

# Superinfection and the coevolution of parasite virulence and host recovery

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## Abstract

Parasite strategies of host exploitation may be affected by host defence strategies and multiple infections. In particular, within-host competition between multiple parasite strains has been shown to select for higher virulence. However, little is known on how multiple infections could affect the coevolution between host recovery and parasite virulence. Here, we extend a coevolutionary model introduced by van Baalen (*Proc. R. Soc. B*, 265, 1998, 317) to account for superinfection. When the susceptibility to superinfection is low, we recover van Baalen's results and show that there are two potential evolutionary endpoints: one with avirulent parasites and poorly defended hosts, and another one with high virulence and high recovery. However, when the susceptibility to superinfection is above a threshold, the only possible evolutionary outcome is one with high virulence and high investment into defence. We also show that within-host competition may select for lower host recovery, as a consequence of selection for more virulent strains. We discuss how different parasite and host strategies (superinfection facilitation, competitive exclusion) as well as demographic and environmental parameters, such as host fecundity or various costs of defence, may affect the interplay between multiple infections and host–parasite coevolution. Our model shows the interplay between coevolutionary dynamics and multiple infections may be affected by crucial mechanistic or ecological details.

## Introduction

There is overwhelming evidence that host and parasite populations coevolve (Imhoof & Schmid-Hempel, 1998; Woolhouse *et al.*, 2002; Decaestecker *et al.*, 2007; Béréanos *et al.*, 2011). In particular, parasite strategies of host exploitation may affect the evolution of host defence traits, which in turn may feedback on the evolution of parasite life-history traits. Because of the complexity of such coevolutionary feedbacks, theoretical models are needed to shed light on the mechanisms that are likely to affect the joint evolution of host and parasite traits. However, most theoretical models typically assume that one of the two interacting species does not evolve, and the vast majority of evolutionary models consider that parasites evolve much faster than the host.

This is motivated by experimental data on the high mutation rates of microbial parasites (Clarke *et al.*, 1994; Moya *et al.*, 2004). However, host evolution rates are not always negligible, especially when parasites represent a major selective pressure for the hosts (Dawkins & Krebs, 1979). On the other hand, most models that consider the evolution of host traits in response to infection do not consider parasite evolution. A coevolutionary framework is therefore needed to further our understanding of the evolution of host–parasite interactions.

Various models have already investigated the coevolution of parasite virulence and host defence traits (van Baalen, 1998; Hochberg & van Baalen, 1998; Gandon & Michalakis, 2000; Gandon *et al.*, 2002b; Day & Burns, 2003; Restif & Koella, 2003). In particular, van Baalen (1998) studied the coevolution of parasite virulence and host recovery rate and showed that, for some parameter values, evolutionarily bistability was possible, with two potential outcomes: a low-virulence/no-recovery coevolutionary endpoint or a high-virulence/high-recovery outcome.

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However, van Baalen (1998)'s results rely on the assumption that infected hosts cannot be infected by more than one parasite strain. Yet, there is strong empirical evidence that most natural infections consist of multiple parasite strains or species (Read & Taylor, 2001; Balmer & Tanner, 2011). Furthermore, at a theoretical level, multiple infections have been shown to affect the evolution of parasite strategies of host exploitation, with the well-known result that within-host competition between co-infecting strains should lead to increased levels of virulence (Bremermann & Pickering, 1983; Antia *et al.*, 1994; Alizon *et al.*, 2013). This prediction has recently found some empirical support (López-Villavicencio *et al.*, 2007; Mideo, 2009). In general, however, the effect of multiple infections on virulence is predicted to depend on the details of within-host interactions (e.g. cooperative vs. competitive interactions, West & Buckling, 2003) and on epidemiological feedbacks (Frank, 1992; van Baalen & Sabelis, 1995; Brown & Grenfell, 2001; Boots *et al.*, 2009; Alizon & Lion, 2011; Lion, 2013).

In this article, we investigate the impact of multiple infections on the coevolution of parasite virulence and host defence. For the sake of simplicity, we do not explicitly track co-infections, but we use the superinfection framework (Nowak & May, 1994; Gandon *et al.*, 2001, 2002a; Adler & Mosquera, 2002). Multiple infections are thus implicitly taken into account by assuming rapid competitive exclusion of one strain by another. Hosts have a variety of defence strategies against parasites. Here, we focus on recovery (i.e. the ability to clear the disease), which can be thought of as the host immune system's response and causes a strong negative impact on parasite fitness (Roy & Kirchner, 2000; Mackinnon & Read, 2004).

Using adaptive dynamics methodology (Metz *et al.*, 1996; Dieckmann & Law, 2000), we study the coevolution of parasite virulence and host recovery rate. Following van Baalen (1998), we use a reference Susceptible-Infected-Susceptible (SIS) model to explore this question. We derive the expressions for the selection gradients on host and parasite traits when the susceptibility to superinfection is constant. Then, we investigate the coevolution of virulence and recovery under more complex scenarios.

First, we examine the effect of multiple infections on the coevolutionary dynamics when infected hosts experience reduced fecundity (called sterility virulence throughout) and when hosts pay an additional cost to up-regulate their immune system. Second, we extend our analysis to allow more virulent strains to have a higher probability of superinfection, thereby reflecting the impact of parasite growth on the outcome of within-host competition between strains. Third, we investigate what happens when investing into fighting against the first infection facilitates or hinders superinfection by another strain.

## Epidemiological model

We consider a classical SIS model (Hethcote, 2000). Hosts can be either susceptible ( $S$ ) or infected by the parasite ( $I$ ). Susceptible and infected hosts can reproduce at rates  $r_S$  and  $r_I$ , respectively, and their natural mortality rate is  $\mu$ . Hosts may become horizontally infected at rate  $\beta$ . Infected hosts can either die from the infection, at rate  $\alpha$ , or recover at rate  $\gamma$ . We further assume that the population is well-mixed, that is there is no spatial structure. With these assumptions, the model is described by the following system of differential equations:

$$\begin{cases} \frac{dS}{dt} = (r_S S + r_I I)[1 - \kappa(S + I)] - (\mu + h)S + \gamma I, \\ \frac{dI}{dt} = hS - (\mu + \alpha + \gamma)I, \end{cases} \quad (1)$$

where  $h = \beta I$  is the force of infection. Note that reproduction is assumed to be density dependent. The factor  $\kappa$  measures the intensity of competition between hosts for resources.

The host-parasite interaction can settle on either of two nontrivial epidemiological equilibria, depending on the basic reproductive ratio  $R_0$  of the parasite (i.e. the number of secondary infections caused by an infected host in a fully susceptible host population, see Appendix 1B, Anderson & May, 1991; Heesterbeek & Dietz, 1996). If  $R_0 < 1$ , the parasite goes extinct and the disease-free equilibrium  $((1 - \mu/r_S)/\kappa, 0)$  is reached. If  $R_0 > 1$ , the parasite will spread in the host population (Anderson & May, 1991; van den Driessche & Watmough, 2002), and the population will settle onto an endemic equilibrium (see Expression A1, in Appendix 1A). Because we are interested in host-parasite coevolution, we shall naturally focus on regions of parameter space where both species may coexist. Table 1 lists the main notations of our model and default values for parameters.

**Table 1** Summary of main notations.

Parameter	Description	Default value
$\mu$	Natural mortality	1
$\alpha$	Disease-induced mortality	
$\gamma$	Host recovery rate	
$\beta_0$	Maximal transmission rate	10
$h$	Force of infection	
$r_S, r_I$	Susceptible and infected host birth rate	
$r_m$	Maximal rate of host reproduction	2
$c$	Maintenance cost of defence	0.05
$c_{up}$	Up-regulation cost of defence	0
$\kappa$	Density dependence factor	0.01
$\sigma$	Susceptibility to superinfection	0.05
$\sigma'$	Within-host competitiveness	0
	between strains (i.e. dominance)	
$\varepsilon$	Relative fecundity of infected hosts	1

## Parasite and host fitness

### Parasite fitness

A common assumption in evolutionary epidemiology is that of a trade-off between transmission and virulence. The rationale is that parasite exploitation of the host has both fitness costs (host lifespan is reduced) and benefits (parasite transmission is enhanced). Following most earlier studies (Levin & Pimentel, 1981; Alizon *et al.*, 2009), we assume a concave trade-off between transmission and virulence. This implies that, as parasites exploit more severely their host, the benefits in transmission increase more slowly than the cost in virulence. In the remainder of this study, we use  $\beta(\alpha) = \beta_0\alpha/(1 + \alpha)$ , where  $\beta_0$  is a constant, for applications.

We consider a resident population infected by a parasite with virulence  $\alpha$ . Following classical adaptive dynamics methodology (Metz *et al.*, 1992; Geritz *et al.*, 1998), we assume that mutations are sufficiently rare for the population to reach the endemic equilibrium  $(\hat{S}, \hat{I})$  on an ecological timescale. Furthermore, we assume the population to be at most dimorphic, with a resident strain with virulence  $\alpha$  and a mutant strain with virulence  $\alpha'$ . We allow for multiple infections, but for the sake of simplicity, we assume a superinfection process: upon reinfection, one strain is assumed to immediately take over the host. Following Gandon *et al.* (2001), we introduce a superinfection parameter,  $\sigma$ , that describes the relative susceptibility of an infected host to infection by another strain. With the above assumptions, we show in Appendix 1B that the invasion fitness (Metz *et al.*, 1992; Geritz *et al.*, 1998) of the mutant parasite is

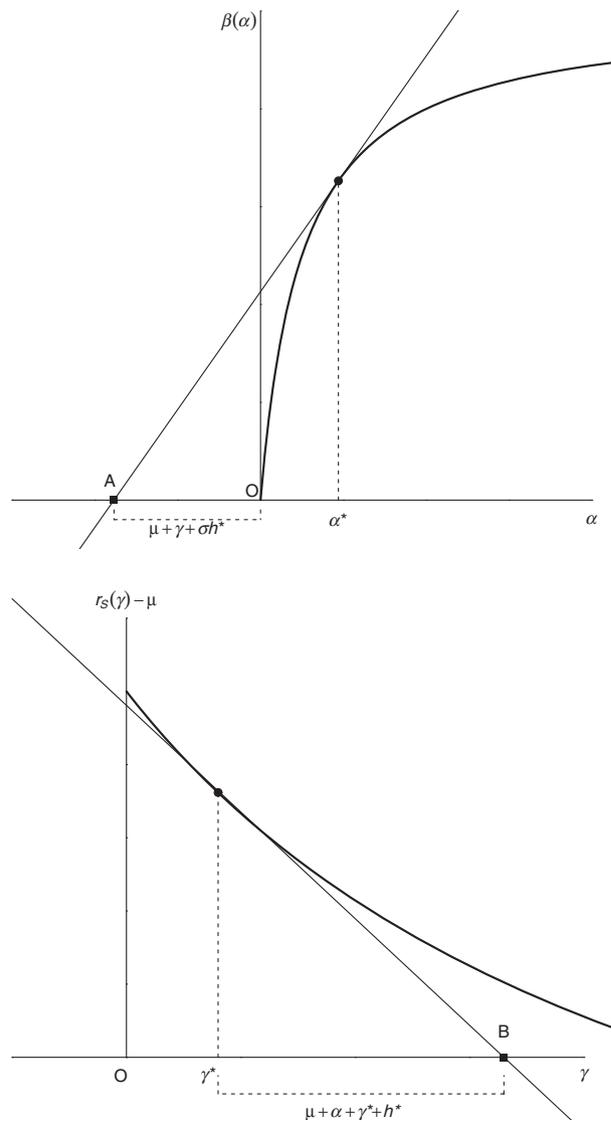
$$s_p(\alpha, \alpha') = \beta(\alpha')(\hat{S} + \hat{I}) - (\mu + \alpha' + \gamma + \sigma h), \quad (2)$$

where  $h$  is the force of infection in the resident population at equilibrium. If we further assume that mutations have small phenotypic effects (weak selection), the direction of selection is given by the selection gradient  $\partial s_p / \partial \alpha'$  evaluated at neutrality ( $\alpha' = \alpha$ ). After some algebra, we find that potential evolutionary endpoints must satisfy

$$\beta'(\alpha) = \frac{\beta(\alpha)}{\mu + \alpha + \gamma + \sigma h}. \quad (3)$$

Conditions for the stability of the evolutionary singularities are found in (Geritz *et al.* (1998) and the appendix of Best *et al.* (2009).

Equation (3) has a simple graphical solution (van Baalen & Sabelis, 1995; Gandon *et al.*, 2001): for a saturating trade-off between transmission and virulence, the ESS virulence is graphically found as the intersection of the trade-off curve  $\beta(\alpha)$  and of the tangent to this curve passing through the point  $\{-(\mu + \gamma + \sigma h), 0\}$  (Fig. 1). This indicates that an increase in host mortality, recovery or the force of infection selects for an increase in vir-



**Fig. 1** Trade-off between virulence and transmission (top panel) or between recovery and the reproductive output of susceptible hosts (bottom panel). In each case, the ESS virulence or recovery is represented by a filled circle, all other parameters being fixed. At the ESS, the tangent to the trade-off curve cuts the x-axis at a specific point, which is  $A\{-(\mu + \gamma + \sigma h^*), 0\}$  for virulence, and  $B\{\mu + \alpha + 2\gamma^* + h^*, 0\}$  for recovery. The notation  $h^*$  indicates that the force of infection is evaluated at the ESS.

ulence. In particular, an increase in the probability of superinfection,  $\sigma$ , will lead to higher values of ES virulence. This is consistent with the well-known prediction that within-host competition in mixed infections selects for increased virulence (Bonhoeffer & Nowak, 1994; Nowak & May, 1994; van Baalen & Sabelis, 1995; Frank, 1996; Alizon *et al.*, 2013; Lion, 2013).

With the trade-off shape  $\beta(\alpha) = \beta_0\alpha/(1 + \alpha)$ , we recover Gandon *et al.* (2001)'s implicit expression for the candidate evolutionarily stable (ES) virulence

$$\alpha^* = \sqrt{\mu + \gamma + \sigma h^*}, \quad (4)$$

where  $h^*$  is the force of infection calculated at the ESS (i.e. for  $\alpha = \alpha^*$ ). Equation (4) shows that ES virulence is an increasing function of host recovery ( $\gamma$ ) and of the force of infection on infected hosts at the ESS,  $\sigma h^*$ .

### Host fitness

To investigate the evolution of the host's recovery rate, we assume that allocating resources to defence is costly and decreases host fecundity (Bonds, 2006; Carval & Ferrière, 2010). We assume that fecundity is a positive, decreasing and saturating function of  $\gamma$ . For most of the examples below, we consider  $r_S(\gamma) = r_I(\gamma) = \frac{r_m}{1+c\gamma}$  with  $r_m$  being the maximum rate of reproduction and  $c$  the cost of maintaining an immune response. This is qualitatively similar to the trade-off used by van Baalen (1998).

As for the parasite, we can compute the invasion fitness of a rare mutant host in a resident population at equilibrium. We show in Appendix 1C that a candidate ES recovery rate satisfies

$$\tilde{r}'_S(\gamma) + \tilde{r}'_I(\gamma) \frac{h}{\mu + \alpha + \gamma} = -\frac{\tilde{r}(\gamma) - \mu}{\mu + \alpha + \gamma}, \quad (5)$$

where  $\tilde{r}'_i = r'_i(1 - \kappa(S + I))$  is the fecundity of the mutant host, discounted by competition for resources.

With the trade-off shape described above, this strategy is evolutionarily stable (see Marrow *et al.*, 1996; Best *et al.*, 2009). In particular, if infection affects neither host fecundity nor the cost of maintaining an immune system ( $r_S = r_I \equiv r$ ), we obtain:

$$\tilde{r}'(\gamma) = -\frac{\tilde{r}(\gamma) - \mu}{\mu + \alpha + \gamma + h}. \quad (6)$$

Note the similarity between equation (6) and (3). They both express the optimal strategy of each species as a form of marginal value theorem (Charnov, 1976; Gandon *et al.*, 2002b). However, it is worth noting that the susceptibility to superinfection,  $\sigma$ , does not appear in eqn (5). This is expected because any infection, at rate  $h$ , will decrease the lifespan of a host, whereas only secondary infections, at rate  $\sigma h$ , will decrease the lifespan of a parasite. Because the force of infection in the resident population does not depend on superinfection, superinfection has no direct effect on the evolution of host traits. Any effect of superinfection on the evolution of the host will therefore be indirectly mediated by the evolution of parasite traits.

Equation (6) also has a graphical interpretation (Fig. 1). In particular, when there is no density dependence ( $\kappa = 0$ ), the tangent at the ESS intersects the  $x$ -axis at the point  $\{\mu + \alpha + 2\gamma + h, 0\}$ . An increase in background mortality, virulence or the force of infection leads to a decrease in recovery.

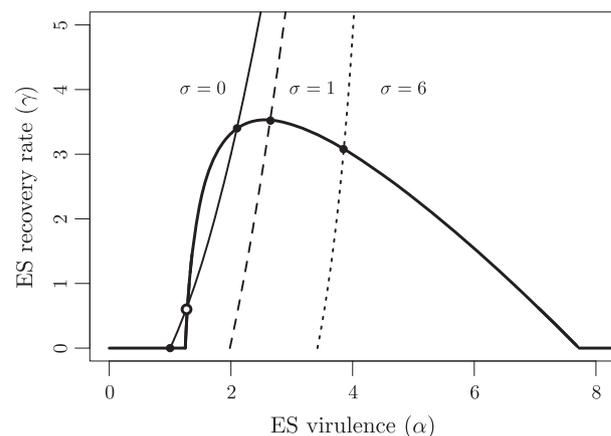
### Host–parasite coevolution

Equations (3) and (5) give the evolutionary isoclines of virulence and recovery, respectively. The potential end-points of host–parasite coevolution are given by the intercepts of the isoclines, that is the values  $(\alpha^{**}, \gamma^{**})$  that simultaneously satisfy eqns (3) and (5). The convergence and evolutionary stability of the co-evolutionary singularities can be assessed using the method given in Best *et al.* (2009)'s appendix. In the next section, we investigate how the coevolution of virulence and recovery is affected by superinfection and other epidemiological parameters.

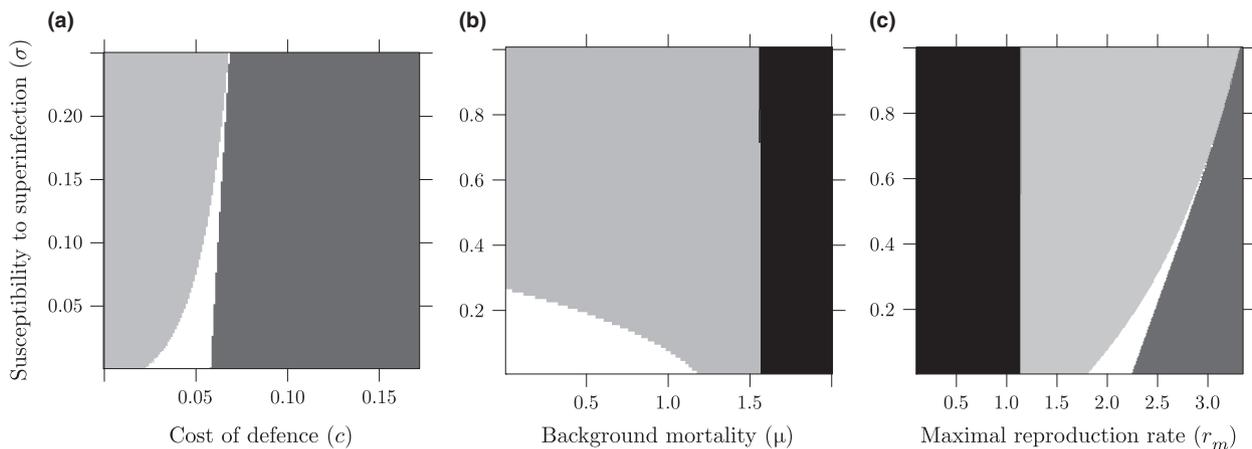
### Coevolution

#### Effect of superinfection

In the absence of superinfection ( $\sigma = 0$ ), we recover van Baalen (1998)'s results. As shown in Fig. 2, we find a bistability characterized by two coevolutionarily stable strategies (CoESSs), one for which hosts are highly defended and parasites highly virulent, and another CoESS, for which hosts do not invest in recovery and parasite virulence is low (but nonzero). Those two CoESSs are separated by a repeller: if virulence and recovery rates are initially below some threshold values, selection drives the host–parasite interaction towards the lower CoESS; in contrast, if virulence and recovery are initially sufficiently high, the higher CoESS is the evolutionary outcome.



**Fig. 2** ES levels of virulence (thin line) and recovery (thick line) in the absence superinfection. The points where the host and parasite isoclines intersect are either coevolutionarily stable singularities (CoESS, filled circle) or evolutionarily unstable singularities (open circle). Parameter values :  $\beta_0 = 10$ ,  $\mu = 1$ ,  $c = 0.05$ ,  $r_m = 2$ ,  $\kappa = 0.01$  and  $\sigma = 0$ . Dashed lines represent the parasite isoclines for increasing values of the susceptibility to superinfection ( $\sigma = 1$ : dashed line,  $\sigma = 6$ : dotted line).



**Fig. 3** Coevolutionary outcomes for virulence and recovery. The white region indicates evolutionary bistability. Outside the bistability zone, there can be either 0 (black), the lower (dark grey) or the upper (light grey) virulence/defence CoESS only. All solutions are strictly for parameter values where the parasite is endemic ( $\hat{i} > 0$ ). Default parameter values are found in Table 1. Note the different scales used on the y-axis for each panel.

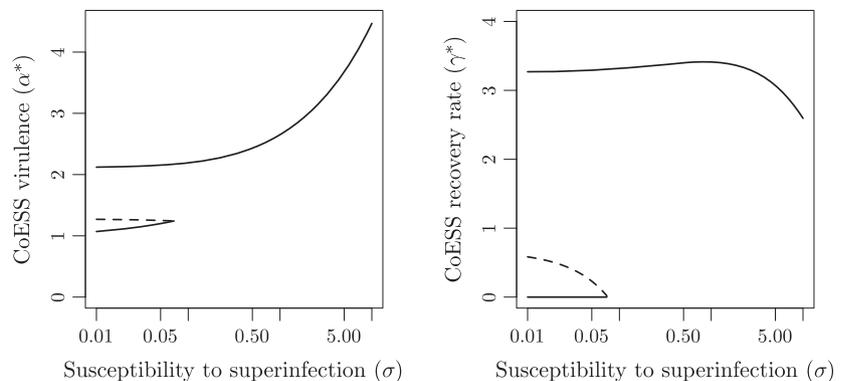
When the susceptibility to superinfection increases ( $\sigma > 0$ ), the evolutionary bistability disappears when  $\sigma$  is above a threshold,  $\sigma_c$ . Figure 2 provides a graphical explanation: when the susceptibility to superinfection increases, the parasite isocline is shifted to the right, which induces the loss of the intermediate intersection point with the host isocline. Because superinfection has no effect on host fitness, this can be solely explained by selection for higher virulence when the frequency of multiple infections increases (van Baalen & Sabelis, 1995; Frank, 1996; Gandon *et al.*, 2001). Thus, a higher frequency of multiple infections leads to higher virulence, and, as a result, to a higher investment in recovery, despite the fact that host fitness does not directly depend on  $\sigma$ .

Interestingly, the threshold above which bistability is lost is quite low. Extensive numerical simulations suggest that  $\sigma_c$  is always below 1 and often as low as 0.1 (see Fig. 4). This implies that even a very low frequency of multiple infections is sufficient to eradicate the possibility of bistability found by van Baalen

(1998). In fact, evolutionary bistability is only possible for very narrow ranges of parameter values characterized by low multiplicity of infections (low values of  $\sigma$ ), high costs of defence, low mortality and sufficiently high fecundity (Fig. 3).

When the susceptibility to superinfection further increases (Fig. 4), selection for increased recovery weakens. Indeed, a higher probability of superinfection selects for higher virulence, and as a result, host survival decreases below a threshold where it no longer pays to invest into defence. Of course, this particular outcome depends on the specific trade-off between fecundity and defence. For the trade-off relationship we use, the host isocline is hump-shaped (Fig. 2). Alternative trade-off shapes may lead to different relationships between recovery and the susceptibility to superinfection.

Host demographic parameters may affect parasite fitness either directly or indirectly (through the force of infection, see eqn 3). Specifically, increasing host reproductive rates ( $r_m$ ) and decreasing background mortality



**Fig. 4** CoESS of virulence and recovery rate for high values of  $\sigma$  (log scale). Filled line represents stable CoESS, whereas the dashed line represents the unstable CoESS. Default parameter values found in Table 1.

( $\mu$ ) both select for higher virulence and defence (figure A1 in Appendix 1D; see also van Baalen (1998); Day & Burns (2003)). Similarly, when the cost of maintaining an immune system,  $c$ , is too high, investment into host defence decreases, leading to longer infectious periods and, therefore, more prudent exploitation of their hosts by parasites (see figure A1 in Appendix 1D).

### Effects of host fecundity and immunological costs

So far, we have considered that uninfected and infected hosts have the same fecundity. This would hold true, for instance, if parasites only exploit the fraction of host resources that is allocated to host survival and if there is no significant cost in activating the immune response. We now consider what happens if we relax either of these assumptions.

#### Sterilizing parasites

Let us first consider that parasites may affect both the fecundity and the survival of their hosts (Bonds, 2006). We postulate that infected hosts reproduce at a rate  $r_I = \varepsilon r_S$ . However, unlike parasite-induced mortality ( $\alpha$ ), the relative infected host fecundity ( $\varepsilon$ ) is not controlled by the parasite. Owing to the host being infected, if  $\varepsilon < 1$ , a fraction  $1 - \varepsilon$  of host reproductive resources is removed. On the other hand, when  $\varepsilon > 1$ , the infection has a positive effect on the reproduction

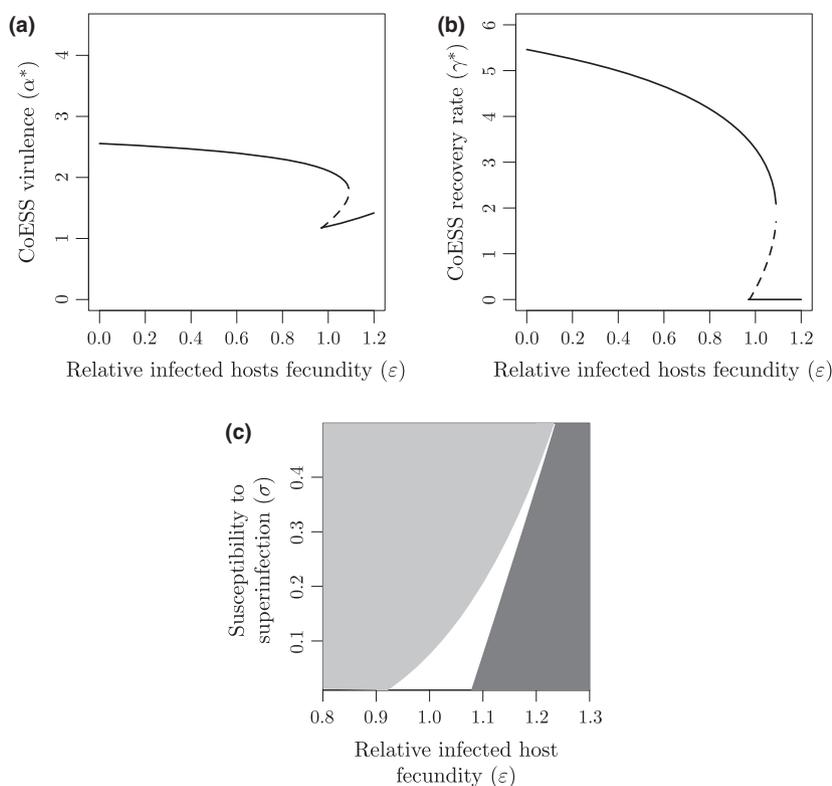
of infected individuals, reflecting for instance, host plasticity or parasite manipulation.

Host fecundity has only an indirect effect on parasite fitness, through the force of infection on infected hosts,  $\sigma h$ . In contrast, host fecundity affects host fitness through both direct and indirect effects. From eqn (5), we see that an asymmetry in the fecundity of infected and uninfected hosts leads to the following equation at the ESS:

$$\tilde{r}'_S(\gamma) = -\frac{\tilde{r}_S(\gamma) - \mu}{\mu + \alpha + \gamma + \varepsilon h}. \quad (7)$$

An increase or decrease in  $\varepsilon$  will therefore, respectively, either magnify or weaken the evolutionary impact of an increase in the force of infection. When susceptible and infected hosts have the same fecundity ( $\varepsilon = 1$ ), the model is identical to van Baalen (1998)'s, and we obtain evolutionary bistability (Fig. 5a,b). However, this bistability region is very narrow and requires a weak asymmetry in the reproductive potentials of uninfected vs. infected hosts ( $\varepsilon \approx 1$ ) and low superinfection rates (Fig. 5c).

When  $\varepsilon$  decreases below 1, the high-recovery/high-virulence CoESS is the only evolutionary endpoint, and a reduced fecundity of infected hosts (low  $\varepsilon$ ) selects for higher recovery and higher virulence (Fig. 5a,b). Two factors explain this result: first, the reduced fecundity of infected hosts directly affects host fitness through the parameter  $\varepsilon$  (eqn 7); second, reduced fecundity of



**Fig. 5** (a) Relationship between the coevolutionarily stable levels of virulence and (b) recovery rate and sterility virulence for  $\sigma = 0.05$ . Filled line represents stable CoESS, whereas dashed line represents unstable CoESS. (c) Coevolutionary outcomes for virulence and recovery rate as a function of the susceptibility to superinfection ( $\sigma$ ) and the sterility virulence ( $\varepsilon$ ). The model predicts either low CoESS only (dark grey), a high-virulence/high-defence CoESS (light grey) or evolutionary bistability (white). Default parameter values used found in Table 1.

infected hosts tends to decrease the supply of susceptible hosts, and consequently disease prevalence, leading to a lower force of infection. The net effect is to decrease the  $\varepsilon h$  term; thus, higher recovery is selected for, and consequently higher virulence. When  $\varepsilon$  increases above 1, the zero-recovery/low-virulence CoESS is the only evolutionary endpoint and an enhanced fecundity of infected hosts selects for higher virulence (Fig. 5a). Here, the positive impact of an increased force of infection on virulence, due to enhanced host reproduction, is the driving force.

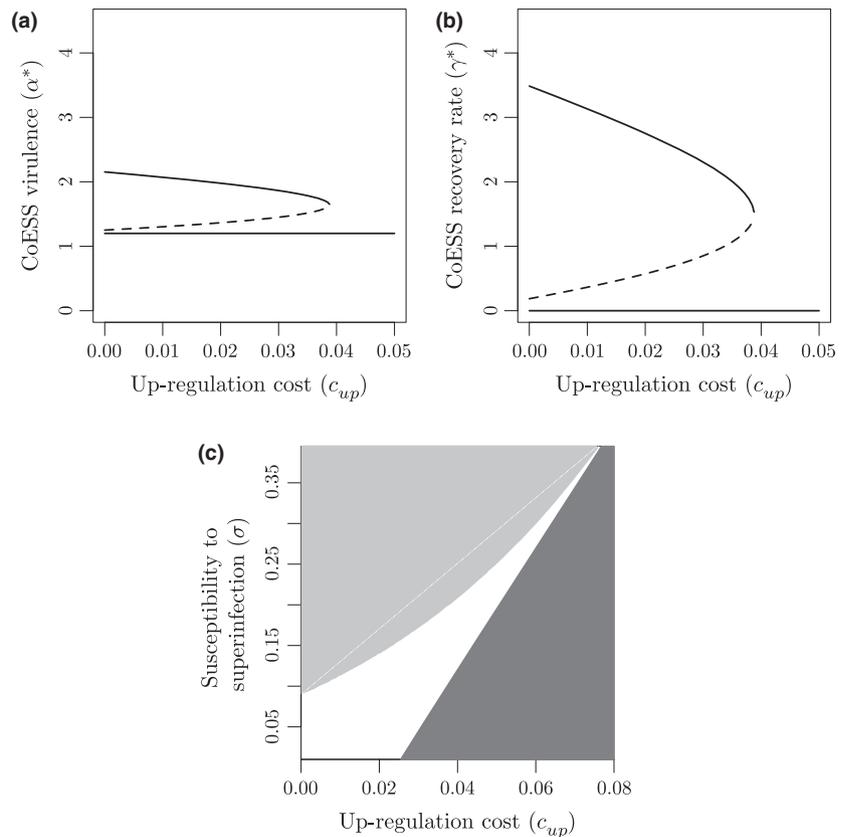
#### Cost of immune system up-regulation

An infection leading to an immune response can be expected to incur a maintenance cost and an up-regulation cost (Lochmiller & Deerenberg, 2000; van Boven & Weissing, 2004). Up to now, we have assumed that the cost of defence is equally paid by susceptible and infected hosts. This entails that the immune system is costly to maintain, but that its activation is free. To take into account the cost of mounting an immune response, we now consider that the reproduction of infected hosts is further dependent on a cost of up-regulation,  $c_{up}$ , through the following relationship:  $r_I = r_S - c_{up}\gamma$ .

Previous models (Day & Burns, 2003) showed that an immunological cost of up-regulation selects for

lower investment in host defence. In the absence of superinfection, the fecundity of infected hosts only affects host fitness, through both direct and indirect effects (the product  $\tilde{r}_I$  in eqn 5), whereas parasite fitness only depends on mortality, recovery and the transmission–virulence trade-off. Superinfection introduces an indirect epidemiological effect of host fecundity on parasite fitness, through the force of infection,  $h$  (eqn 3). The effect of the force of infection on parasite fitness is scaled by the susceptibility to superinfection ( $\sigma h$ ). We therefore investigate the effect of multiplicity of infection on the existence of a bistability region. We find that when the cost of up-regulation increases, the bistability regions becomes narrower (Fig. 6c). For high values of  $\sigma$  and low  $c_{up}$ , the higher virulence/higher defence coevolutionarily stable strategy is the only evolutionary endpoint (Fig. 6c).

An increase in the cost of immune system up-regulation has both a direct and indirect negative effect on host fitness. First, it leads to reduced host fecundity. Second, the resulting decrease in the density of susceptible hosts leads to a lower disease prevalence and a lower force of infection. In the bistability region, both factors act to select for lower virulence and lower recovery as  $c_{up}$  increases, as illustrated in Fig. 6a,b. However, when the cost of immune system up-regulation is above a threshold, investment into recovery



**Fig. 6** (a) Relationship between the coevolutionarily stable level of virulence and (b) recovery rate and up-regulation cost for  $\sigma = 0.05$ . Filled line represents stable CoESS, whereas the dashed line represents the unstable CoESS. (c) Coevolutionary outcomes for virulence and recovery rate as a function of the susceptibility to superinfection ( $\sigma$ ) and the cost of up-regulation ( $c_{up}$ ). The model predicts either low CoESS (dark grey), a high-virulence/high-defence CoESS (light grey) or evolutionary bistability (white). Default parameter values used found in Table 1.

becomes counterselected and the low-virulence/zero-recovery endpoint is the only viable evolutionary outcome (Fig. 6a).

### Superinfection as a function of within-host competitiveness

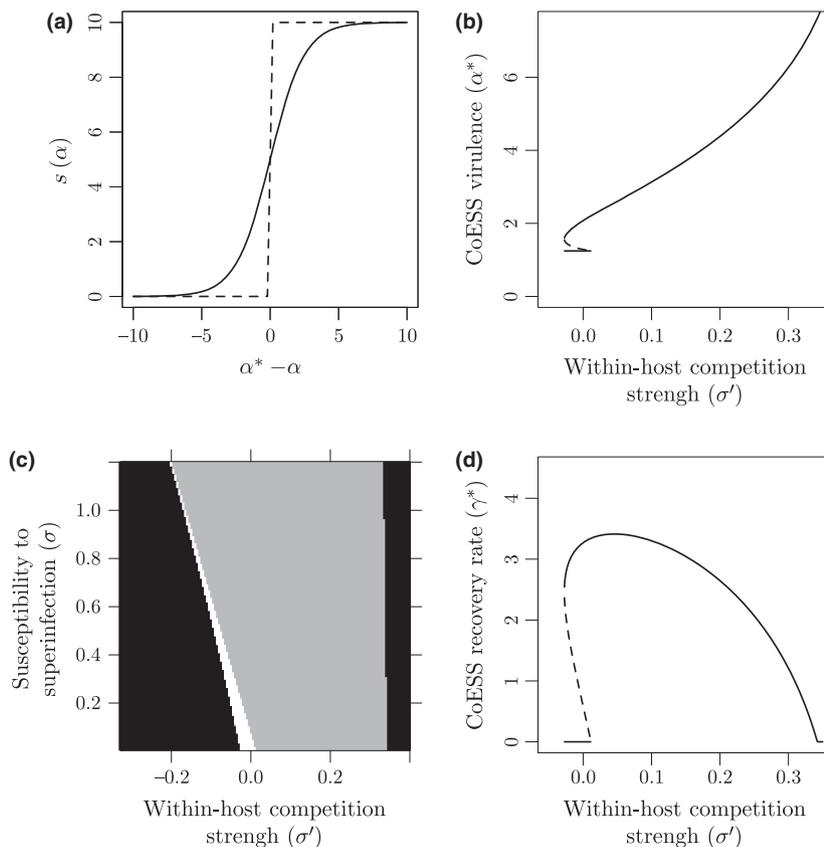
So far, we have assumed that the susceptibility to superinfection is independent of within-host parasite interactions. In particular, it does not depend on parasite virulence, which implies that parasite virulence has no effect on within-host competitiveness. Following Gandon *et al.* (2001), we now suppose that the susceptibility to superinfection is a function of the difference between the two parasite strains' virulence,  $s(\alpha_2 - \alpha_1)$ . Hence, if both strains have the same virulence ( $\alpha_2 = \alpha_1$ ), there is a baseline susceptibility to superinfection  $\sigma = s(0)$ . If the second strain to arrive in the host is more virulent than the first, the susceptibility to superinfection increases beyond the baseline takeover rate (Fig. 7a). As in Gandon *et al.* (2001), the strength of the effect of virulence on within-host competitiveness can be measured using the parameter  $\sigma' = ds(\alpha' - \alpha)/d\alpha'$  evaluated at  $\alpha' = \alpha$ , which we refer below as the mutant strain's dominance (Bonhoeffer & Nowak, 1994).

With these additional assumptions, parasite fitness takes a slightly different form. Candidate ESSs now

have to satisfy the following equation (Gandon *et al.*, 2001)

$$\beta'(\alpha) = \frac{\beta(\alpha)(1 - 2h\sigma')}{\mu + \alpha + \gamma + \sigma h} \quad (8)$$

Numerical explorations show that the effect of dominance is qualitatively similar to the effect of  $\sigma$  we have described in the previous section: virulence increases when dominance (i.e. the competitive advantage given by virulence) increases (Fig. 7b). This is consistent with classical predictions on the effect of within-host competition on virulence (Nowak & May, 1994; Gandon *et al.*, 2001; Boldin & Diekmann, 2008). However if high within-host competition first selects for an increase in recovery, this rapidly leads to a decrease in recovery after a point where it does not pay anymore to invest into defence (Fig. 7d). As previously, our results show the existence of a narrow region of coevolutionary bistability for low values of  $\sigma$  and values of  $\sigma'$  close to zero (Fig. 7c). Indeed, hosts can stay without an immune system (i.e. lower CoESS) only when parasites are relatively avirulent and therefore when competitive ability and virulence are less tightly linked ( $\sigma'$  close to 0). We note that other functional relationship between the probability of superinfection and virulence can be derived from alternative within-host assumptions, with distinct evolutionary consequences (Boldin & Diekmann, 2008).



**Fig. 7** (a) The relationship between the susceptibility to superinfection ( $\sigma$ ), the mutant strain's dominance ( $\sigma'$ ) and the parasite virulence,  $\alpha$ . Default parameter values found in Table 1,  $\sigma' = 2$  and  $\sigma = 5$ . The takeover rate approaches a step function when  $\sigma$  is small or when  $\sigma'$  approaches infinity (see dashed line,  $\sigma' = 100$ ). Coevolutionary stable virulence (b) and recovery (d) as a function of the mutant strain's dominance ( $\sigma'$ ). Default parameter values found in Table 1 and  $\sigma = 0.01$ . (c) Number of positive solutions for virulence when both the susceptibility to superinfection  $\sigma$  and the mutant strain's dominance  $\sigma'$  vary. The values for the number of CoESSs are indicated by colour (white = bistability, light grey = upper CoESS, black = no positive CoESS). All solutions are strictly for parameter values where the parasite is endemic ( $\dot{i} > 0$ ). Default parameter values as in Table 1.

## Superinfection facilitation and inhibition

Within-host interactions between genetically different parasites involve complex interactions between parasites (e.g. inhibiting or facilitating processes, Eswarappa *et al.*, 2012), mostly through the host immune system (Mideo, 2009). We further hypothesize that investment in the immune system by the host facing multiple enemies might directly affect the level of susceptibility to superinfection. To account for this potential interplay between superinfection and host defence, we assume that the susceptibility to superinfection may either increase with an investment into the immune system (superinfection facilitation) or decrease (superinfection inhibition). Specifically, we introduce the following relationship between  $\sigma$  and  $\gamma$ :  $\sigma(\gamma) = \sigma_0 e^{a\gamma}$  (Fig. 8a). Superinfection facilitation occurs for  $a > 0$  and reflects, for instance, additional costly side effect of immune system activation (e.g. a trade-off between specific and general immune response). Superinfection inhibition ( $a < 0$ ) describes the possibility that an activated non-specific immune system makes the host more resistant to further infections by similar pathogenic strains.

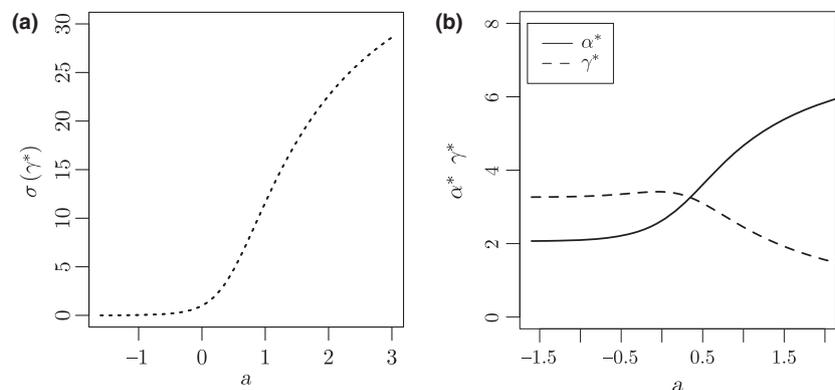
Because superinfection does not affect host fitness, the only effect of superinfection facilitation or inhibition is to enhance or weaken the effect of the force of infection on parasite fitness. Under superinfection facilitation, recovery directly increases the frequency of multiple infections, and this selects for increased virulence: an increase of  $a$  for a fixed value of recovery will move point A in the top panel of Fig. 1 to the left and therefore select for higher virulence. Higher virulence will result in turn in either higher or lower recovery, depending on the resulting force of infection. In contrast, under superinfection inhibition, the effect of multiple infections on virulence is buffered. Hence, as the immune system becomes more efficient at preventing superinfections ( $a$  becomes more negative), lower virulence and therefore lower recovery should evolve. Figure 8b illustrates this effect at high baseline superinfection rates (i.e. when the high-recovery/high-virulence CoESS is the only viable evolutionary outcome).

## Discussion

### Coevolution of host recovery and parasite virulence

Most natural infections consist of several parasite strains (Read & Taylor, 2001; Balmer & Tanner, 2011). There is overwhelming evidence that such multiple infections may have a strong effect on parasite strategies of host exploitation. Here, we show that multiple infections may also impact the coevolution of parasite virulence and host recovery. Using an extension of a coevolutionary model introduced by van Baalen (1998), we show that there are two strikingly different coevolutionary outcomes, depending on the probability of superinfection. When the susceptibility to superinfection is low, the model predicts an evolutionary bistability, which is consistent with van Baalen (1998)'s main result: depending on the initial conditions, the host-parasite interaction may evolve either to a high-virulence, high-recovery coevolutionary attractor or to a low-virulence, no-recovery coevolutionary endpoint. However, when the probability of superinfection increases above a (relatively low) threshold, this evolutionary bistability vanishes and the only possible coevolutionary endpoint is that of high virulence and high recovery. This suggests that the evolutionary bistability predicted by van Baalen (1998) is highly sensitive to epidemiological feedbacks (e.g. Restif, 2013), such as those due to multiple infections. Such epidemiological feedbacks have been shown to be critical for the evolution of host and parasite life-history traits (Frank, 1992; van Baalen & Sabelis, 1995; Gandon *et al.*, 2002b; Ebert *et al.*, 2004; Bonds, 2006; Boots *et al.*, 2009; Carval & Ferrière, 2010). Here, we show that evolutionary bistability for the coevolution of host recovery and parasite virulence is only possible in a narrow region of parameter space, characterized by low superinfection rate, low mortality, high fecundity and high costs of defence.

Interestingly, this shift away from evolutionary bistability is only governed by selection on the parasite.



**Fig. 8** (a) Relationship between the susceptibility to superinfection ( $\sigma(\gamma)$ ) with varying intensity of interaction ( $a$ ). Evolutionary stable virulence ( $\alpha^*$ ) and recovery rate ( $\gamma^*$ ) with varying intensity of interaction ( $a$ ), where  $a$  determines the shape of the relationship between  $\sigma$  and  $\gamma$ . Default parameter values used as in Fig. 2,  $\sigma_0 = 1$ .

When the frequency of multiple infections increases, higher levels of parasite virulence are selected for (Nowak & May, 1994; van Baalen & Sabelis, 1995; Frank, 1996; Gandon *et al.*, 2001; Buono *et al.*, 2014), and in turn this selects for higher investment into host defence, provided the cost of defence is not too high. Mathematically, this can be clearly expressed by noting that superinfection only affects parasite fitness: any change in recovery when the frequency of multiple infections increases has to be mediated by a change in parasite traits.

Multiple infections introduce new selective pressures on parasite traits. In the absence of multiple infections, selection on parasite virulence does not depend on host fecundity, but only on mortality and recovery (Frank, 1992, 1996). In contrast with previous coevolutionary models of host defence and parasite virulence (Best *et al.*, 2009, 2010, 2014), coevolutionary dynamics in our model are affected by the feedback of the force of infection on parasite fitness (through the term  $\sigma h$ ). This implies that other epidemiological or physiological parameters than mortality or recovery may affect parasite evolution through their effect on the force of infection. We show that, when the fecundity of infected hosts decreases, higher virulence and recovery are selected for, because lower host fecundity causes the force of infection to decrease, which selects for higher recovery. Note that, although a lower risk of infection selects for less virulent pathogens when host traits do not evolve, the relationship between the force of infection and parasite traits is less straightforward when the coevolution of host and parasite traits is considered. If the net effect of increased recovery tends to overcome the impact of a reduction in the force of infection, the coevolutionary endpoint may be characterized by an increase in virulence, as we observe. Similarly, we show that different costs of defence (such as those associated with the maintenance or activation of the immune system) potentially affect both host and parasite fitness through direct and indirect effects. Here, we show that an increase in the cost of immunological up-regulation and an increased sterility of infected hosts both lead to a decrease in recovery and virulence. Note that we assumed that the parasite has no effect on host sterility. Because many parasites affect both host mortality and fecundity, a potential extension of our model would be to consider the joint evolution of host recovery and of parasite allocation to sterility vs. mortality virulence.

### Strain dominance

We also investigated what happens when superinfection depends on the relative virulence of two competitive strains, so that more virulent strains are better competitors (Nowak & May, 1994; Gandon *et al.*, 2001; Boldin & Diekmann, 2008; Alizon & Michalakis, 2011;

Alizon *et al.*, 2013). We show that, when within-host competitiveness strongly depends on the relative virulence of competing parasite strains, higher virulence and lower recovery are favoured. This is consistent with experimental studies on competitive exclusion for which less virulent strains suffered more from competition than did more virulent strains (Bell *et al.*, 2006; Råberg *et al.*, 2006; Ben-Ami *et al.*, 2008; Bashey *et al.*, 2012; McWhorter *et al.*, 2013; but see Hughes & Boomsma, 2004), including when competition occurs between different species (Lysenko *et al.*, 2005). Although we did not study the underlying process of competitive exclusion, our predictions are similar to those of Alizon & van Baalen (2008), who used a coinfection model: when the occurrence of multiple infection is high, highly virulent parasites might benefit from triggering an immune response that would wipe out avirulent strains. Additionally, a recent experimental study by Susi *et al.* (2015) supports our prediction that higher frequency of multiple infection can lead to the evolution of lower recovery rates. This study revealed that coinfecting hosts of *Plantago lanceolata* experienced lower levels of quantitative resistance at the peak of the epidemic. We observe the same pattern with our model: a very narrow bistability region for which avirulent strain is sustained and a large zone where only highly virulent strains exist.

### Multiple consequences of investment into defence

An increasing number of experimental and theoretical studies are showing that the outcome of within-host competition may be regulated by the host's immune system (Pedersen & Fenton, 2007; Mideo, 2009). We described two antagonistic immune-mediated mechanisms of potential importance. First, a primary infection triggering an immune response may weaken the immune system and facilitate subsequent infections. For example, HIV infections can facilitate subsequent infection through the reduction of functional immune responses in coinfection studies (Lawn, 2004; Fenner *et al.*, 2013; Van Geertruyden, 2014). Other analysis using specific parasite associations such as *Schistosoma mansoni* and *Plasmodium chabaudi* (Helmsby *et al.*, 1998) and time series data between micro- and macroparasites (Telfer *et al.*, 2010) showed that primary infection could increase host susceptibility to subsequent infections. Our model describing the positive relation between immune system activation and susceptibility to superinfection shows that this mechanism may select for higher virulence and lower defence. The positive effect on virulence of a unit investment in defence is amplified by the higher susceptibility to further infections, which causes defence to become too costly.

Given the evolutionary impact of within-host competition on parasite virulence, we expect host resistance strategy against multiple infections to be under strong

selective pressure (van Baalen & Sabelis, 1995). Although this idea appears attractive, much remains to be performed to provide empirical support for this theory (see Allander & Schmid-Hempel, 2000). On the other hand, reduction of multiple infection controlled by the parasite has been described in some host–parasite systems (e.g. schistosome system, Smithers & Terry, 1969). This behaviour can emerge, in theory, through parasite manipulation (Brown & Grenfell, 2001), when strains use the immune system by inducing a strong immune response against competitors. Experimental studies have shown that an infection can reduce the burden of concomitant infection and actively decrease the probability of superinfection, possibly by enhancing the host nonspecific response (Rajakumar *et al.*, 2006; Zélé *et al.*, 2012). This strategy is successful at reducing subsequent infections, which would also benefit the host and lead to cooperative behaviour. Our model shows that such superinfection inhibition may select for lower virulence and recovery. This results in an alignment of host and parasite interests. This idea has similarly been discussed in another model by Restif (2013), where coevolution towards low-virulence, low-resistance endpoint was found under certain conditions. In Restif (2013)'s model, this is driven by phenotypic plasticity over the course of an infection, but our model suggests that other mechanisms, such as superinfection inhibition, can also lead to the alignment of the interests of hosts and parasites.

### Future research

On a more technical note, we stress that, although our results have been obtained for specific trade-off shapes, mostly for the sake of simplicity, critical function analysis (Geritz *et al.*, 2007; Boldin *et al.*, 2009) could be used to assess the generality of our conclusions when other trade-off relationships are assumed.

Although we restricted our analysis to superinfection, it is clear that superinfection only gives an oversimplified representation of the diversity of multiple infections, because, at a given time, a host may only be infected by a single parasite strain. This limitation might be addressed using a coinfection model. Although many studies of parasite evolution have concluded that modelling multiple infections as a superinfection or coinfection process leads to the same qualitative outcome (van Baalen & Sabelis, 1995; Gandon *et al.*, 2001; Lion, 2013), it is not clear that the same would hold true in a coevolutionary setting. Indeed, in a coinfection model, the frequency of multiple infections will directly feed back into host fitness, through the force of infection. Thus, multiple infections may directly affect the strategy of host defence, as well as indirectly through increasing virulence. It would be interesting to see whether this has a qualitative impact on our conclusions. Taking coinfections into account would require

us to explicitly track the distribution of pathogen genotypes among hosts (van Baalen & Sabelis, 1995; Lion, 2013). For parasite evolution, it is known that the resulting fitness measure needs to take into account the class structure of the host population and the reproductive values of a parasite infecting each class of hosts (Gandon, 2004; Lion, 2013). Further work is needed to understand how this would affect the coevolution of hosts and parasites.

Spatial structuring is another factor affecting the distribution of pathogen genotypes. Because neighbouring infected hosts will tend to harbour-related strains of parasites, the effective rate of superinfection is likely to be lower than in a well-mixed population. This has been shown to alter selective pressures on parasite traits (Caraco *et al.*, 2006) and can also be expected to affect the coevolutionary dynamics.

To conclude, our study shows that the outcome of coevolution depends critically on the specific ecological and biological ingredients of the system. Although evolutionary bistability is predicted in the absence of multiple infections (van Baalen, 1998), a higher superinfection probability selects for intermediate levels of virulence and recovery, irrespective of initial conditions. Our results call for a better understanding of two main factors affecting the coevolution of parasite and host traits. First, hosts may suffer different costs following infection (e.g. cost of activating the immune system or reduced fecundity). Second, the nature of within-host interactions between parasites may also play a role. Previous studies have shown that within-host competition may select for higher virulence. Here, we also show that it may select for lower host recovery. Our model provides a first step towards a better understanding of the interplay between coevolutionary dynamics and multiple infections.

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## Appendix 1

### A. Epidemiological SIS model

We find that the model admits two types of dynamics: either the pathogen dies out ( $\hat{I} = 0$ ) or the population reaches an endemic equilibrium, which is determined by setting  $\frac{dS}{dt} = \frac{dI}{dt} = 0$  in system (1):

$$\hat{S} = \frac{\mu + \alpha + \gamma}{\beta} \quad \text{and} \quad \hat{I} = \frac{(\mu + r)(\mu + \alpha + \gamma)}{\beta(r - \mu - \alpha)} \quad (\text{A1})$$

The endemic equilibrium is reached only if the parasite can spread in the host population, which happens if  $R_0 > 1$  (Anderson & May, 1991; van den Driessche & Watmough, 2002). This unique endemic equilibrium is globally stable (Zhou & Hethcote, 1994). Inversely, if  $R_0 < 1$ , the parasite dies out. In epidemiology, the basic reproductive number,  $R_0$ , of a parasite is defined as the number of secondary infections generated by a single infectious individual in an otherwise naive population (Macdonald, 1957; Diekmann *et al.*, 1990; Anderson & May, 1991; Heesterbeek & Dietz, 1996).

This gives us the expression of the  $R_0$ , the basic reproductive number:

$$R_0 = \frac{\beta}{\mu + \alpha + \gamma}. \quad (\text{A2})$$

### B. Parasite evolution

Using adaptive dynamics methodology (Metz *et al.*, 1992; Diekmann & Law, 1996; Geritz *et al.*, 1998), we make two key assumptions about mutations. First, we assume that mutations are rare. We can thus separate the ecological dynamics of the resident population from the evolutionary dynamics and consider that the resident population is monomorphic. The invasion fitness of a phenotype in a given environment is defined as the long-term per capita growth rate of the type of interest, when rare. We obtain

$$s_p(\alpha, \alpha') = \beta'(\hat{S} + \hat{\sigma}\hat{I}) - (\mu + \alpha' + \gamma + \sigma\beta I).$$

Another way of expressing the fitness of the parasite is to write it as a ratio, using a notation similar to the life-time reproductive ratio,  $R_0$ :

$$\mathcal{R}'(\alpha, \alpha') = \frac{\beta'(\hat{S} + \hat{\sigma}\hat{I})}{\mu + \alpha' + \gamma + \sigma\beta I}. \quad (\text{A3})$$

The invasion condition with  $s_p(\alpha, \alpha') > 0$  is equivalent to the condition  $\mathcal{R}'(\alpha, \alpha') > \infty$  (Diekmann *et al.*, 2002).

Second, we assume that mutations have small phenotypic effects: the mutant trait is close to the resident's. This allows us to calculate the selection gradient  $D(\alpha)$  from expression (A3), that is the partial derivative of invasion fitness with respect to the mutant trait, evaluated at neutrality ( $\alpha' = \alpha$ ). We obtain

$$D(\alpha) = \left. \frac{\partial s'(\alpha, \alpha')}{\partial \alpha'} \right|_{\alpha' = \alpha}.$$

An increase in virulence is selected for if the selection gradient is positive. Zeros of the selection gradient give the potential evolutionary singularities for virulence. For an increasing and saturating transmission–virulence trade-off, we have a unique evolutionary singularity,  $\alpha^*$  (Anderson & May, 1982), which is evolutionarily stable if the second derivative is negative (Geritz *et al.*, 1998; Best *et al.*, 2009). In our model, the singularity is an ESS, because  $\partial^2 s'_p(\alpha, \alpha') / \partial \alpha'^2 = \partial^2 \beta(\alpha) / \partial \alpha^2$ , which is negative for a concave trade-off curve.

### C. Host evolution

We now compute the fitness of the host,  $\mathcal{W}'$ , using the next-generation theorem (Diekmann *et al.*, 1990; van den Driessche & Watmough, 2002; Hurford *et al.*, 2010). The dynamics of the mutant host with a mutant trait  $\gamma'$  can be written in a matrix form as

$\frac{d}{dt} \begin{pmatrix} S \\ I \end{pmatrix} = A \begin{pmatrix} S \\ I \end{pmatrix}$  where:

$$A = \begin{pmatrix} \tilde{r}_S(\gamma') - \mu - h & \gamma' + \tilde{r}_I(\gamma') \\ h & -(\mu + \alpha + \gamma') \end{pmatrix}, \quad (\text{A4})$$

where  $\tilde{r}_i = r_i(1 - \kappa(S + I))$ . We can write  $A = F - V$ , where:

$$F = \begin{pmatrix} \tilde{r}_S(\gamma') & \tilde{r}_I(\gamma') \\ 0 & 0 \end{pmatrix}, \quad V = \begin{pmatrix} h + \mu & -\gamma' \\ -h & \mu + \alpha + \gamma' \end{pmatrix}, \quad (\text{A5})$$

and  $F$  and  $V$  satisfy:  $s(-V) < 0$ , that is that the maximum real part of all eigenvalues of  $-V$  are negative,  $V^{-1} \geq 0$  and  $F \geq 0$ . We can apply the next-generation theorem (Diekmann *et al.*, 1990; van den Driessche & Watmough, 2002; Hurford *et al.*, 2010), which states that it is equivalent to compute fitness from  $A$  or from the dominant eigenvalue of  $FV^{-1}$ . We have the following equation:

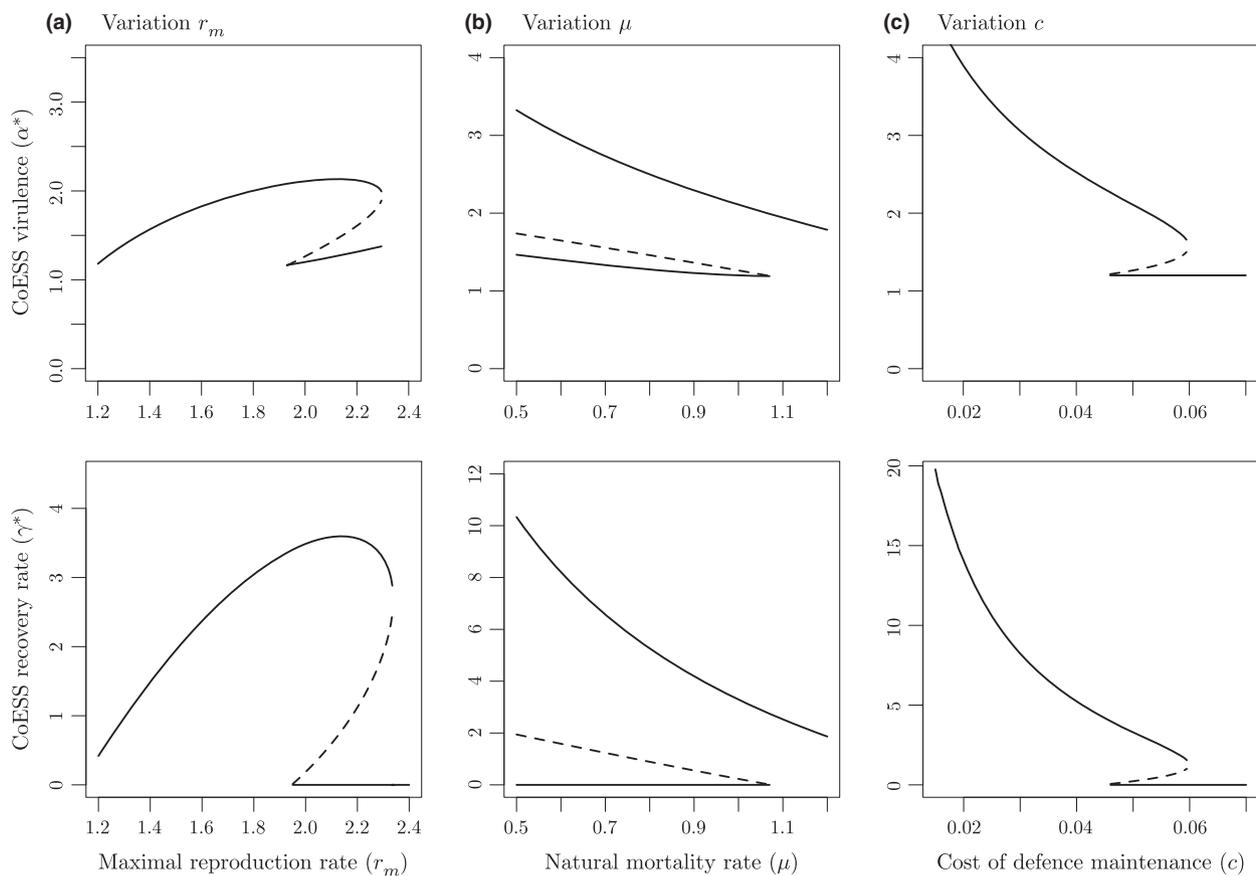
$$F.V^{-1} = \begin{pmatrix} \frac{\tilde{r}_S(\gamma')(\mu + \alpha + \gamma') + \tilde{r}_I(\gamma')h}{h\alpha + \mu(\mu + \alpha + \gamma' + h)} & \frac{\tilde{r}_S(\gamma')\gamma'}{h\alpha + \mu(\mu + \alpha + \gamma' + h)} \\ 0 & 0 \end{pmatrix}. \quad (\text{A6})$$

There is only one strictly positive eigenvalue (the first entry on the diagonal); therefore, the host fitness,  $\mathcal{W}'$ , is as follows:

$$\mathcal{W}'(\gamma, \gamma') = \frac{\tilde{r}_S(\gamma')(\mu + \alpha + \gamma') + \tilde{r}_I(\gamma')h}{h\alpha + \mu(\mu + \alpha + \gamma' + h)}. \quad (\text{A7})$$

The sign of the host fitness thus depends on the values of the resident and the mutant recovery rate, but not on the susceptibility to superinfection,  $\sigma$ . Then again, with the assumption of weak selection, the mutant can invade under the condition that the derivative of the host fitness,  $\partial\mathcal{W}'$ , with respect to the mutant recovery strategy  $\gamma'$  is positive. An evolutionary singularity,  $\gamma^*$ , must satisfy  $\partial\mathcal{W}'/\partial\gamma' = 0$ , when the mutant strategy equals the resident's (eqn 5). Finally, this singularity is evolutionarily stable (ESS), if  $\frac{\partial^2\mathcal{W}'}{\partial\gamma'^2} |_{\gamma^*=\gamma'=\gamma} < 0$ .

### D. Epidemiological feedback



**Fig. A1** Virulence and recovery ESSs, with superinfection of host reproduction ( $r_m$ ), cost of immunity ( $c$ ) and host mortality ( $\mu$ ) varying. The drawn lines indicate stable CoESS, whereas the dashed lines indicate evolutionarily stable but not convergence stable equilibrium (repellor). Note that above  $\mu = 1.1$ , only the high virulence/ high defence is found. Parameter values are  $\beta_0 = 10$ ,  $\mu = 1$ ,  $c = 0.05$ ,  $r_m = 2$ ,  $\sigma = 0.05$ .