is $-q/\beta$ and if a trade-off function intersects it
 236 with a larger gradient parasite extinction is possible. Choosing the trade-off function

$$a(\tau) = a^* - \frac{a'(\tau^*)^2}{a''(\tau^*)} \left(1 - e^{\frac{a''(\tau^*)}{a'(\tau^*)}(\tau - \tau^*)}\right), \quad (25)$$

237 in Fig.5 we check if the conditions for extinction hold for different values of $a''(\tau^*)$, namely
 238 the value of the second derivative of the trade off function evaluated at τ^* .

239 Accordingly, the evolutionary outcomes of tolerance evolution can be observed in Fig.4.
 240 In the first two panels parasite extinction occurs through reduced tolerance, while in the

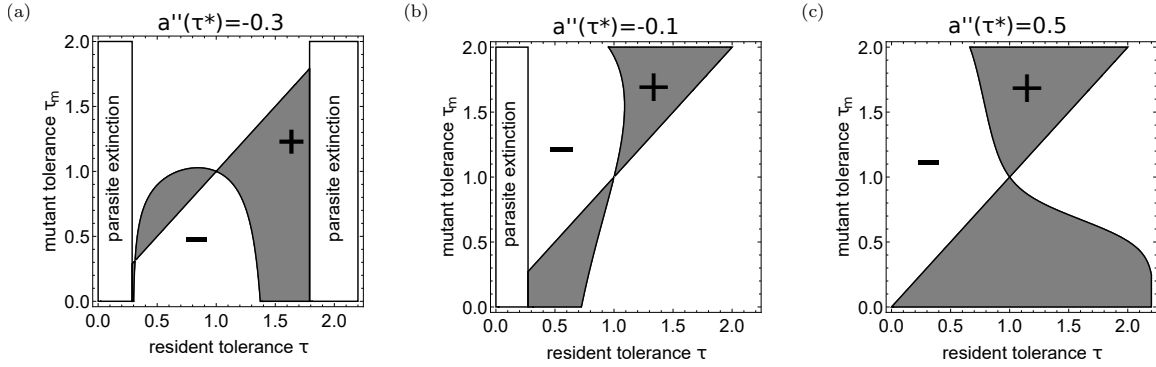


Figure 4: Pairwise invasibility plot for tolerance evolution with costs. In the τ - τ_m plane, $s_\tau(\tau, \tau_m)$ is positive in correspondence with gray regions. The three panels are related to different values of the parameter $a''(\tau^*)$ of the trade-off function $a(\tau)$. $\alpha = 2$; $\tau^* = 1$; $a(\tau^*) = 1.5$; $a'(\tau^*) = -0.049$.

241 third panel condition (24) is satisfied before evolution reaches the extinction boundary and
 242 the disease persists.

243 It can be noticed that in the first panel of Fig.4, extinction occurs for a narrower range
 244 of initial strategies than in the second panel. To quantify the range of initial strategies
 245 from which natural selection leads to parasite clearance, we define the basin of attraction
 246 of the extinction boundary as the difference between the extinction value of τ that satisfies
 247 conditions (20), (21) and (24) and either the closest singular strategy, which is always a
 248 repeller, or 0 when there are not positive singular strategies. As it can be seen in Fig.6,
 249 extinction can occur for a wide range of choices of trade-off parameters $a'(\tau^*)$ and $a''(\tau^*)$
 250 and different combinations of q and β . Particularly, extinction happens mostly for negative
 251 $a''(\tau^*)$, i.e. for increasingly accelerating costs. For low values of $a'(\tau^*)$, the basin of attraction
 252 is narrow due to a repeller strategy close to the boundary. When $a'(\tau^*)$ increases the repeller
 253 strategy either disappears through a fold bifurcation (black curve in Fig.6) or its value
 254 decreases and the basin of attraction increases. Moreover, when q/β increases extinction
 255 occurs for a wider range of values with smaller basin of attraction due to a decrease in R_0
 256 and an increase in the steepness of the bold line in Fig.5.

257 Numerical simulations (performed as in Fig.3), where we relaxed the hypothesis of a
 258 timescale separation between evolutionary and ecological time, showed the occurrence of
 259 parasite extinction due to tolerance evolution. Furthermore, we questioned whether such

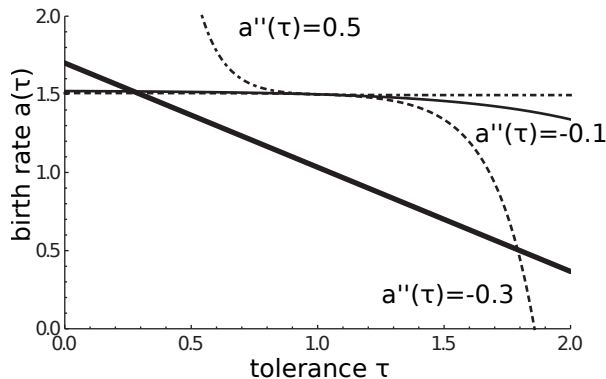


Figure 5: Conditions for parasite extinction. The thick line represents the RHS of (21) and the thin curves are plots of (20) for different values of $a''(\tau^*)$. The parasite population is viable, when $a(\tau)$ is above the thick line, and the extinction boundaries are at the cross between $a(\tau)$ and the thick line. For $a''(\tau^*) = -0.3$ (dashed curve) parasites are not viable for both high and low values of tolerance, for $a''(\tau^*) = -0.1$ (continuous curve) parasites are not viable for low values of tolerance and for $a''(\tau^*) = 0.5$ (dot-and-dashed curve) parasites are always viable. Parasite extinction can occur only for the lower value of τ , since at the lower one the gradient of the trade-off is higher than $-q/\beta$. $\tau^* = 1$; $a(\tau^*) = 1.5$; $a'(\alpha^*) = -0.049$.

260 extinctions could still occur when the parasite is able to co-evolve its virulence strategy and
 261 gain faster transmission by increasing virulence. Running numerical simulations of the co-
 262 evolution of host tolerance and parasite virulence we found it easy to obtain examples where
 263 extinction did still occur (Fig.7a). Depending upon initial values, co-evolution can also lead
 264 to parasites avoiding extinction by lowering virulence as in Fig.7b.

265 4. Discussion

266 We analysed the possibility for parasite extinction due to the evolution of costly host de-
 267 fence and found that only tolerance can lead to deterministic host-driven parasite extinction.
 268 Interestingly, it is by lowering tolerance, and therefore suffering more damaging effects from
 269 infection, that eradication of the parasite occurs. To our knowledge, this is the first study
 270 to demonstrate this possibility through a dynamic evolutionary process. We have also re-
 271 covered previously known results that hosts can eradicate the disease by evolving resistance
 272 mechanism if costs are not present (Antonovics and Thrall, 1994), but that eradication of

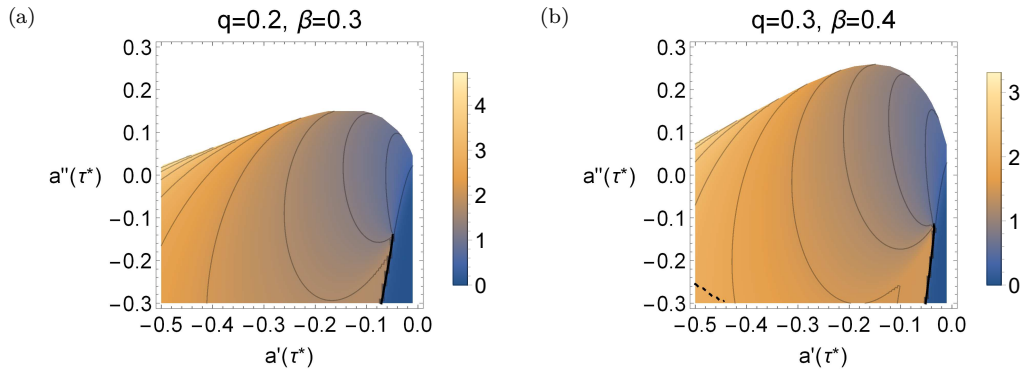


Figure 6: Density plots of the attraction basin of the extinction boundary as function of $a'(\tau^*)$ and $a''(\tau^*)$ for different values of q and β . The basin is measured as the difference between the value of τ that satisfies conditions (20)-(21) and the closest singular strategy, which is an evolutionary repeller. In the white regions, equation (21) does not have a real and positive solution and extinction cannot occur. The continuous black line marks a discontinuity in the basin of attraction due to a fold bifurcation between two singular strategies. Below the dashed curve in the third panel, there are not positive singular strategies and extinction occurs for every initial value of t . $\alpha = 5$; $\tau^* = 1$; $a(\tau^*) = 1.5$.

273 infection is impossible through costly resistance since selection for resistance always vanishes
 274 before parasite extinction (Roy and Kirchner, 2000). Our work not only identifies a potential
 275 route for host-driven parasite extinction but also further highlights the crucial distinction
 276 between resistance and tolerance mechanisms.

277 An important question that arises is whether such host-driven extinctions are possible
 278 in natural systems. Experimental studies of coevolutionary bacteria-phage interactions have
 279 found that phage can be driven to extinction through the evolution of host resistance when
 280 the pathogen is subjected to some external pressure, for example population bottlenecks
 281 (Hesse and Buckling, 2016) or reduced resource availability (Zhang and Buckling, 2016).
 282 Interestingly, a similar result has been predicted theoretically by Hoyle et al. (2012), where it
 283 was found that the presence of a predator species adds environmental pressure on the parasite
 284 that can lead to parasite extinction. Further experimental work is required to determine
 285 whether the evolution of tolerance mechanisms can lead to extinction in the absence of
 286 external pressures as we have predicted here.

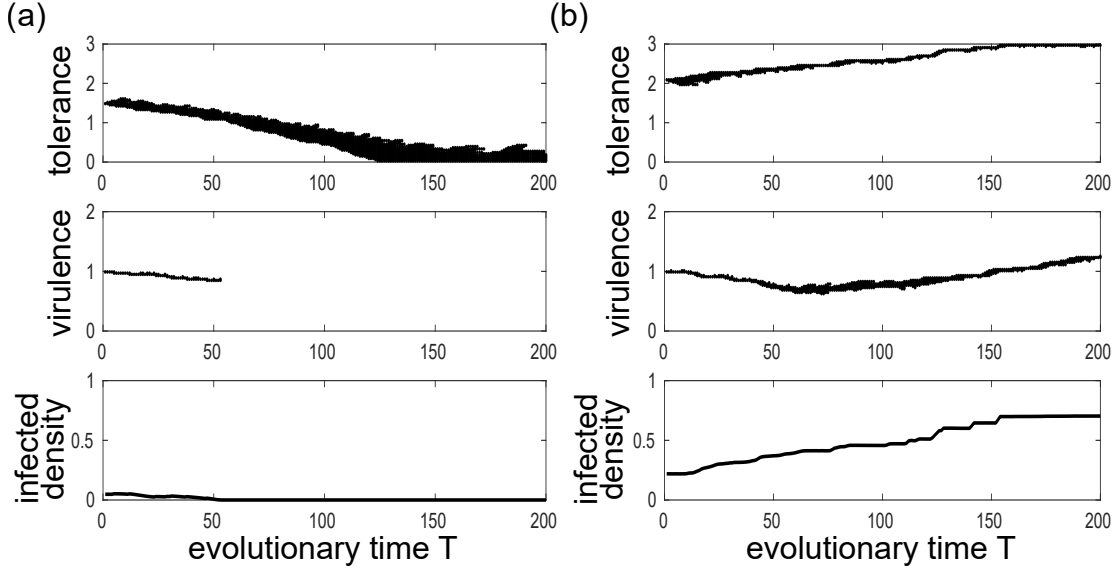


Figure 7: Numerical simulations of host-parasite co-evolution (for details see Appendix C) for two different initial values. Parasite virulence α^P is linked with disease transmission by the function $\beta(\alpha^P) = 0.3 - 0.05 \left(1 - e^{-2(\alpha^P-1)}\right)$. $\alpha^H = 2, \tau^* = 1; a(\tau^*) = 1.5; a'(\tau^*) = -0.049; a''(\tau^*) = -0.1; n_P = 100; n_H = 100$.

287 Questioning if parasite extinction would be possible requires understanding whether se-
 288 lection could promote the lowering of tolerance in an already tolerant population. A few
 289 potential routes can be hypothesized. Firstly, tolerance that has evolved due to exposure
 290 to different pathogens in the past could be lost due to different selection pressures from a
 291 novel pathogen. Evidence of such a change has been found by Ayres and Schneider (2008),
 292 where a single gene was found lowering tolerance in *Drosophila* according to different mi-
 293 crobial challenge. Secondly, the concept of "behavioural tolerance" has been described by
 294 Sears et al. (2013) and Adelman and Hawley (2017). In this case organisms may evolve be-
 295 havioural adaptations to face infection, like anorexia or lethargy, that increase the severity
 296 of disease symptoms. Similarly there is the potential for hosts to evolve immunopathological
 297 responses (Read et al., 2008; Medzhitov et al., 2012), whereby the host immune response
 298 inflicts damage to infected hosts, and can in some sense be seen as the opposite side of the
 299 coin to tolerance. There continues to be much interest in exploring tolerance mechanisms
 300 across a range of host-pathogen interactions (Råberg, 2014; Kutzer and Armitage, 2016;
 301 Soares et al., 2017).

302 Previous evolutionary studies on tolerance focused either on the changing of the optimal
303 evolutionary strategy according to environmental gradients or on the possibility of speciation
304 through evolutionary branching (Restif and Koella, 2003; Miller et al., 2005, 2007; Best et al.,
305 2008, 2014). These have generally reinforced the distinction that resistance mechanisms
306 produce a negative feedback to prevalence to evolution while tolerance mechanisms produce
307 a positive feedback. Here we have shown that, under certain trade-off shapes, prevalence can
308 in fact increase as tolerance is lowered, while it always decreases in absence of costs. The key
309 to this result is in including costs in to our understanding of ecological feedbacks. This trend
310 occurs when the increase in reproduction rate for lower values of tolerance is large enough to
311 compensate for the decrease in the infectious period. Therefore, if costs play an important
312 role, there will be cases where high parasite density does not relate to high tolerance, as
313 we would expect given the traditional theory on tolerance (Boots and Bowers, 1999; Roy
314 and Kirchner, 2000). Another example of non-monotonous relation between tolerance and
315 disease prevalence can be observed in Miller et al. (2006). This may be in contradiction with
316 the assumption that tolerance should increase parasite prevalence (Read et al., 2008; Kutzer
317 and Armitage, 2016). We suggest that long-term evolutionary studies that include data on
318 population densities are vital for fully understanding the potential evolutionary outcomes,
319 including the potential for pathogen extinction.

320 It is interesting to note that the mechanism for parasite extinction occurs such that selec-
321 tion starts to promote traits that at the individual level worsen the possibility of mortality
322 under infection. In this sense we see a paradox when the gain at the population level (re-
323 duced prevalence and ultimately disease eradication) is achieved by a loss at the individual
324 level (increased mortality) in favour of reproduction. Conceptually, this phenomena is rem-
325 iniscent of evolutionary suicide, which is the catastrophic extinction of a population caused
326 by natural selection (Parvinen, 2005; Ferrière et al., 2009). One of the possible routes to evo-
327 lutionary suicide occurs when natural selection favours a trait - like prey timidity (Matsuda
328 and Abrams, 1994) or "the tragedy of the commons" (Hardin, 1968), virulence for parasite
329 (Boldin and Kisdi, 2016)- that is beneficial for the individual but in the long term reduces
330 the population reproductive rate under the threshold of viability. Naively, it appears that
331 here we see the opposite case. However, it is important to note that across both the increased

332 mortality and increased reproduction, lowered tolerance is still beneficial for the individual's
333 fitness.

334 A future development of this study would be to investigate the robustness of extinc-
335 tion against parasite counter-adaptation of virulence. Preliminary simulations showed that
336 both parasite extinction and parasite survival are possible outcomes when higher virulence
337 is linked with faster transmission. It is worth noting that as the parasite population declines
338 due to host evolution, its relative mutation rate will slow, limiting its co-evolutionary re-
339 sponse. However, it has been shown theoretically that selection for tolerance might promote
340 an increase in virulence by lowering its cost when virulence is linked with an advantage in
341 pathogen replication or transmission (Miller et al., 2006; Best et al., 2014). This result ex-
342 plains why tolerance could impose selection upon parasites without lowering their prevalence
343 and igniting the co-evolutionary arms race typical of resistance (van Baalen, 1998). When
344 tolerance decreases we might therefore expect a reduction in transmission rate (Restif and
345 Koella, 2003), which would increase the chances of extinction, or a reduction in virulence
346 (Miller et al., 2006), which would decrease the extinction risk. Moreover, co-evolution might
347 end in forms of commensalism. This poses an additional challenge in discerning the effects
348 of host tolerance and parasite virulence in experimental work in a way that (Little et al.,
349 2010) detected as the problem of intimacy. Another possible expansion of this model would
350 be to add a recovery class. It is likely that parasite extinction would still occur due to the
351 reduction of the susceptible class.

352 The gap between the theoretical dichotomy of resistance and tolerance and the complexity
353 of experimental results is still wide. In the theoretical framework, tolerance and resistance
354 are clearly defined as distinct and predicted to lead to different evolutionary consequences.
355 In experimental studies, even when it is possible to distinguish among the two traits it
356 is still challenging to unravel all the implication of their interplay. While some studies
357 found a trade off between tolerance and resistance (Råberg, 2014), others suggest a more
358 complementary dynamics, as tolerance contributes to reducing the effects on tissues caused
359 by resistance mechanisms (Medzhitov et al., 2012; Soares et al., 2017). Filling this gap would
360 be beneficial for both theoretical and experimental development. A better understanding of
361 the mechanisms behind tolerance would improve the reliability of evolutionary models that

362 in return could facilitate the design of experimental studies. In this sense, the aim of this
 363 work is to further highlighted the crucial role that host tolerance may play in host-parasite
 364 systems, and as such it is vital that modellers and empiricists identify avenues for further
 365 research with closer integration.

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370 Appendix A Invasion fitness

371 We give now a quick explanation for the fitness proxy $s_r(r, r_m)$ and analogous arguments
 372 hold for $s_\gamma(\gamma, \gamma_m)$ and $s_\tau(\tau, \tau_m)$. Given a resident population of trait r at the demographic
 373 equilibrium (\bar{X}, \bar{Y}) , the dynamics for a new mutant strain r_m is

$$\begin{aligned} \frac{dX_m}{dt} &= (a(r_m) - b - q(\bar{X} + \bar{Y}) - (\beta - r_m)\bar{Y}) X_m + \gamma Y_m \\ \frac{dY_m}{dt} &= (\beta - r_m) X_m - (\alpha - \tau + b + \gamma) Y_m. \end{aligned} \tag{A1}$$

374 The underlying assumption is that at the beginning mutant prevalence is low and does
 375 not influence the environment set by the resident. The mutant strain can spread if the
 376 equilibrium (3) is unstable in the full system, i.e. if the Jacobian matrix with respect to the
 377 mutant variables

$$\begin{pmatrix} a(r_m) - b - q(\bar{X} + \bar{Y}) - (\beta - r_m)\bar{Y} & \gamma \\ (\beta - r_m)\bar{Y} & -\Gamma \end{pmatrix} \tag{A2}$$

378 has at least one eigenvalue with positive real part. Therefore, the mutant fitness is defined as
 379 the leading eigenvalue of (A2). Hoyle et al. (2012) proved that the negative of the determinant
 380 of (A2) has equivalent sign of the leading eigenvalue and thus it can be used as fitness proxy.

381 Appendix B Impact of fertility under infection

382 We show here that even when hosts reproduce while infected, parasite extinction through
 383 tolerance evolution can still occur. We assume that the reproduction rate of infected indi-

384 individuals is reduced by a coefficient f . Considering this hypothesis, the model is

$$\begin{aligned}\frac{dX}{dt} &= a(X + fY) - bX - q(X + Y)(X + fY) + (\beta - r)XY + \gamma Y \\ \frac{dY}{dt} &= (\beta - r)XY - (\alpha - \tau + b + \gamma)Y.\end{aligned}\tag{B1}$$

385 The dynamics of (B1) differs from the one of (1) as it can show more than one internal
386 equilibrium. Here, we assume that the dynamics reaches a stable internal equilibrium (\bar{X}, \bar{Y}) ,
387 leaving the details to a more deepened study. The invasion fitness for a mutant strategy with
388 tolerance t_m , calculated as in Appendix A, is:

$$\begin{aligned}s_\tau(\tau, \tau_m) &= (\alpha - \tau_m + b + \gamma) [a(\tau_m) - b - q(\bar{X} + \bar{Y}) - (\beta - r)\bar{Y}] \\ &\quad + (\beta - r)\bar{Y} [\gamma + af - qf(\bar{X} - \bar{Y})].\end{aligned}\tag{B2}$$

389 Consequently, the selection gradient is

$$\left. \frac{\partial s_\tau(\tau, \tau_m)}{\partial \tau_m} \right|_{\tau_m=\tau} = - [a(\tau) - b - q(\bar{X} + \bar{Y}) - (\beta - r)] + a'(\tau)(\alpha - \tau + b + \gamma),\tag{B3}$$

390 which, taking the limit at the extinction boundary, becomes

$$\lim_{\substack{\bar{Y} \rightarrow 0 \\ \bar{X} \rightarrow \bar{X}_0}} \left. \frac{\partial s_\tau(\tau, \tau_m)}{\partial \tau_m} \right|_{\tau_m=\tau} = a'(\tau)(\alpha - \tau + b + \gamma) < 0\tag{B4}$$

391 as the reproduction rate is decreasing with respect of τ . Equation (B4) shows that the
392 selection gradient at the extinction boundary for low level of tolerance points towards the
393 region of parasite extinction. Therefore, parasite extinction due to tolerance minimisation
394 occurs also when infected individuals can reproduce. In fact, PIP (not shown) realised as in
395 Fig.4 show a qualitatively similar behaviour as in Fig.4 for different values of f between 0
396 and 1.

397 Appendix C Numerical simulations

398 To perform numerical simulations we followed a method similar to Hoyle et al. (2012).
399 For tolerance evolution, we set a system for 200 possible host strain values of τ and initialised
400 as non zero the initial condition for a random strain. At every step the system is solved for
401 a fixed time that is not long enough for the population dynamics to reach the dynamical
402 equilibrium. In this way it can be relaxed the hypothesis of time-scale separation between

403 ecological and evolutionary dynamics. Strains with frequency less than 0.1% are then re-
 404 moved from the system and a new mutant close to the most frequent strain is introduced
 405 randomly. Moreover, the parasite is removed from the system when its prevalence drops
 406 under 0.01%. Similarly, to simulate co-evolution between host tolerance (τ) and parasite
 407 virulence (α_P) at every step we solve the system

$$\frac{dX_i}{dt} = a(\tau_i) X_i - q \left(\sum_i^{n_H} \sum_j^{n_P} Y_{ij} + \sum_i^{n_P} X_i \right) X_i - X_i \sum_{i=1}^{n_H} \sum_{j=1}^{n_P} \beta(\alpha_j^P) Y_{ij} + \gamma \sum_{j=1}^{n_P} Y_{ij}, \quad i = 1, \dots, n_H \quad (\text{C1})$$

$$\frac{dY_{ij}}{dt} = \beta(\alpha_j^P) Y_{ij} X_i - ((\alpha^H - \tau_i) \alpha_j^P + b + \gamma) Y_{ij}, \quad i = 1, \dots, n_H \quad j = 1, \dots, n_P,$$

408 where X_i is the density of the host population with tolerance strain t_i and Y_{ij} is the density
 409 of infected with tolerance strain t_i from the parasite strain α_j^P . The parameter α^H has been
 410 introduced to avoid that the term for infected mortality becomes positive. The number of
 411 host strains is n_H and the number of parasite strains is n_P , $a(\tau_i)$ is defined as in (25), $\beta(\alpha_j^P)$
 412 is a monotonously increasing function (e.g. Fig.7) and the others parameters have same
 413 interpretation as in (1). After a fixed time, populations with frequency under 0.1% are set
 414 to zero and a new mutant strain is introduced randomly with same probability of being a
 415 new host or a new parasite.

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