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Host lifespan and the evolution of resistance to multiple parasites.

Hosts are typically challenged by multiple parasites, but to date theory on the evolution of resistance has mainly focused on single infections. We develop a series of models that examine the impact of multiple parasites on the evolution of resistance under the assumption that parasites coexist at the host population scale as a consequence of superinfection. In this way we are able to explicitly examine the impact of ecological dynamics on the evolutionary outcome. We use our models to address a key question of how host lifespan affects investment in resistance to multiple parasites. We show that investment in costly resistance depends on the specificity of the immune response and on whether or not the focal parasite leads to more acute infection than the co-circulating parasite. A key finding is that investment in resistance always increases as the immune response becomes more general independently of whether it is the focal or the co-circulating parasite that exploits the host most aggressively. Long-lived hosts always invest more than short-lived hosts in both general resistance and resistance that is specific to relatively acute focal parasites. However, for specific resistance to parasites that are less acute than co-circulating parasites it is the short-lived hosts that are predicted to invest most. We show that these results apply whatever the mode of defence i.e. whether it is through avoidance or through increased recovery, with or without acquired immunity, or through acquired immunity itself. As a whole, our results emphasise the importance of considering multiple parasites in determining optimal immune investment in eco-evolutionary systems.

Key words: epidemiology, ecology, host resistance, density dependence, superinfection, coexistence, lifespan.

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1. Introduction

1 In natural settings hosts are subject to attack from a multitude of parasites (Morand and
2 Poulin, 2000; Nunn et al., 2003, 2005). The impact of multiple infection on the evolution of
3 parasite virulence has been well studied (Bremermann and Pickering, 1983; Bonhoeffer and
4 Nowak, 1994; Nowak and May, 1994; van Baalen and Sabelis, 1995; Frank, 1996; Mosquera
5 and Adler, 1998; Gandon et al., 2001) with this theory suggesting that parasite diversity
6 is associated with higher parasite virulence (though collective action between co-infecting
7 parasites can alter this result, see Brown et al. (2002)). Furthermore, of particular interest is
8 that the strength of this effect can decrease with the relatedness of the parasites (Frank,
9 1996; Gandon and Michalakis, 2002). The role of multiple infections in the evolution of
10 host resistance, on the other hand, is less well studied (Poitrineau et al. (2003); Jokela
11 et al. (2000); Kada and Lion (2015)) with all of the evolution of resistance theory that
12 explicitly takes account of ecological feedbacks restricted to defence against a single parasite
13 (or transient parasite diversity, see Kada and Lion (2015)). Parasites clearly interact directly
14 through competition for susceptible hosts, but when the host evolves resistance to a focal
15 parasite the extent to which the resistance also counters co-circulating parasites constitutes
16 an additional, less obvious interaction between parasites. Therefore, the relationship between
17 parasite diversity and the pattern of evolved resistance is likely to be complex. In particular
18 there is considerable interest in the role that host lifespan plays in determining optimal
19 investment in costly defence (van Boven and Weissing, 2004; Miller et al., 2007; Boots et al.,
20 2013; Donnelly et al., 2015) but it is not yet understood how this will depend on the nature
21 of co-circulating parasites.

22 There is a large body of work that examines the evolution of immunity in the context of
23 ecological feedbacks and the presence of a single parasite strain (Bowers et al., 1994; Antonovics
24 and Thrall, 1994; Boots and Haraguchi, 1999; van Baalen, 1998; van Boven and Weissing,
25 2004; Miller et al., 2007; Boots et al., 2013; Donnelly et al., 2015). In addition there are a
26 few models that have considered parasite (or enemy) diversity in the study of defence (Jokela

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27 et al., 2000; Poitrineau et al., 2003; Kada and Lion, 2015). Poitrineau et al. (2003) explored
28 defence against two natural enemies and examined how cross resistance (synergy in resistance)
29 influences optimal defence investment, while Jokela et al. (2000) focused on how the level of
30 parasite diversity impacts on the optimal level of defence allocation. Both studies consider
31 only evolutionary dynamics and do not incorporate ecological feedbacks so that the role of
32 life-histories that influence evolutionary outcomes through population dynamics is not clear.
33 In Kada and Lion (2015) which included a type of superinfection that did not involve stably
34 coexisting parasites at the host population scale (rather, a rare invading parasite lineage
35 superinfected a stably circulating parasite and vice versa), the co-evolutionary dynamics of
36 recovery resistance and virulence were studied. They found that superinfection can lead to
37 high virulence and high investment in defence but crucially, resistance developed to counter
38 one parasite did not simultaneously feedback to the prevalence of the other in the form of
39 superinfection modelled in Kada and Lion (2015). Here, we make a novel extension to these
40 studies by applying an eco-evolutionary approach to the question of how stable co-circulating
41 parasitic challenges determine natural selection for host resistance achieved through avoidance,
42 recovery and acquired immunity. For the first time in a framework that allows multi-parasite
43 coexistence at the host population scale and encompasses specific as well as non-specific
44 immune response we account for the complex ecological feedbacks between the dynamics of
45 multiple parasites and evolving resistance. In this way, we examine how traits such as host
46 lifespan determine patterns of optimal investment in host defence.

47 The framework of evolutionary invasion analysis (Metz et al., 1996; Geritz et al., 1998)
48 uses explicit ecological dynamics to derive fitness and provides tools for assessing the stability
49 of evolutionary trajectories. Here we use these methods to examine resistance evolution in
50 the presence of multiple parasites. This requires parasite coexistence, here referring to stable
51 persistence of more than one parasite at the host population scale. To achieve this we assume
52 a superinfection interaction, where individual hosts infected with a less virulent parasite
53 are susceptible to infection, with displacement of the original parasite by a more virulent
54 parasite (Nowak and May, 1994). Once co-existing multiple infections are incorporated in
55 host parasite models the question of the specificity of resistance naturally arises, and in

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56 this study we examine how the level of cross resistance impacts on the evolution of host
57 resistance to infection. The ecological derivation of host fitness for a range of disease and
58 host characteristics provides clear insight into the effect of co-circulating parasites on host
59 resistance, and demonstrates consistent patterns of investment regardless of the type, or actual
60 mechanism, of resistance.

61 There has been considerable interest in how host immune investment differs between
62 populations of contrasting lifespans (van Boven and Weissing, 2004; Miller et al., 2007; Boots
63 et al., 2013; Donnelly et al., 2015). In particular, a naive view of immune investment is that it
64 will increase monotonically as lifespan and hence exposure increases. However, recent theory
65 using evolutionary invasion analysis has shown that when ecological feedbacks are included
66 the relationship between life-span and immune investment can be complex (van Boven and
67 Weissing, 2004; Miller et al., 2007; Boots et al., 2013; Donnelly et al., 2015). However, as yet
68 none of this theory has taken account of parasite diversity. Here, by incorporating ecological
69 dynamics we achieve a key aim of our study: an examination of how investment in resistance
70 varies with host lifespan when hosts are challenged by multiple parasites.

71

2. Methods

72

(a) Epidemiological Model

73 We assume a host structure based on susceptible, infected, and recovered/immune sub-
74 populations (Kermack and McKendrick, 1927; Macdonald, 1957; Anderson and May, 1979).
75 We extend the classical framework so that susceptible hosts, with density X , can be infected
76 by either hosts with a focal infection, Y_1 or a co-circulating infection, Y_2 . Hosts can recover and
77 gain life-long immunity to the focal infection, Z_1 and related to this the host may be infected
78 by the co-circulating parasite but immune to the focal parasite, $Y_2^{Z_1}$. We allow therefore for
79 a range of resistance mechanisms (to the focal parasite) in the presence of a co-circulating
80 parasite but for simplicity there is no acquired immunity to the co-circulating parasite, see
81 figure 1 for schematic depiction. Nevertheless immunity to the focal parasite and resistance in

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82 general can carry over to the co-circulating parasite if it is non-specific. The epidemiological
 83 dynamics are governed by the following equations:

$$\frac{dX}{dt} = aH - qH^2 - bX - \beta_1XY_1 - \beta_2X(Y_2 + Y_2^{Z1}) + (1 - \nu_1)\gamma_1Y_1 + \gamma_2Y_2 \quad (1)$$

$$\frac{dY_1}{dt} = \beta_1XY_1 - (\alpha_1 + b + \gamma_1)Y_1 - s\beta_2Y_1(Y_2 + Y_2^{Z1}) \quad (2)$$

$$\frac{dY_2}{dt} = \beta_2X(Y_2 + Y_2^{Z1}) - (\alpha_2 + b + \gamma_2)Y_2 + s\beta_2Y_1(Y_2 + Y_2^{Z1}) \quad (3)$$

$$\frac{dZ_1}{dt} = \nu_1\gamma_1Y_1 - bZ_1 - \sigma\beta_2Z_1(Y_2 + Y_2^{Z1}) + \gamma_2Y_2^{Z1} \quad (4)$$

$$\frac{dY_2^{Z1}}{dt} = \sigma\beta_2Z_1(Y_2 + Y_2^{Z1}) - (\alpha_2 + b + \gamma_2)Y_2^{Z1} \quad (5)$$

84

85 All parameters are non-negative and the total host density is given by $H = X + Y_1 + Y_2 +$
 86 $Y_2^{Z1} + Z_1$. All hosts produce susceptible offspring at rate a which is limited by intra-specific
 87 crowding, q . Hosts die at natural death rate b . In addition, infected hosts suffer additional
 88 disease induced mortality (virulence) at rate α_1 for the focal parasite and α_2 for the co-
 89 circulating parasite. The dynamics of transmission and recovery are shown in schematic form
 90 in Figure 1. In detail we assume that transmission of infection is a mass action process
 91 between susceptible and infected types, with transmission coefficient β_1 for the focal infection
 92 and β_2 for the co-circulating infection. Virulence is assumed to be correlated with the rate
 93 at which parasites exploit individual hosts. As a consequence, individuals infected with the
 94 less virulent parasite are susceptible to infection by the more virulent parasite (since the
 95 competitive advantage of high host exploitation leads to competitive replacement within the
 96 host i.e. *superinfection*, see e.g. Nowak and May (1994)). If $\alpha_2 > \alpha_1$ the more aggressive co-
 97 circulating parasite superinfects the focal parasite and this is the situation represented by
 98 equations 1 – 5 and depicted as model 1 in figure 1. If $\alpha_1 < \alpha_2$ the focal parasite is more
 99 virulent and superinfects the co-circulating one and this is depicted as model 2 in figure 1 (for
 100 brevity the equations for this model are not shown but it is simply the above model with the

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101 direction of superinfection reversed and a transmission coefficient for the superinfection term
102 of β_1 rather than β_2). The superinfection coefficient s controls the strength of the interaction
103 and for our purposes $0 \leq s \leq 1$. Infected hosts recover at rate γ_1 from the focal infection and
104 γ_2 from the co-circulating infection, with a proportion of recoveries from the focal infection,
105 $\nu_1 \in (0, 1)$, becoming immune to the focal parasite and the remaining individuals returning to
106 a susceptible state. Immunity to the focal parasite can carry over to the co-circulating parasite
107 if it is non-specific. This occurs if $\sigma < 1$ and implies that immunity to the focal parasite reduces
108 the likelihood of infection to the co-circulating parasite, see figure 1 which shows that infection
109 by the co-circulating parasite of class Z_1 occurs at σ the rate of that of X .

110 This general model form can be used to capture a wide range of classical infection
111 scenarios. For example, if $\nu_1 = 0$ the model represents a Susceptible–Infected–Susceptible
112 (SIS) framework, where there is no immune memory and recovered individuals are
113 completely susceptible to both infections. On the other hand if $\nu_1 = 1$ we have the
114 Susceptible–Infected–Recovered (SIR) model with specific ($\sigma = 1$) or non-specific ($\sigma < 1$) life-
115 long immunity (though, for simplicity, the structure due to the co-circulating parasite remains
116 *SIS*). In this SIR example specificity (of acquired immunity) is denoted by σ i.e. if σ is high
117 then specificity is high. In all the other forms of resistance, specificity is denoted by c , and is
118 defined as a parameter in the host trait that resists the co-circulating infection (i.e. $\beta_2 = \beta_2(c)$
119 for avoidance and $\gamma_2 = \gamma_2(c)$ in the case of recovery) and here high values of c correspond to low
120 specificity (see later for more details). The fundamental forms of host defence can be defined
121 as follows (Boots et al., 2013): (i) avoidance reduces the probability of becoming infected and
122 resistant hosts therefore have a lower transmission rate (β_1), (ii) recovery increases the rate of
123 clearance of infection (γ_1) and (iii) acquired immunity increases the probability of recovering
124 to a life-long immune state (ν_1). We first consider routes of innate resistance, i.e. avoidance
125 and recovery (*i* and *ii* above) in an SIS setting, then in an SIR setting with specific life-long
126 immunity and later evolution of acquired immunity itself.

7

127 (b) Population Dynamics

128 A key measure of the ability of a parasite to spread in a host population is R_0 , the basic
129 reproduction number, given here by

$$R_0^i = \beta_i X^0 / (\alpha_i + b + \gamma_i) \quad (6)$$

130 for parasite i in the absence of the alternative parasite. In equation 6 X^0 represents the
131 equilibrated density of susceptible hosts in the absence of any infection (i.e. the host carrying
132 capacity, $X^0 = (a - b)/q$). A second key measure is endemic disease prevalence, the frequency
133 of infected individuals in the equilibrium host population. In single infection models of this
134 type, whether the population structure is SI , SIS , SIR (i.e. our model with $s = 0$) or $SIRS$,
135 prevalence at the endemic equilibrium satisfies,

$$\alpha \frac{Y}{H} = a - qH - b \quad (7)$$

136 i.e. prevalence scaled by virulence equals per capita host population turnover (i.e. density
137 dependent net reproduction). However, when there are two infections in the population, as
138 per the model represented by equations 1 – 5, per capita turnover at equilibrium equals the
139 sum of the prevalences of the two infections weighted by their respective rates of virulence,

$$\alpha_1 \frac{Y_1}{H} + \alpha_2 \frac{Y_2}{H} = a - qH - b \quad (8)$$

140 Therefore, as per single infection models, equilibrium infection in the host population is
141 determined by the supply of susceptible individuals (i.e. turnover) but with the key difference
142 that host turnover is shared amongst the multiple infections. One consequence of equation 8 is
143 that coexistence of parasites means that equilibrium prevalence of any one parasite is always
144 less than it would be if it were circulating in the host population alone. A condition for the

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145 stable coexistence of parasites at the host population scale can be found in Nowak and May
146 (1994) for a similar model.

147 *(c) Trade-off*

148 There is strong empirical evidence for the association of resistance with physiological costs
149 through the diversion of resources to the development and maintenance of the resistance. For
150 example, in Fuxa and Richter (1989) the percentage of eggs that hatch as well as the number
151 produced per female were all lower in fall armyworm lines selected for resistance to NPV.
152 Longer development time, reduction in egg viability as well as an increase in pupal weight
153 were a consequence of selection for resistance to a granulosis virus in *Plodia interpunctella*
154 (Boots and Begon, 1993). There is also evidence of reduced larval competitive ability in
155 immune-selected *Drosophila melanogaster* (Kraaijeveld and Godfray, 1997). Taken together
156 these studies represent a sound basis for assuming that costs to resistance can be manifested
157 in reduced host reproduction or reduced competitive ability. In this study we assume an
158 association between level of resistance and reproduction rate such that recovery, avoidance
159 and acquired immunity are all positive decreasing functions of host reproduction rate. This is
160 consistent with the majority of previous studies that examine the evolution of resistance to
161 parasites (see Boots et al. (2009)).

162 *(d) Specificity of Immune Response*

163 We begin by considering an *SIS* framework where the focal parasite is less virulent
164 than the co-circulating parasite (i.e. $\alpha_1 < \alpha_2$). Hosts invest in costly resistance, $0 \leq \theta(a) \leq 1$,
165 through avoidance of the focal infection (i.e. $\hat{\beta}_1 = \beta_1(1 - \theta(a))$) and resistance may carry
166 over to the co-circulating infection depending on the specificity of resistance ($0 \leq c \leq 1$, when
167 $c = 0$ the resistance is specific to the focal infection), i.e. $\hat{\beta}_2 = \beta_2(1 - c\theta(a))$). As c increases
168 the resistance becomes more general. Alternatively resistance can be through recovery (i.e.
169 $\hat{\gamma}_1 = \gamma_1(1 + \theta(a))$ and $\hat{\gamma}_2 = \gamma_2(1 + c\theta(a))$). Similarly the focal infection can be more virulent
170 than the co-circulating parasite for each of the above cases (i.e. $\alpha_1 > \alpha_2$). When it comes to
171 an *SIR* framework we consider all of the above cases but, for brevity, only present results for

172 cases where the focal parasite is less virulent than the co-circulating parasite. Finally in an
173 *SIR* framework resistance may be through acquired immunity, corresponding to $\hat{\nu}_1 = \theta(a)\nu$.
174 For convenience we view specificity of acquired immunity not in terms of the probability
175 of clearance of the co-circulating infection to an immune state, but rather as the decrease
176 in transmission of the co-circulating infection to individuals who are immune to the focal
177 infection. For this reason, specificity in acquired immunity is a fixed coefficient, σ , in equations
178 4-5 with $\sigma = 1$ when resistance is specific or $\sigma < 1$ when it is not specific. For simplicity, we
179 do not allow the less intuitive case where σ exceeds 1 (i.e. resistance developed to counter a
180 focal parasite is more effective against a co-circulating parasite). See table 1 for a summary
181 of the cases studied.

182 3. Results

183 Using the next generation method (Diekmann et al., 1990; van den Driessche and Watmough,
184 2002; Hurford et al., 2010), see *supporting information S1*, we derive a proxy for invasion
185 fitness, denoted $s_r(m)$, for the set of models outlined in the *methods* section for each of the cases
186 detailed in table 1. Under the assumptions of adaptive dynamics (Metz et al., 1996; Geritz
187 et al., 1998) a population will evolve through small, rare mutations in the direction of the
188 gradient of the invasion fitness until an evolutionary singularity, where the mutant derivative
189 of invasion fitness is zero, is reached (alternatively the evolving population may reach the
190 limit of the phenotypic range). Evolutionary singularities can be classified according to their
191 evolutionary and convergence stability properties (Metz et al., 1996). If a singularity is both
192 evolutionary and convergence stable it is an uninvadable evolutionary attractor and an end
193 point of evolution (Eshel, 1983). We wish to examine how the position of such singularities,
194 which is determined by selection pressures, change when model parameters, in particular
195 host lifespan, are varied. The results presented throughout are obtained using mathematical
196 software for symbolic computation (Maple). They are additionally supported with simulations
197 of the adaptive dynamics process whereby population dynamics of interacting resident and
198 mutant host sub-populations are numerically solved with mutants, of similar effect to residents,

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199 randomly introduced on a time scale slower than that of the ecological dynamics (for further
200 detail on adaptive dynamics simulations see Donnelly et al. (2015)).

201 For *SIS* innate resistance we use the invasion fitness proxy, $s_r(m)$, for hosts bearing a
202 mutant investment phenotype, $\theta^m(a^m)$, to locate evolutionary attractors and to show how the
203 evolved level of the resistance phenotype varies with host lifespan, see figure 2a – d. This can
204 be shown when resistance is specific (black curves, figure 2a – d) and also when resistance
205 is non-specific (grey curves, figure 2a – d). It can also be shown when resistance is through
206 avoidance (figure 2a & b, i.e. cases 1 – 4 table 1) and when resistance is through recovery
207 (figure 2c & d, i.e. cases 5 – 8 table 1), when the resistance is developed primarily to counter
208 a relatively avirulent focal infection (figure 2a & c) or to counter a relatively virulent focal
209 infection (figure 2b & d). The resulting graphs indicate that regardless of the route of innate
210 resistance, investment increases with host lifespan except when it is specific to an avirulent
211 infection.

212 Focusing on the case where resistance evolves to counter an avirulent focal infection we
213 show that these results extend to an *SIR* framework, arising through the presence of acquired
214 immunity specific to the avirulent focal infection (i.e. $\sigma = 1$), see figure 3a & b for avoidance,
215 i.e. cases 9 – 10 table 1, and see figure 3c & d for recovery, i.e. cases 11 – 12 in table 1. As the
216 proportion of immune individuals in the population increases (due to changing the value of ν ,
217 i.e. the probability of inducing acquired immunity upon recovery, from $\nu = 0$ represented by a
218 black curve to $\nu = 1$ represented by a light grey curve) there is no qualitative change, though
219 the overall magnitude of investment tends to decrease (because recovery to immunity decreases
220 prevalence, reducing the need for resistance). Finally, we analyse optimal acquired immunity
221 developed to counter the less virulent parasite. Here, the mutant investment phenotype is
222 $\nu_1^m(a^m)$ and immunity extends to the virulent infection if $\sigma < 1$. When immunity is non-
223 specific, investment increases with increasing lifespan, when immunity is specific investment
224 decreases with increasing lifespan, see figure 4a, i.e. cases 13 – 14 in table 1.

225 As a whole, the results show that resistance to a relatively avirulent focal infection in the
226 presence of a co-circulating virulent infection varies with host lifespan in a manner that is
227 dependent on the specificity, but significantly, is not dependent on the route of resistance.

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228 In general, investment increases as the level of specificity in resistance decreases. We provide
229 a further illustration of this in figure 4*b – d* where curves are given for different lifespans
230 for evolving avoidance, 4*b*, recovery, 4*c* and acquired immunity, 4*d*, respectively. Investment
231 is greater at low lifespans when resistance is specific (*c* is low) but investment is greater at
232 long lifespans when resistance is relatively general (*c* is high). Therefore, there is a level of
233 specificity for each form of resistance below which investment decreases with increasing host
234 lifespan and above which investment increases with increasing host lifespan. This transition
235 occurs for relatively small values of specificity for the innate forms of resistance (i.e. avoidance
236 and recovery) compared to the relatively high value of specificity at which it occurs for acquired
237 immunity.

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4. Discussion

239 Hosts are typically challenged by multiple parasites, but to date theory on the evolution of
240 resistance has mostly focused on single infections. We have developed a series of models that
241 have examined the impact of multiple parasites on the evolution of resistance with explicit
242 feedbacks between the ecological and evolutionary dynamics. Our key assumption is that
243 parasites coexist as a consequence of superinfection which assumes that a more virulent
244 parasite can replace a less virulent parasite within an individual host. Our results show
245 that co-circulating parasitism dramatically impacts on the evolution of resistance to a focal
246 parasite. In particular, the specificity of the resistance with respect to co-circulating parasites
247 is critical to the outcome. A key, intuitive, result is that investment in resistance increases
248 as the immune response becomes more general. This finding is related to those of previous
249 studies that considered the impact of multiple enemies on resistance evolution in the absence
250 of ecological dynamics. Jokela et al. (2000) considered the evolution of resistance for different
251 levels of parasite diversity. They showed that specific host resistance is less effective when
252 faced with a diverse range of parasites and therefore that host resistance increases as parasite
253 diversity decreases. Poitrineau et al. (2003) examined the evolution of defence to two separate
254 enemies and considered scenarios of synergy or interference in defence response, showing that
255 investment increases as the level of synergy increases. Our finding that resistance increases
256 as immune investment becomes more general is related to these results, and extends them to
257 systems including explicit feedbacks between the ecological and evolutionary dynamics.

258 Risk of infection by pathogens and parasites has led hosts to evolve a wide range of defence
259 mechanisms from behavioural strategies (Joop et al., 2014) to the bio-chemical cascades of the
260 complement system and the memory B and T cells of acquired vertebrate immunity (Schmid-
261 Hempel, 2002; Frank, 2002). Intuition suggests that the longer a host lives the more it is
262 likely to benefit from immunity. This observation has been used to explain macro-evolutionary
263 patterns of investment such as the lack of acquired immunity in invertebrates (Ricklefs and
264 Wikelski, 2002; Tieleman et al., 2005) and is supported by a number of empirical studies.
265 For example, a positive correlation between immunity and lifespan in avian hosts has been

266 demonstrated for humoral, cell mediated, and constitutive immune responses (Ardia, 2005;
267 Tella et al., 2002; Versteegh et al., 2012; Lee et al., 2008). Theoretical models that have
268 examined the evolution of resistance in the face of a single parasite make the assumptions
269 underlying this intuition explicit. They have provided some support for this pattern but also
270 deviate from it in important ways (van Boven and Weissing, 2004; Miller et al., 2007; Boots
271 et al., 2013; Donnelly et al., 2015). For example, in contradiction to the intuition, optimal
272 resistance in hosts capable of permanent acquired immunity can be maximal at intermediate
273 lifespan (Boots et al., 2013; Donnelly et al., 2015) and in the case of innate resistance this can
274 be true even in the absence of acquired immunity (Miller et al., 2007; Donnelly et al., 2015).
275 However, a key aspect of these studies is that host populations are burdened by only one
276 infection. Here we address the key question of how optimal investment changes with lifespan
277 in the face of co-circulating parasites.

278 When a host population is challenged by multiple parasites the investment in immunity
279 is critically dependent on the specificity of the defence. When the resistance is relatively
280 general, then investment increases with host lifespan. In contrast, when immunity is specific
281 the pattern of investment relative to host lifespan depends on the nature of the co-circulating
282 parasite. If the co-circulating parasite is less aggressive in exploiting the host than the focal
283 infection, then investment increases with lifespan. However, if the co-circulating parasite is
284 more aggressive, then specific immune investment decreases as host lifespan increases because
285 the ratio of infected individuals with the co-circulating parasite to individuals with the focal
286 parasite increases (since there is a higher incidence of superinfection at high host lifespans).
287 These patterns are true in our model when the evolving resistance is innate in a host incapable
288 of immune memory, is innate in a host responding additionally with immune memory or when
289 the evolving resistance is itself acquired. This is an important insight since it shows that
290 the life-history patterns will depend on the nature of the co-circulating parasite, and the
291 specificity of the response, but not the mode of resistance itself, which is in stark contrast to
292 single infection models where patterns fundamentally depend on the type of resistance (i.e.
293 innate vs acquired) but not the exact mode (for example avoidance vs recovery within the
294 innate type) (van Boven and Weissing, 2004; Miller et al., 2007; Boots et al., 2013; Donnelly

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295 et al., 2015). Therefore, a key implication of our work is that, in contrast to single infection
296 models, the classic idea that more investment should occur in longer-lived hosts is generally
297 supported when there are multiple parasites.

298 What are the underlying processes that lead to these different findings (i.e. in the effect of
299 host lifespan on optimal immune defence) when host are faced by multiple rather than single
300 parasites? Single infection models deviate from the intuition that investment increases with
301 lifespan because of two important effects that are undermined by the presence of co-circulating
302 infections (see detailed analysis in Donnelly et al. (2015)). In single infection models, optimal
303 investment that is maximal at intermediate lifespans (Miller et al., 2007) is a hallmark of
304 innate resistance because it is characterised by the return or maintenance of individuals to
305 a susceptible state as opposed to the conversion of them into an immune state (Donnelly
306 et al., 2015). Since susceptible individuals are vulnerable to reinfection which is likely at high
307 levels of prevalence, the benefit of innate resistance is low at high prevalence and therefore low
308 at high lifespans (in *SIS* systems prevalence increases with increasing host lifespan). With
309 multiple parasites and superinfection, more virulent parasites take over hosts infected with less
310 virulent parasites. When hosts live longer, the period during which these conversions occur is
311 longer and this favours the virulent parasite. However, the higher virulence of these parasites
312 also acts to reduce the infectious period and as a consequence, prevalence does not rise to the
313 high levels that are seen in equivalent single infection models. As such, optimal investment
314 increases with lifespan in the face of multiple infections and superinfection in models where it
315 would be maximal at intermediate lifespans without the co-circulating infection because the
316 prevalence of the focal parasite is strongly limited due to the share of susceptible hosts taken
317 by the co-circulating parasite, see equation 8.

318 There is a second process that comes into play once there is permanent immunity to the
319 parasite. In single infection models where the host is long-lived, permanent immunity leads
320 to high host density. When host density approaches the carrying capacity there is little host
321 turnover and prevalence levels are low (see equation 7). Therefore long-lived host populations
322 with permanent immunity have a relatively small risk of infection and will evolve weaker
323 resistance (Miller et al., 2007; Boots et al., 2013; Donnelly et al., 2015). For this reason a

324 long-lived immune class can decrease the need for immunity in general at high lifespans.
325 However, crucially, when there are multiple infections the impact of an especially long-living
326 class arising from recovery to a permanent immune state will be substantially less because the
327 immune individuals will be susceptible (at least to some degree) to infection by co-circulating
328 parasites. Therefore, when acquired immunity evolves in the face of multiple parasites and
329 superinfection, just as for innate immunity, optimal investment is higher in long-lived host
330 populations in models where it would be maximal at intermediate lifespans without the co-
331 circulating infection.

332 There is one important exception to our general prediction that investment in immunity
333 rises with host lifespan. When the co-circulating parasite is more virulent and the evolving
334 response is specific to the less virulent focal parasite, then investment decreases with increasing
335 lifespan. Two simple interactions are responsible for this result: 1) if the co-circulating parasite
336 is more virulent then it is the superinfector and it is favoured at high lifespans. Therefore the
337 benefit of specific resistance to the focal parasite, which by definition is not effective against
338 the co-circulating parasite, diminishes as lifespan increases. 2) Responding through resistance
339 to the less virulent focal parasite can actually increase the risk of infection with the more
340 virulent co-circulating parasite (since there is an increase in the availability of susceptible
341 individuals for the co-circulating infection). Therefore, taken together, there is little fitness
342 benefit to investing resources into fighting the lesser of your enemies and specific resistance
343 to the less aggressive parasite is not favoured at high host lifespans under an assumption of
344 superinfection. We note that several of these interactions are a consequence of the interplay
345 between strain prevalence, their relative virulence and virulence associated superinfection. For
346 this reason it is important to acknowledge that alternative mechanisms of coexistence may
347 lead to different results.

348 In conclusion, there are multiple factors that determine the relationship between optimal
349 investment in immunity and host lifespan. This results in a variety of patterns for single
350 infection models (Miller et al., 2007; Boots et al., 2013; Donnelly et al., 2015; van Boven and
351 Weissing, 2004) but here we have shown that this intricacy can be lost when diversity in the

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352 parasite burden of the host population is considered. Instead it is the classic idea that long-
353 lived hosts invest more in immunity that is generally supported when this key aspect of natural
354 populations is included. Our main focus has been on how multiple parasites impact on the
355 relationship of host lifespan to resistance, but more generally our inclusion of realistic ecological
356 feedbacks in evolutionary models of resistance extends results of previous multi-enemy models
357 that assumed constant rather than dynamic populations (Poitrineau et al. (2003); Jokela
358 et al. (2000)). Future work should relax the assumption that superinfection occurs and may
359 therefore involve different population feedbacks whose effects should be assessed. Such co-
360 infection models would be more challenging theoretically, but the importance of including
361 ecological feedbacks is emphasized by our work. Furthermore, there is a need for a variety
362 of defence interactions against a range of enemies beyond resistance to two parasites to be
363 examined in this broader eco-evolutionary context.

364

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Case	Resistance type under evolution	Infection hierarchy	Specificity	Figure
1	SIS avoidance ($\beta_1(a), \nu = 0$)	acute co-circulating ($\alpha_1 < \alpha_2$)	specific, $c = 0$	see figure 2a
2	SIS avoidance ($\beta_1(a), \nu = 0$)	acute co-circulating ($\alpha_1 < \alpha_2$)	general, $c > 0$	see figure 2a
3	SIS avoidance ($\beta_1(a), \nu = 0$)	acute focal ($\alpha_1 > \alpha_2$)	specific, $c = 0$	see figure 2b
4	SIS avoidance ($\beta_1(a), \nu = 0$)	acute focal ($\alpha_1 > \alpha_2$)	general, $c > 0$	see figure 2b
5	SIS recovery ($\gamma_1(a), \nu = 0$)	acute co-circulating ($\alpha_1 < \alpha_2$)	specific, $c = 0$	see figure 2c
6	SIS recovery ($\gamma_1(a), \nu = 0$)	acute co-circulating ($\alpha_1 < \alpha_2$)	general, $c > 0$	see figure 2c
7	SIS recovery ($\gamma_1(a), \nu = 0$)	acute focal ($\alpha_1 > \alpha_2$)	specific, $c = 0$	see figure 2d
8	SIS recovery ($\gamma_1(a), \nu = 0$)	acute focal ($\alpha_1 > \alpha_2$)	general, $c > 0$	see figure 2d
9	SIR avoidance ($\beta_1(a), \nu > 0$)	acute co-circulating ($\alpha_1 < \alpha_2$)	general, $c > 0$	see figure 3a
10	SIR avoidance ($\beta_1(a), \nu > 0$)	acute co-circulating ($\alpha_1 < \alpha_2$)	specific, $c = 0$	see figure 3b
11	SIR recovery ($\gamma_1(a), \nu > 0$)	acute co-circulating ($\alpha_1 < \alpha_2$)	general, $c > 0$	see figure 3c
12	SIR recovery ($\gamma_1(a), \nu > 0$)	acute co-circulating ($\alpha_1 < \alpha_2$)	specific, $c = 0$	see figure 3d
13	SIR acquired immunity ($\nu_1(a)$)	acute co-circulating ($\alpha_1 < \alpha_2$)	general, $\sigma < 1$	see figure 4a
14	SIR acquired immunity ($\nu_1(a)$)	acute co-circulating ($\alpha_1 < \alpha_2$)	specific, $\sigma = 1$	see figure 4a

Table 1. Table of evolving resistance scenarios detailing the infection framework and type of resistance to the focal parasite that can evolve.

1

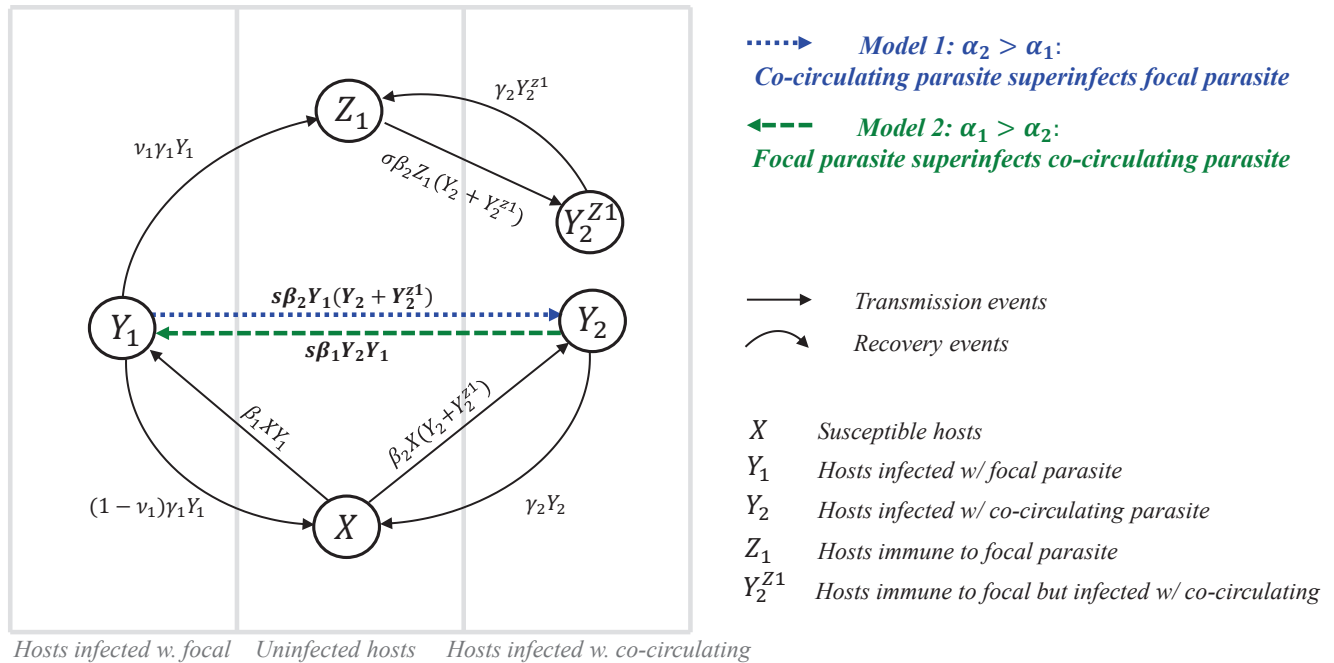


Figure 1. Flow chart showing epidemiological transitions for a situation where a host can recover to immunity against a focal parasite but where there is in addition a second parasite co-circulating in the host population (for simplicity there is no immunity to the co-circulating parasite). Parasite coexistence in the host population (and not within individual hosts) is facilitated by virulence associated superinfection. In *model 1* the co-circulating parasite (represented by the density of hosts infected with that parasite, Y_2) is more virulent than the focal parasite (represented by Y_1) and therefore individuals move from the focal infection class Y_1 to the co-circulating infection class Y_2 when the co-circulating infection is transmitted to an individual infected with the focal infection. In *model 2* the focal parasite is more virulent than the co-circulating parasite and therefore individuals move from the co-circulating infected class Y_2 to the focal infected class Y_1 when the focal infection is transmitted to an individual already infected with the co-circulating infection. Birth and death of hosts also occur but are omitted here for simplicity.

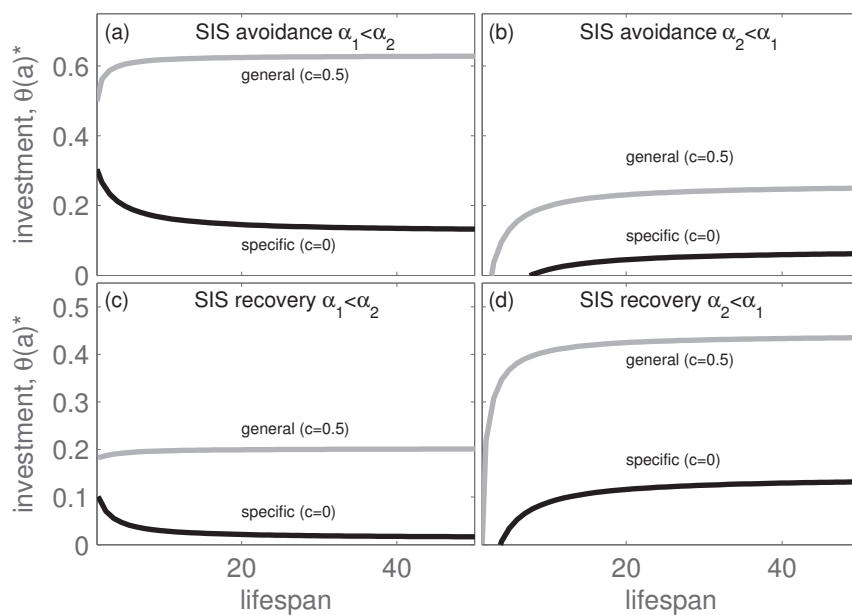


Figure 2. Optimal investment in specific and non-specific resistance in an *SIS* structured host population. In (a) and (b) the function of the resistance is avoidance. In (c) and (d) the function of the resistance is recovery (i.e. increased rate of disease clearance). In (a) and (c) resistance is evolved to counter the relatively avirulent infection while in (b) and (d) resistance is evolved to counter the relatively virulent infection. In all cases both infections will be equally countered when resistance is completely general ($c = 1$). Parameters were: $q = 0.1$ $\beta_1 = 2$ $\beta_2 = 4$ $\alpha_1 = 2$ $\alpha_2 = 8$ with $s = 0.45$, in the case of evolving avoidance $\hat{\beta}_i = \beta_i(1 - 0.5\theta)$ with $\gamma_1 = \gamma_2 = 0.35$ and in the case of evolving recovery $\hat{\gamma}_i = \gamma_i(1 + 2.5\theta)$ with $\beta_1 = \beta_2 = 1$. In all cases investment in resistance relates to reproduction according to $\theta(a) = 1 - (a^\mu)/(a_{max}^\mu)$ with $a_{max} = 1.9$ and $\mu = 12$.

1

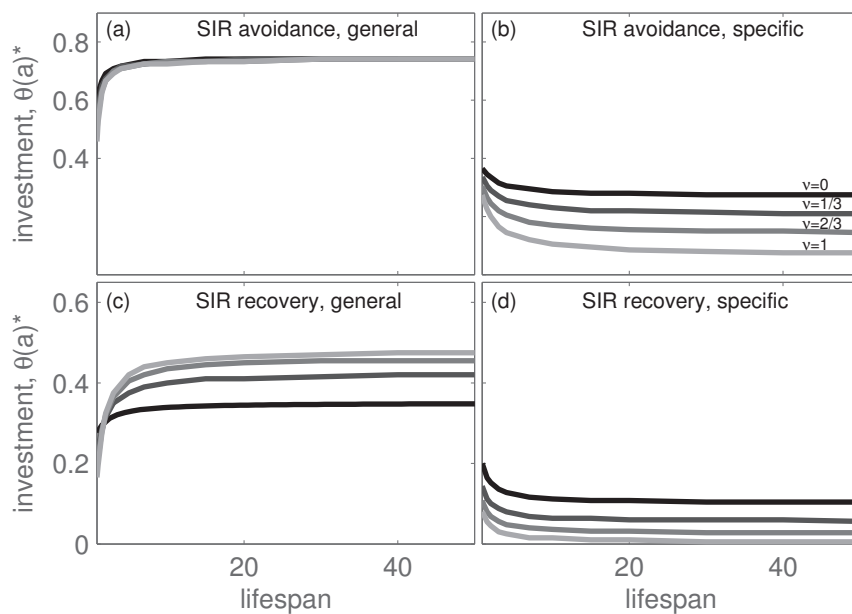


Figure 3. Optimal investment in specific and non-specific resistance in an *SIR* structured population developed to counter the relatively avirulent infection. In (a) and (b) resistance is through avoidance while in (c) and (d) resistance is through increased recovery. The proportion of recovered individuals entering the immune class is ν while the proportion returning to a susceptible state is $1 - \nu$. As ν increases above 0 towards 1 the population becomes *SIR* (dark grey through to light grey curves). In (a) and (c) $c = 0.5$ while in (b) and (d) $c = 0$. In (a) and (b) the trade-off exponent is $\mu = 18$, in (c) and (d) $\mu = 24$. Note, $\alpha_1 < \alpha_2$ and $\sigma = 1$ throughout, for other parameter values see caption of figure 2.

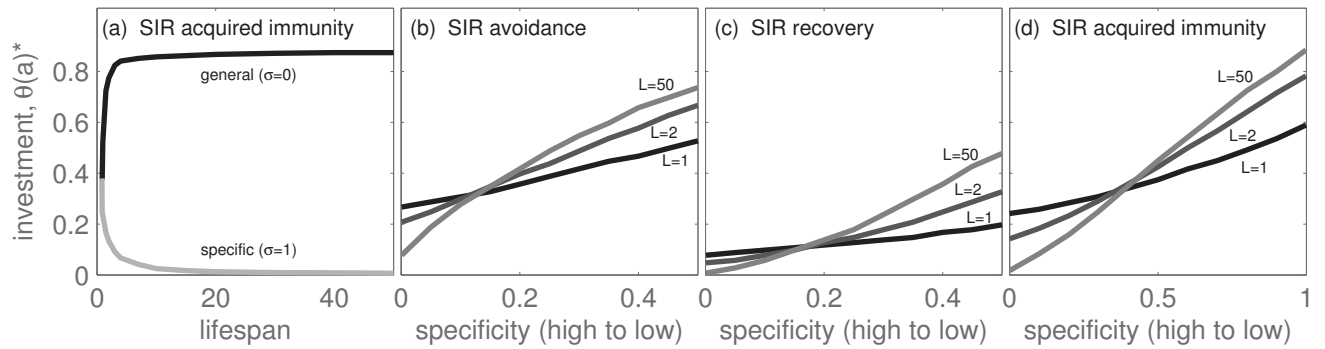


Figure 4. Optimal investment in specific (grey curve) and non-specific (black curve) acquired immunity developed to counter the relatively avirulent infection is given in (a). In (b), (c) and (d) optimal investment for a range of values of specificity is given for avoidance, recovery and acquired immunity respectively in an *SIR* structured population. In each case three separate curves are displayed for the following values of host lifespan, $1/b = 1$ (black curve), $1/b = 2$ (dark grey curve) and $1/b = 50$ (grey curve). (b), (c) and (d) indicate that there is a critical value of specificity below which, where resistance is general, high lifespans are associated with higher investment than low lifespans. On the other hand, beyond this critical value, where resistance is specific to the relatively avirulent infection, low lifespans are associated with higher investment than high lifespans. In (a), (c) and (d) the trade-off exponent is $\mu = 24$ and in (b) $\mu = 18$. In (b) and (c) $\sigma = 1$ and $\nu = 1$. Note, $\alpha_1 < \alpha_2$ and for other parameter values see caption of figure 2.

1

Supporting Information S1 Next Generation Matrix

1 Invasion fitness (Metz et al., 1996; Geritz et al., 1998) can be derived through a linear stability
 2 analysis of a mutant ecological model in a population consisting of residents at their population
 3 attractor (usually a stable point equilibrium). If the steady state corresponding to no mutants
 4 but positive residents is unstable then the mutant can invade. Hence, eigenvalues (of the
 5 coefficient matrix, A , of the linearised system, $\dot{x} = Ax$) determine the invasion potential
 6 of the mutant and in particular the dominant eigenvalue is a measure of invasion fitness.
 7 When a mutant host invades a resident population that is challenged by multiple infections,
 8 high dimensionality prevents direct derivation of invasion fitness. Instead, following the next
 9 generation method (Diekmann et al., 1990), the linearised system can be decomposed into
 10 two matrices, $A = F - V$. If the largest absolute value of the eigenvalues of the matrix FV^{-1}
 11 is greater (smaller) than 1, then by the next generation theorem (van den Driessche and
 12 Watmough, 2002; Hurford et al., 2010) the invasion fitness is positive (negative), but note
 13 that conditions on the matrices F and V apply, see van den Driessche and Watmough (2002).

14 For general resistance as described in the main text, i.e. allowing for the possibility
 15 of evolving avoidance ($\beta_1(a^m), \beta_2(a^m)$), or evolving recovery ($\gamma_1(a^m), \gamma_2(a^m)$) or evolving
 16 acquired immunity ($\nu(a^m)$), the corresponding birth and death matrices are:

$$17 \quad F = \begin{bmatrix} a^m - qH^r & a^m - qH^r & a^m - qH^r & a^m - qH^r & a^m - qH^r \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{bmatrix},$$

18 $V =$

$$19 \quad \begin{bmatrix} \beta_1(a^m)Y_1^r + \beta_2(a^m)(Y_2^r + Y_{21}^r) + b & -(1 - \nu_1(a^m))\gamma_1(a^m) & -\gamma_2(a^m) & 0 & 0 \\ -\beta_1(a^m)Y_1^r & \alpha_1 + b + \gamma_1(a^m) + s\beta_2(a^m)(Y_2^r + Y_{21}^r) & 0 & 0 & 0 \\ -\beta_2(a^m)(Y_2^r + Y_{21}^r) & -s\beta_2(a^m)(Y_2^r + Y_{21}^r) & \alpha_2 + b + \gamma_2(a^m) & 0 & 0 \\ 0 & -\nu_1(a^m)\gamma_1(a^m) & 0 & b + \sigma\beta_2(a^m)(Y_2^r + Y_{21}^r) & -\gamma_2(a^m) \\ 0 & 0 & 0 & -\sigma\beta_2(a^m)(Y_2^r + Y_{21}^r) & \alpha_2 + b + \gamma_2(a^m) \end{bmatrix}$$

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