

Provided for non-commercial research and education use.  
Not for reproduction, distribution or commercial use.



**This article was published in an Elsevier journal. The attached copy is furnished to the author for non-commercial research and education use, including for instruction at the author's institution, sharing with colleagues and providing to institution administration.**

**Other uses, including reproduction and distribution, or selling or licensing copies, or posting to personal, institutional or third party websites are prohibited.**

**In most cases authors are permitted to post their version of the article (e.g. in Word or Tex form) to their personal website or institutional repository. Authors requiring further information regarding Elsevier's archiving and manuscript policies are encouraged to visit:**

**<http://www.elsevier.com/copyright>**



## Evolutionary implications for interactions between multiple strains of host and parasite

Pei Zhang<sup>a</sup>, Gregory J. Sandland<sup>b</sup>, Zhilan Feng<sup>a,\*</sup>, Dashun Xu<sup>c</sup>, Dennis J. Minchella<sup>b</sup>

<sup>a</sup>Department of Mathematics, Purdue University, West Lafayette, IN 47907, USA

<sup>b</sup>Department of Biological Sciences, Purdue University, West Lafayette, IN 47907, USA

<sup>c</sup>Department of Mathematics, Southern Illinois University Carbondale, Carbondale, IL 62901, USA

Received 16 September 2006; accepted 7 May 2007

Available online 18 May 2007

### Abstract

The interaction between multiple parasite strains within different host types may influence the evolutionary trajectories of parasites. In this article, we formulate a deterministic model with two strains of parasites and two host types in order to investigate how heterogeneities in parasite virulence and host life-history may affect the persistence and spread of diseases in natural systems. We compute the reproductive number of strain  $i$  ( $\mathcal{R}_i$ ) independently, as well as the (conditional) “invasion” reproductive number for strains  $i$  ( $\mathcal{R}_i^j, j \neq i$ ) when strain  $j$  is at a positive equilibrium. We show that the disease-free equilibrium is locally asymptotically stable if  $\mathcal{R}_i < 1$  for both strains and is unstable if  $\mathcal{R}_i > 1$  for one strain. We establish the criterion  $\mathcal{R}_i^j > 1$  for strain  $i$  to invade strain  $j$ . Subthreshold coexistence driven by coinfection is possible even when  $\mathcal{R}_i$  of one strain is below 1. We identify conditions that determine the evolution of parasite specialism or generalism based on the life-history strategies employed by hosts, and investigate how host strains may influence parasite persistence.

© 2007 Elsevier Ltd. All rights reserved.

**Keywords:** Host–parasite dynamics; Multiple strains; Invasion; Subthreshold coexistence; Evolution of virulence

### 1. Introduction

Understanding the interaction between parasite infection and host life-history responses is critical for predicting the persistence and spread of diseases in natural systems. Because of this, mathematical models have been developed to explore the evolutionary dynamics that arise when variation occurs in these parameters (May and Anderson, 1979, 1990; Anderson and May, 1981, 1982; Levin, 1982; Bremermann and Pickering, 1983; Frank, 1992).

Under natural conditions, parasites can co-occur within both host populations and host individuals. In the absence of coinfection within individual hosts, it is often assumed that parasite strains expressing higher exploitation (i.e., more virulent) will outcompete those expressing lower exploitation (i.e., a more ‘prudent parasite’) (Minchella, 1985). However, when parasites coinfect the same host,

patterns should emerge that are more complex than when parasite strains occur independently (Bremermann and Pickering, 1983; Mosquera and Adler, 1998; Nowak and May, 1994; Davies et al., 2002). For example, Tanaka and Feldman (1999) found that the process of coinfection actually facilitated the invasion and establishment of a novel parasite strain, even though the invader’s reproductive value was less than that of the resident parasite. Moreover, empirical work by Gower and Webster (2004) demonstrated that coinfection among multiple parasite strains could favor the evolution of less, rather than more-virulent parasites.

Hosts have evolved life-history strategies that mitigate infection and the subsequent damage caused by parasitism (Minchella, 1985). In some cases, some host strains may actively resist parasite attack by altering morphological, physiological or immunological factors (Sandland and Minchella, 2003a). However, these strategies can generate fitness trade-offs with other host traits such as growth, reproduction and survival (Beck et al., 1984; Bowers et al.,

\*Corresponding author. Tel.: +1 765 494 1901; fax: +1 765 494 0548.

E-mail address: [zfeng@math.purdue.edu](mailto:zfeng@math.purdue.edu) (Z. Feng).

1994; Boots and Bowers, 1999; Sandland and Minchella, 2003b). Alternatively, other host strains may express strategies that increase fitness through early reproductive enhancement (termed ‘fecundity compensation’) (Minchella and Loverde, 1981; Sandland and Minchella, 2004) or suppression of immunological responses that can cause pathology (termed ‘tolerance’). Recently, a study by Miller et al. (2005) investigated the evolutionary consequences of hosts employing two different strategies in the face of infection: *control*, in which hosts reduced infection pathogenicity by actively reducing parasite replication rates, and *tolerance*, where hosts accommodated infection but did not reduce pathogen replication rates.

Few studies have mathematically investigated the interactions between multiple strains of hosts and parasites while allowing for coinfection. Mosquera and Adler (1998) developed a unified framework for coinfection and superinfection which considered the association between one host type and two strains of parasites. Their coinfection model favored the evolution of increased virulence and promoted the coexistence of more virulent parasites. Using a two host/multiple parasite strain model that allowed for coinfection, Regoes et al. (2000) suggested that virulence would evolve to intermediate values, and that host heterogeneity itself was sufficient to explain the pattern. This model incorporated virulence trade-offs between host strains as opposed to the more traditional approach of trading off parasite virulence with infectivity (May and Anderson, 1979, 1990; Anderson and May, 1981, 1982; Frank, 1992). Although this work provides insight into the coevolutionary dynamics of host–parasite interactions, assumptions within these models may prevent direct comparisons with empirical studies. Thus, additional research is required to determine the generality of parasite–virulence evolution and host strategies favored for mitigating parasitic attack.

In this study we expand on previous research and develop a general framework for assessing the interaction between two-host strains and two-parasite strains while allowing for coinfection. In our model we explore the different scenarios that can arise when the coinfection process is introduced into a two-host/two-parasite strain model. For this investigation, host strains are assumed to have different recruitment rates when infected (i.e., parasite virulence influences the host) and parasite strains vary in both their infectivity and virulence for each host type.

In Sections 2 and 3, we introduce the model and outline the equilibrium analysis. In Section 4, we utilize simulations to demonstrate that coinfection can actually allow for the persistence of parasite strains that would otherwise go extinct if hosts were only infected separately. Additionally in Section 4, we assess whether specialist or generalist parasites evolve when hosts employ different defense strategies (control, tolerance or threshold strategies—Miller et al., 2005). We investigate also in this section how variation in host strains, and the differential ability of parasites to reproduce in these strains, interact with

coinfection to drive parasite evolution. Finally, we discuss our results in Section 5.

## 2. Two-host and two-parasite strain model

Consider a host population that consists of two sub-populations with different genotypes,  $k = a, b$ . Each of the two sub-populations is divided into four epidemiological classes: uninfected ( $S_k$ ), infected with parasites of strain  $i$  only ( $I_{ki}$ ,  $i = 1, 2$ ), and coinfecting with both strains ( $I_{k12}$ ). Let  $P_i$  denote the density of parasites of strain  $i$ . Assume that  $P_i$  is proportional to the number of hosts infected with parasites of strain  $i$  (both singly and doubly infected hosts), i.e.,

$$P_i = \sum_{k=a,b} (c_{ki}I_{ki} + d_{ki}I_{k12}), \quad i = 1, 2,$$

where  $c_{ki}$  and  $d_{ki}$  denote the rates at which strain  $i$  parasites are produced from the infection of hosts of type  $k$  which can be singly and doubly infected (coinfecting) with parasites of strain  $i$ . It is also assumed that the uninfected hosts cannot become infected with both strains directly (i.e., they always become infected with a single strain of parasite first before coinfection of both strains can occur) and that an infected host with strain  $i$  parasite will remain infected for life (i.e., no recovery). Finally, we assume that the infection rate of susceptible hosts of type  $k$  by parasites of strain  $i$  is proportional to both the number of uninfected hosts of the same type ( $S_k$ ) and the density of parasites of the same strain ( $P_i$ ), and that the rate at which a host of type  $k$  that is already infected with strain  $j$  becomes infected with strain  $i$  ( $i \neq j$ ) is proportional to both  $I_{kj}$  and  $P_i$ . Under the above assumptions our model reads:

$$\begin{aligned} \frac{d}{dt}S_k &= A_k - \rho_{k1}P_1S_k - \rho_{k2}P_2S_k - \mu S_k, \\ \frac{d}{dt}I_{k1} &= \rho_{k1}P_1S_k - \rho'_{k2}P_2I_{k1} - (\mu + \delta_{k1})I_{k1}, \\ \frac{d}{dt}I_{k2} &= \rho_{k2}P_2S_k - \rho'_{k1}P_1I_{k2} - (\mu + \delta_{k2})I_{k2}, \\ \frac{d}{dt}I_{k12} &= \rho'_{k1}P_1I_{k2} + \rho'_{k2}P_2I_{k1} - (\mu + \delta_{k12})I_{k12}, \quad k = a, b, \\ P_i &= \sum_{k=a,b} (c_{ki}I_{ki} + d_{ki}I_{k12}), \quad i = 1, 2, \\ S_k(0) &= \check{S}_k, \quad I_{ki}(0) = \check{I}_{ki}, \quad I_{k12}(0) = \check{I}_{k12}. \end{aligned} \quad (1)$$

$A_k$  is the recruitment rate of hosts of type  $k$  ( $k = a, b$  for all parameters defined below except where otherwise specified);  $\rho_{ki}$  is the rate at which a susceptible host of type  $k$  is infected by a parasite of strain  $i$  ( $i = 1, 2$  for all parameters defined below except where otherwise specified);  $\rho'_{ki}$  is the rate at which a type  $k$  host, that is already infected with strain  $j$  parasites, is infected by a parasite of strain  $i$  ( $i \neq j$ );  $\mu$  is the per-capita natural death rate of hosts (of both types);  $\delta_{ki}$  is the disease-induced death rate of hosts of type  $k$  due to parasite infection by strain  $i$ ;  $\delta_{k12}$  is the disease-induced death rate of hosts of type  $k$  coinfecting with both

Table 1  
Definitions of variables and parameters ( $k = a, b$  and  $i = 1, 2$ )

$S_k$	Number of susceptible hosts of type $k$
$I_{ki}$	Number of hosts of type $k$ infected with parasites of strain $i$
$I_{k12}$	Number of hosts of type $k$ coinfecting with both strains of parasites
$P_i$	Number of parasites of strain $i$
$\Lambda_k$	Recruitment rate of hosts of type $k$
$\rho_{ki}$	Rate at which a susceptible host of type $k$ is infected by a strain $i$ parasite
$\rho'_{ki}$	Rate at which a type $k$ host that is already infected with strain $j$ is infected by a parasite of strain $i$ ( $j \neq i$ )
$c_{ki}$	Reproduction rate of strain $i$ parasite in a singly infected host of type $k$
$d_{ki}$	Reproduction rate of strain $i$ parasite in a coinfecting host of type $k$
$\mu$	Per capita natural death rate of all hosts
$\delta_{ki}$	Per capita disease-induced death rate of singly infected hosts of type $k$
$\delta_{k12}$	Per capita disease-induced death rate of coinfecting hosts of type $k$

strains of parasite. Here we have assumed that the order of infection with different parasite strains does not play a role in parasite establishment. All variables, parameters, and their definitions are listed in Table 1.  $\check{S}_k, \check{I}_{ki}$  and  $\check{I}_{k12}$  are all non-negative constants.

### 3. Analysis of the model

Let  $N_k = S_k + I_{k1} + I_{k2} + I_{k12}$  denote the total population size of the type  $k$  host ( $k = a, b$ ). Thus we see that  $N_k(t) \leq \Lambda_k/\mu$  for all  $t \geq 0$  as  $\frac{dN_k}{dt} \leq \Lambda_k - \mu N_k$ . Hence, the total host population as well as each of the sub-classes remain bounded for all time. It is clear that all solutions of model (1) are defined on  $t \in [0, \infty)$  and remain non-negative for all time  $t > 0$ .

#### 3.1. Reproductive numbers and parasite extinction

As in most epidemiological models, the model behaviors are largely determined by reproductive numbers of parasite strains. The reproductive number for strain  $i$  in model (1) is

$$\mathcal{R}_i = \frac{c_{ai}\rho_{ai}}{(\mu + \delta_{ai})} \frac{\Lambda_a}{\mu} + \frac{c_{bi}\rho_{bi}}{(\mu + \delta_{bi})} \frac{\Lambda_b}{\mu}, \quad i = 1, 2. \quad (2)$$

These quantities have a clear biological interpretation. Consider the case when a parasite of strain  $i$  is introduced into a purely susceptible host population in which the two sub-populations have sizes  $\Lambda_a/\mu$  and  $\Lambda_b/\mu$ , respectively. The number of susceptible hosts that will become infected per unit of time is  $\rho_{ki} \frac{\Lambda_k}{\mu}$  from which the number of new parasites  $c_{ki}\rho_{ki} \frac{\Lambda_k}{\mu}$  will be produced ( $k = a, b$ ).  $1/(\mu + \delta_{ki})$  is the mean life span of a parasite of strain  $i$  within a host of type  $k$ . Thus,  $\frac{c_{ki}\rho_{ki}}{(\mu + \delta_{ki})} \frac{\Lambda_k}{\mu}$  is the number of new parasites of strain  $i$  produced by a typical parasite during its life time through hosts of type  $k$ . Therefore,  $\mathcal{R}_i$  gives the total

number of secondary parasites of strain  $i$  produced in a susceptible host population. The basic reproductive number for the full model is

$$\mathcal{R}_0 = \max\{\mathcal{R}_1, \mathcal{R}_2\}. \quad (3)$$

Arrange the variables in the following order:  $E = (S_a, S_b, I_{a1}, I_{b1}, I_{a2}, I_{b2}, I_{a12}, I_{b12})$ . The parasite-free equilibrium is  $E_0 = (\Lambda_a/\mu, \Lambda_b/\mu, 0, 0, 0, 0, 0, 0)$ . The following result shows that the basic reproductive number  $\mathcal{R}_0$  provides a threshold condition for parasite extinction.

**Result 1.** *The parasite-free equilibrium  $E_0$  is locally asymptotically stable (l.a.s.) if  $\mathcal{R}_0 < 1$ , and it is unstable if  $\mathcal{R}_0 > 1$ .*

A proof of Result 1 can be found in Appendix A. The global stability of  $E_0$  cannot be obtained when  $\mathcal{R}_0 < 1$ . Notice that the reproductive number  $\mathcal{R}_i$  is the number of secondary parasites of strain  $i$  produced in the host population when there are no other strains of parasites and hence no coinfection in the population. When another strain of parasite is introduced into the host population, the new secondary reproduction number of strain  $i$  parasites could be larger than the original  $\mathcal{R}_i$  due to coinfections (if two strains of parasites are affiliated within infected hosts). Therefore, coinfection may lead to some coexistence states and hence a global property of  $E_0$  cannot be followed when  $\mathcal{R}_0 < 1$ . Fig. 1 illustrates this point clearly. In the figure, the parameter values are chosen such that  $\mathcal{R}_1 = 0.972 < 1$ ,  $\mathcal{R}_2 = 0.945 < 1$ , and hence  $\mathcal{R}_0 < 1$ . It shows time plots of the fraction of infected hosts  $I/N$ , where  $I = I_{a1} + I_{b1} + I_{a2} + I_{b2} + I_{a12} + I_{b12}$  is the total number of infected hosts and  $N = S_a + S_b + I$  is the total number of hosts. For the purpose of demonstration all coinfection rates are assumed equal, i.e.,  $\rho'_{ki} = \rho$  ( $k = a, b$  and  $i = 1, 2$ ). We see that for low coinfection rate  $\rho$  the fraction of infected hosts  $I/N$  converges to zero (Fig. 1(a)), whereas for large  $\rho$  the fraction  $I/N$  converges to a positive value (Fig. 1(b)), implying the persistence of parasites.

To see the role of coinfection in the coexistence of two parasite strains, we trace the change of positive equilibria as the parameter  $\rho$  varies while holding all other parameters fixed. The fraction  $I_1/N$  of infected hosts by strain 1 parasites at positive equilibria is plotted versus the parameter  $\rho$  in Fig. 2. At about  $\rho = 0.00012$ , a saddle-node bifurcation occurs. For  $\rho > 0.00012$ , besides the parasite-free equilibrium  $E_0$ , the model (1) has two positive equilibria, one of which is stable (the solid curve in the figure) and the other one is unstable (the dashed curve). Therefore, depending on the initial parasite population sizes, the population either goes extinct (i.e., converges to  $E_0$ ) or is stabilized at the stable positive equilibrium. For  $\rho < 0.00012$ , the parasite population goes extinct due to the stability of  $E_0$ .

Next we investigate what happens when a novel parasite is introduced into a host population (via mutation or immigration) infected with a resident parasite strain at its positive equilibrium. More specifically, we assess whether

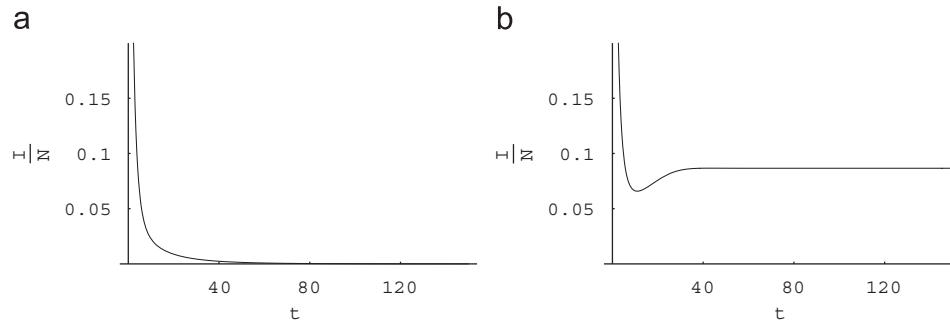


Fig. 1. Time plots of the fraction of infected hosts  $I/N$  for the case when  $\mathcal{R}_1 = 0.972 < 1$  and  $\mathcal{R}_2 = 0.945 < 1$  (i.e.,  $\mathcal{R}_0 < 1$ ). It shows that  $I/N$  converges to zero when the coinfection rate  $\rho$  is low (see (a)), and that  $I/N$  converges to a positive value when  $\rho$  is high enough (see (b)). The parameter values used are:  $A_a = 150$ ,  $A_b = 120$ ,  $c_{ki} = 150$ ,  $d_{ki} = 200$ ,  $\rho_{k1} = 0.000018$ ,  $\rho_{a2} = 0.000015$ ,  $\rho_{b2} = 0.000018$ ,  $\mu = 0.5$ ,  $\delta_{k1} = 1$ ,  $\delta_{k2} = 0.9$  and  $\delta_{k12} = 1.2$ . The coinfection rates in (a) and (b) are  $\rho = 0.00004$  and  $\rho = 0.00012$ , respectively.

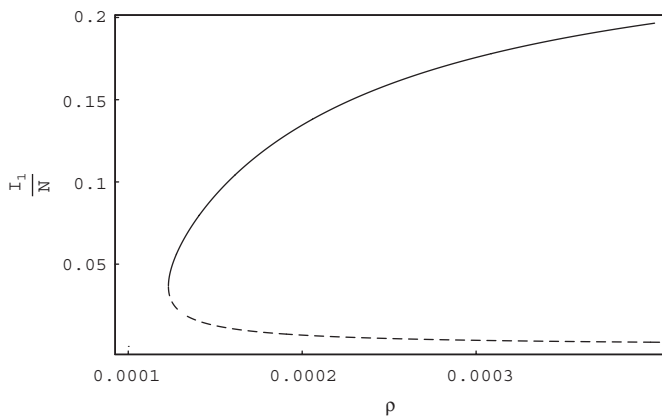


Fig. 2. The existence of positive equilibria for the coinfection model (1) in the case of  $\mathcal{R}_i < 1$ ,  $i = 1, 2$ . The y-axis is the fraction  $I_1/N$  of infected hosts by strain 1 parasites over the total population size. At  $\rho = 0.00012$ , a saddle-node bifurcation occurs. Here the parameter values except  $\rho$  are the same as those in Fig. 1.

strain  $j$  parasites can invade a resident strain  $i$  ( $i \neq j$ ). To study this question we first consider the dynamical properties of a reduced system of model (1) in which only one parasite strain is present.

### 3.2. Reduced model with a single-parasite strain

Without loss of generality, we assume that parasite strain 1 is the resident strain. To explore the possibility of invasion by parasite strain 2 we first consider the following model which is a reduction of (1) when parasite strain 2 is absent:

$$\begin{aligned} \frac{d}{dt} S_a &= A_a - \rho_{a1} P_1 S_a - \mu S_a, \\ \frac{d}{dt} S_b &= A_b - \rho_{b1} P_1 S_b - \mu S_b, \\ \frac{d}{dt} I_{a1} &= \rho_{a1} P_1 S_a - (\mu + \delta_{a1}) I_{a1}, \\ \frac{d}{dt} I_{b1} &= \rho_{b1} P_1 S_b - (\mu + \delta_{b1}) I_{b1}, \\ P_1 &= c_{a1} I_{a1} + c_{b1} I_{b1}. \end{aligned} \tag{4}$$

We need to find the condition under which parasite strain 1 can establish itself. The formula for  $\mathcal{R}_1$  defined in (2) also gives the basic reproductive number of parasite strain 1 for the reduced model. It is easy to show that, for the reduced model (4), the parasite-free equilibrium (which we denote by  $U_0$ ) is locally stable if  $\mathcal{R}_1 < 1$ . In fact, a stronger result can be obtained for the reduced model. That is,  $U_0$  is globally attractive for the reduced system (4), implying that the parasite population will go extinct as long as  $\mathcal{R}_1 < 1$ . Let  $\bar{U} = (\bar{S}_a, \bar{S}_b, \bar{I}_{a1}, \bar{I}_{b1})$  denote an interior equilibrium (i.e., all components are positive). The existence and stability of  $\bar{U}$  is given in the following result.

**Result 2.** *The parasite-free equilibrium  $U_0$  for the model (4) is globally asymptotically stable if  $\mathcal{R}_1 < 1$ , and unstable if  $\mathcal{R}_1 > 1$ . The interior equilibrium  $\bar{U}$  exists and is unique if and only if  $\mathcal{R}_1 > 1$ . Moreover,  $\bar{U}$  is stable if conditions (34) are satisfied.*

The proof of Result 2 can be found in Appendix B. It is not obvious how the stability condition (34) for  $\bar{U}$  is related to the existence condition  $\mathcal{R}_1 > 1$ , nevertheless, conditions (34) are satisfied for all parameter values used (which are biologically realistic) in our simulations. Therefore, it is reasonable to suspect that  $\bar{U}$  is stable whenever it exists. Fig. 3 illustrates the dependence on  $\mathcal{R}_1$  of the stability of  $U_0$  and  $\bar{U}$ . In this figure, all parameter values are fixed except  $\rho_{a1}$  and  $\rho_{b1}$ . Different  $\mathcal{R}_1$  values are obtained by varying  $\rho = \rho_{a1} = \rho_{b1}$ . It shows that the fraction of infected hosts,

$$\frac{I_1}{N} = \frac{I_{a1} + I_{b1}}{S_a + S_b + I_{a1} + I_{b1}}, \tag{5}$$

goes to zero for  $\mathcal{R}_1 < 1$  (see Fig. 3(a)), and it stabilizes at a positive level for  $\mathcal{R}_1 > 1$  (see Fig. 3(b),(c)) and the fraction of infected hosts at the equilibrium increases with  $\mathcal{R}_1$ .

### 3.3. Invasion criterion

In this section, we focus on the possibility of invasion by parasite strain 2 in an environment in which strain 1 is at the positive equilibrium  $\bar{U}$  (note that this is true if and only

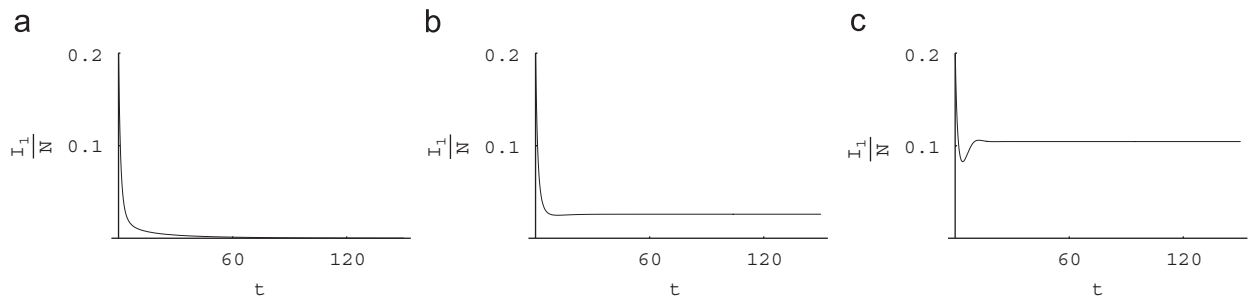


Fig. 3. Time plots of the reduced system (4) for different values of  $\mathcal{R}_1$ . It shows that the fraction of infected hosts  $I_1/N$  (see (5)) converges to zero for  $\mathcal{R}_1 < 1$  and it converges to a positive value for  $\mathcal{R}_1 > 1$ . Here,  $\Lambda_a = 150$ ,  $\Lambda_b = 120$ ,  $c_{a1} = c_{b1} = 150$ ,  $\mu = 0.5$ ,  $\delta_{a1} = \delta_{b1} = 1$ .  $\rho$  is chosen to be 0.000018, 0.00002, and 0.000025 in (a), (b) and (c), respectively. The time unit is year.

if  $\mathcal{R}_1 > 1$ ). Clearly, this positive equilibrium  $\bar{U}$  of the reduced model (4) corresponds to the boundary equilibrium,  $\bar{E} = (\bar{S}_a, \bar{S}_b, \bar{I}_{a1}, \bar{I}_{b1}, 0, 0, 0, 0)$ , of the full model (1).

Our invasion criterion is derived as follows. Consider the full system (1) and assume that it is at the equilibrium  $\bar{E}$ . Suppose that a small number of parasites of strain 2 is introduced into the population. Then whether the strain 2 parasite can invade is determined by its invasion reproductive number,  $\mathcal{R}_2^1$ , which is the secondary number of strain 2 parasites produced by an average strain 2 parasite when its “susceptible” host population size is  $\bar{S}_a + \bar{S}_b + \bar{I}_{a1} + \bar{I}_{b1}$ . Thus, to derive a formula for  $\mathcal{R}_2^1$ , we consider another reduced system of the full system (1) by assuming that  $S_a, S_b, I_{a1}, I_{b1}$  are fixed at  $\bar{E}$  and only  $I_{a2}, I_{b2}, I_{a12}$  and  $I_{b12}$  are changing with time:

$$\begin{aligned} \frac{d}{dt} I_{k2} &= \rho_{k2} P_2 \bar{S}_{k1} - \rho'_{k1} P_1 I_{k2} - (\mu + \delta_{k2}) I_{k2}, \\ \frac{d}{dt} I_{k12} &= \rho'_{k1} P_1 I_{k2} + \rho'_{k2} P_2 \bar{I}_{k1} - (\mu + \delta_{k12}) I_{k12}, \quad k = a, b, \\ P_1 &= \sum_{k=a,b} (c_{k1} \bar{I}_{k1} + d_{k1} I_{k12}), \\ P_2 &= \sum_{k=a,b} (c_{k2} I_{k2} + d_{k2} I_{k12}), \end{aligned} \quad (6)$$

with the initial conditions  $I_{k2}(0) = \check{I}_k$ ,  $I_{k12}(0) = \check{I}_{k12}$ . Let the vector of variables in (6) be denoted by  $x = (I_{a2}, I_{b2}, I_{a12}, I_{b12})$ . Then an invasion criterion can be determined by the condition under which the strain 2 parasite-free equilibrium,  $x_0 = (0, 0, 0, 0)$ , of the reduced system (6) is unstable.

Using the method developed in van den Driessche and Watmough (2002) we obtain the following formula (see Appendix C for the derivation):

$$\mathcal{R}_2^1 = \sum_{k=a,b} \left( \frac{c_{k2} \rho_{k2} \bar{S}_k}{T_{k2}} + \frac{w_{k1} d_{k2} \rho_{k2} \bar{S}_k}{T_{k12}} + \frac{d_{k2} \rho'_{k2} \bar{I}_{k1}}{T_{k12}} \right), \quad (7)$$

where

$$w_{k1} = \frac{\rho'_{k1} \bar{P}_1}{\rho'_{k1} \bar{P}_1 + \mu + \delta_{k2}}, \quad T_{k2} = \rho'_{k1} \bar{P}_1 + \mu + \delta_{k2},$$

$$T_{k12} = \mu + \delta_{k12},$$

$\bar{S}_k, \bar{P}_1, \bar{I}_{k1}$  satisfy (16)–(20) in Appendix C.

The biological interpretation of the formula (7) is clear. For type  $k$  host, the three terms in  $\mathcal{R}_2^1$  represent contributions of parasite strain 2 from hosts in the following three categories: (1) singly infected hosts with parasite strain 2 (the term  $c_{k2} \rho_{k2} \bar{S}_k / T_{k2}$ ), (2) doubly infected hosts that were infected by parasite strain 1 first (the term  $w_{k1} d_{k2} \rho_{k2} \bar{S}_k / T_{k12}$ ) and (3) doubly infected hosts that were infected by parasite strain 2 first (the term  $d_{k2} \rho'_{k2} \bar{I}_{k1} / T_{k12}$ ). Notice that  $w_{k1}$  is the fraction of hosts in the  $I_{k2}$  class that will survive and become doubly infected. Notice also that the mean time a host of category 1 stays in the  $I_{k2}$  class is  $1/T_{k2} = 1/(\rho'_{k1} \bar{P}_1 + \mu + \delta_{k2})$ , while the mean time a doubly infected host stays in the  $I_{k12}$  class is  $1/T_{k12} = 1/(\mu + \delta_{k12})$ . Therefore, the formula for  $\mathcal{R}_2^1$  in (7) gives the total number of new (secondary) parasites of strain 2 generated by a typical strain 2 parasite during its life time.

The following result shows that the quantity  $\mathcal{R}_2^1$  determines the stability of the boundary equilibrium  $\bar{E} = (\bar{S}_a, \bar{S}_b, \bar{I}_{a1}, \bar{I}_{b1}, 0, 0, 0, 0)$  of the full model (1) and hence provides an invasion criterion.

**Result 3.** Let  $\mathcal{R}_1 > 1$  and let the positive equilibrium  $\bar{U}$  be stable for the system (4). The boundary equilibrium  $\bar{E}$  of the system (1) is l.a.s. if  $\mathcal{R}_2^1 < 1$  and unstable if  $\mathcal{R}_2^1 > 1$ .

A proof of Result 3 is given in Appendix D. This result suggests that the threshold condition,  $\mathcal{R}_2^1 > 1$ , can be used as an invasion criterion for the full system (1). Some numerical simulations are shown in Fig. 4. In the figure,  $I_i$  represents the total number of hosts infected with strain  $i$  parasites, i.e.,  $I_i = I_{ai} + I_{bi} + I_{a12} + I_{b12}$ ,  $i = 1, 2$ . Different values of  $\mathcal{R}_2^1$  are obtained by varying the coinfection rates  $\rho'_{a2}$  and  $\rho'_{b2}$  which for simplicity are assumed equal, i.e.,  $\rho'_{a2} = \rho'_{b2} = \rho$ .

Our simulations also suggest that the competitive ability of parasite strain 2 increases with the invasion reproductive number  $\mathcal{R}_2^1$ . Fig. 5 is a bifurcation diagram for the full system (1), which plots the steady-state value of the fraction of infected hosts by each of the two strains ( $I_1^*/N$  or  $I_2^*/N$ ) as a function of the parameter  $\mathcal{R}_2^1$ . The solid curves represent a stable steady state and dashed lines represent an unstable steady state. It shows that the fraction of hosts infected by parasite strain 2 becomes positive as  $\mathcal{R}_2^1$  passes 1 and strictly increases with  $\mathcal{R}_2^1$ .

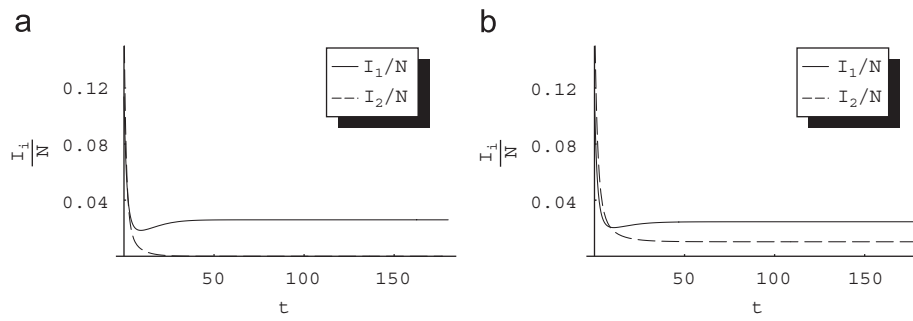


Fig. 4. Time plots of the full system (1) for different values of the invasion reproductive number  $\mathcal{R}_2^1$ . It illustrates that strain 2 parasite cannot invade if  $\mathcal{R}_2^1 < 1$  as shown in (a), and that strain 2 can invade and establish if  $\mathcal{R}_2^1 > 1$  as shown in (b). Here we assume  $\rho'_{a2} = \rho'_{b2} = \rho$ , where  $\rho$  is 0.00006 in (a) and 0.0001 in (b). Parameter values are:  $\rho_{k1} = 0.00002$ ,  $\rho_{k2} = 0.000018$ ,  $\rho'_{k1} = 0.00002$ ,  $\delta_{k2} = 0.9$ ,  $\delta_{k12} = 1.2$ ,  $d_{ki} = 200$  ( $k = a, b, i = 1, 2$ ), other parameters have the same values as in Fig. 3.

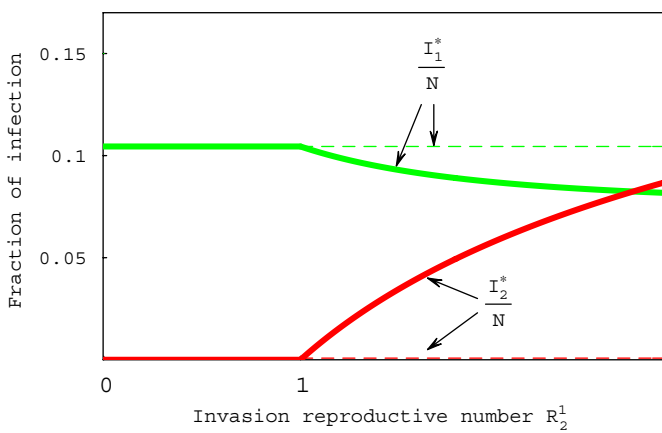


Fig. 5. Bifurcation diagram showing the fraction,  $I_i^*/N$  ( $i = 1, 2$ ), of infected hosts at steady states as a function of the invasion reproductive number  $\mathcal{R}_2^1$ . Solid curves represent stability and dashed curves represent instability. It shows that  $I_2^*/N = 0$  for  $\mathcal{R}_2^1 < 1$  and the interior equilibrium is stable (i.e.,  $I_i^*/N > 0$ ,  $i = 1, 2$ ) for  $\mathcal{R}_2^1 > 1$ . Parameters take the same values as in Fig. 4 except  $\rho$ , which varies to get different values of  $\mathcal{R}_2^1$ .

Notice that the magnitude of  $\mathcal{R}_2^1$  depends on several parameters related to coinfections including  $c_{ki}$ ,  $d_{ki}$ ,  $\rho'_{ki}$  and  $\delta_{k12}$  ( $k = a, b$  and  $i = 1, 2$ ). Therefore, the assumptions underlying these parameters may have significant influence on the outcomes of the host–parasite interaction. This will be considered next.

### 3.4. Effect of coinfection on parasite persistence

To make it transparent of the effect of coinfection on the persistence of a parasite strain, when the two parasite strains are competing for the same source of hosts, we first consider the special case where  $\rho_{a1} = \rho_{b1}$ . In this case,  $\bar{S}_k$  are given by (33) in Appendix B. If we set all coinfection rates to be zero, i.e.,  $\rho'_{ki} = 0$  ( $k = a, b$  and  $i = 1, 2$ ), then

$$\mathcal{R}_2^1 = \frac{\mathcal{R}_2}{\mathcal{R}_1}. \quad (8)$$

Therefore, the boundary equilibrium  $\bar{E}$  (recall that  $\bar{E}$  exists only if  $\mathcal{R}_1 > 1$ ) is stable if  $\mathcal{R}_2 < \mathcal{R}_1$  and unstable if  $\mathcal{R}_2 > \mathcal{R}_1$ . A symmetric result holds for the boundary equilibrium representing strain 2 only in the host population. This

implies that, if the two parasite strains do not specialize on different type of hosts, i.e.,

$$\rho_{ai} = \rho_{bi}, \quad i = 1, 2, \quad (9)$$

then the usual principle of competitive exclusion holds when coinfection is not permitted. Thus, the following result holds, which is also confirmed by numerical simulations (see Fig. 6).

**Result 4.** Let condition (9) hold and  $\mathcal{R}_i > 1$  ( $i = 1, 2$ ). In the absence of coinfection, the parasite strain  $i$  will exclude strain  $j$  ( $j \neq i$ ) if and only if  $\mathcal{R}_i > \mathcal{R}_j$ . That is, coexistence of both parasite strains is impossible if coinfection is not permitted.

It is also interesting to notice from (7) that  $\mathcal{R}_2^1$  is an increasing function of the coinfection rate  $\rho'_{k2}$  ( $k = a, b$ ). In the case of  $\rho_{a1} = \rho_{b1}$ , from (8) and  $\mathcal{R}_1 > 1$  we have

$$\mathcal{R}_2^1 < \mathcal{R}_2 \quad \text{if } \rho'_{ki} = 0. \quad (10)$$

This implies that if  $\mathcal{R}_2 < 1$  (i.e., parasite strain 2 cannot persist in the absence of strain 1), then the invasion of strain 2 is impossible when  $\rho'_{k2} = 0$  (i.e., parasite strain 2 cannot infect hosts that are already infected by strain 1 in the absence of coinfection). Since  $\mathcal{R}_2^1$  increases with  $\rho'_{k2}$ , it is possible that  $\rho'_{k2}$  is large enough so that  $\mathcal{R}_2^1$  exceeds 1. That is, if coinfection is allowed then the following conditions may hold:

$$\mathcal{R}_2^1 > 1, \quad \mathcal{R}_2 < 1. \quad (11)$$

In this case, parasite strain 2 is able to invade, but only in the presence of parasite strain 1.

This is confirmed by our numerical simulations shown in Fig. 7. In this figure  $\rho = \rho'_{a2} = \rho'_{b2}$ , and the equilibrium fractions of infected hosts,  $I_i/N$ , are plotted as a function of  $\tilde{\rho} = 10^4 \rho$ , where  $I_i = I_{ai} + I_{bi} + I_{a12} + I_{b12}$ ,  $i = 1, 2$ . It shows that when the coinfection rate is low (i.e.,  $\tilde{\rho} < 0.8$  for the chosen set of parameter values)  $I_2/N = 0$  at the equilibrium, and when  $\tilde{\rho} > 0.8$  there is a stable equilibrium at which  $I_2/N > 0$  (the solid curve). Other parameter values used in this figure are the same as those in Fig. 4.

From the above observations we know that if  $\mathcal{R}_2 < 1$ , a bifurcation occurs as  $\rho'_{k2}$  increases from 0. That is, there

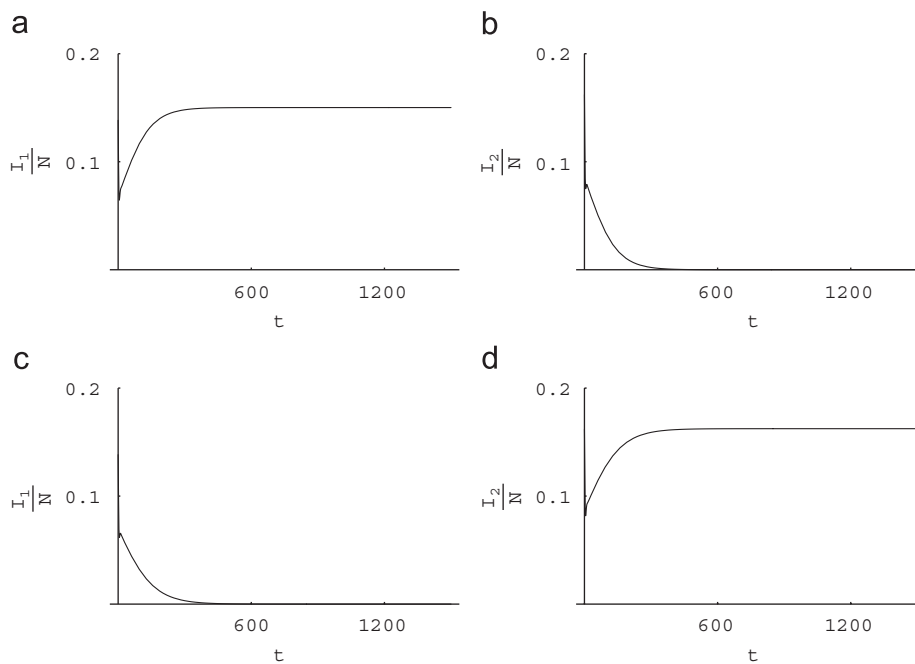


Fig. 6. Numerical solutions of the system (1) showing that the strain  $i$  with a larger value of  $\mathcal{R}_i$  excludes the strain  $j$  ( $j \neq i$ ).  $\mathcal{R}_1 > \mathcal{R}_2$  in (a) and (b), and it shows that strain 1 excludes strain 2.  $\mathcal{R}_1 < \mathcal{R}_2$  in (c) and (d), and it shows that strain 2 excludes strain 1. The parameter values used are:  $\rho'_{ki} = 0$ ,  $A_a = 150$ ,  $A_b = 120$ ,  $\rho_{k1} = 0.000017$ ,  $c_{k1} = 250$ ,  $\delta_{k1} = 1$ ,  $\delta_{k2} = 0.9$ ,  $\mu = 0.5$ . For (a) and (b),  $\rho_{k2} = 0.000016$ , corresponding to  $\mathcal{R}_2 = 1.513 < 1.53 = \mathcal{R}_1$ ; for (c) and (d),  $\rho_{k2} = 0.0000157$ , corresponding to  $\mathcal{R}_2 = 1.542 > 1.53 = \mathcal{R}_1$ .

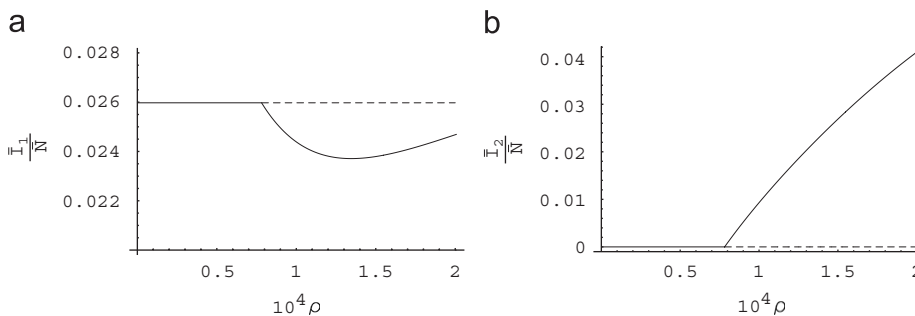


Fig. 7. Bifurcation diagram for the case when  $\mathcal{R}_1 = 1.08 > 1$ ,  $\mathcal{R}_2 = 0.945 < 1$ . Solid curves represent stable equilibria while dashed curves represent unstable equilibria.

exists a threshold value  $\hat{\rho}$  such that

$$\begin{cases} \mathcal{R}_2^1 < 1 & \text{if } \rho < \hat{\rho}, \\ \mathcal{R}_2^1 > 1 & \text{if } \rho > \hat{\rho}. \end{cases}$$

Hence, parasite strain 2 can invade if  $\rho > \hat{\rho}$  and it cannot invade if  $\rho < \hat{\rho}$ .

### 3.5. Co-existence of both strains

Similarly to the derivation of the invasion criterion  $\mathcal{R}_2^1 > 1$  for parasite strain 2 to invade strain 1, we can also derive an equivalent condition under which parasite strain 1 can invade strain 2, which is  $\mathcal{R}_1^2 > 1$ , where  $\mathcal{R}_1^2$  is the invasion reproductive number of parasite strain 1 given by

$$\mathcal{R}_1^2 = \sum_{k=a,b} \left( \frac{c_{k1}\rho_{k1}\tilde{S}_k}{T_{k1}} + \frac{w_{k2}d_{k1}\rho_{k1}\tilde{S}_k}{T_{k12}} + \frac{d_{k1}\rho'_{k1}\tilde{I}_{k2}}{T_{k12}} \right), \quad (12)$$

where

$$w_{k2} = \frac{\rho'_{k2}\tilde{P}_2}{\rho'_{k2}\tilde{P}_2 + \mu + \delta_{k1}}, \quad T_{k1} = \rho'_{k2}\tilde{P}_2 + \mu + \delta_{k1},$$

$$T_{k12} = \mu + \delta_{k12}.$$

$\tilde{S}_k$  and  $\tilde{I}_{k2}$  are components of the equilibrium for strain 2,  $\tilde{U} = (\tilde{S}_a, \tilde{S}_b, \tilde{I}_{a2}, \tilde{I}_{b2})$ . The components satisfy the same equations as in (16)–(20) for  $\tilde{U}$  with the switch of index from 1 to 2.

We can also show that for the full model (1) the boundary equilibrium

$$\tilde{E} = (\tilde{S}_a, \tilde{S}_b, 0, 0, \tilde{I}_{a2}, \tilde{I}_{b2}, 0, 0),$$

where only parasite strain 2 is present, is stable if  $\mathcal{R}_1^2 < 1$  and unstable if  $\mathcal{R}_1^2 > 1$ . Combining this with Result 3 and some numerical simulations we have the following result.



**Result 5.** (a) If  $\mathcal{R}_j^i < 1$  then parasite strain  $j$  cannot invade strain  $i$  ( $i, j = 1, 2, j \neq i$ ). (b) If both of the invasion reproductive numbers exceed 1, i.e.,  $\mathcal{R}_1^1 > 1$  and  $\mathcal{R}_2^1 > 1$ , then the coexistence of two parasite strains is possible due to the instability of both boundary equilibria,  $\tilde{E}$  and  $\tilde{E}$ .

We remark that the part (b) of Result 5 on coexistence is shown only via numerical computations (e.g., see Fig. 7). The results obtained in this section will be applied to the study of evolutionary consequences of the two-parasite and two-host interaction.

#### 4. Host life-history strategies and parasite evolution

In this section we investigate numerically the evolutionary outcomes of the host–parasite interaction mediated by coinfection. We consider three scenarios characterized by the defense mechanisms adopted by the hosts. Differences in the mechanisms are generated by varying the relationship between parasite virulence and parasite reproduction within hosts. Two of the cases are termed *tolerance* and *control* (see Miller et al., 2005), and an additional case is the one that we term *threshold*.

For the tolerance case, it is assumed that there is no correlation between parasite reproductive rate  $c_{ki}$  and the infection-induced host death rate  $\delta_{ki}$ . For the control case, we assume a correlation between infection-induced death rate and parasite reproductive rate, whereby reductions in host pathology is achieved by constraining parasite release (i.e., exploitation) via defense mechanisms. A particular form we consider here is

$$c_{ki} = \phi \delta_{ki}, \quad d_{ki} = \phi \delta_{k12},$$

$$k = a, b, \quad i = 1, 2, \tag{13}$$

where  $\phi$  is a positive constant. Unlike the model by Miller et al. (2005) we do not assume a life-history cost associated with host defense. Finally, for the threshold case, we assume that parasite release rates saturate with increasing rates of disease-induced mortality. Initially, a positive correlation exists between parasite release rate and mortality; however the release rate of the parasite asymptotes when host mortality is large. In this case, we see that contour curves are very similar when there is no coinfection. We describe the threshold function as,

$$c_{ki} = \frac{e_1 \delta_{ki}}{e_2 + \delta_{ki}}, \quad d_{ki} = \frac{e_1 \delta_{k12}}{e_2 + \delta_{k12}},$$

$$k = a, b, \quad i = 1, 2, \tag{14}$$

where  $e_1$  and  $e_2$  are positive constants. For ease of reference we list the mathematical representations of the three cases in Table 2.

The parasite strategies for invasion may depend on many factors associated with both hosts and parasites. Our model (1) is capable of incorporating many heterogeneities in hosts and parasites. For demonstration purposes we present only some of the possibilities. For example, our

Table 2  
Three host defense mechanisms ( $k = a, b$  and  $i = 1, 2$ )

	Tolerance	Control	Threshold
Assumption for $c_{ki}$	Constant	$c_{ki} = \phi \delta_{ki}$	$c_{ki} = e_1 \delta_{ki} / (e_2 + \delta_{ki})$
Assumption for $d_{ki}$	Constant	$d_{ki} = \phi \delta_{k12}$	$d_{ki} = e_1 \delta_{k12} / (e_2 + \delta_{k12})$

numerical results presented in Fig. 8 have used the following constraints on the parameters.

- (i)  $\rho_{a1} > \rho_{a2}$  and  $\rho_{b1} < \rho_{b2}$ , i.e., parasite strain 1 has a higher infection rate in susceptible hosts of type  $a$  while parasite strain 2 has a higher infection rate in susceptible hosts of type  $b$ .
- (ii)  $\delta_{a1} < \delta_{b1}$ , i.e., the virulence of parasite strain 1 (for a singly infected host) is lower in hosts of type  $a$  than in hosts of type  $b$ .
- (iii)  $\rho'_{ki} = \rho$  ( $k = a, b; i = 1, 2$ ), i.e., all coinfection rates are equal.
- (iv)  $\delta_{k12} = 0.8 (\delta_{k1} + \delta_{k2})$ ,  $k = a, b$ , i.e., the virulence in coinfecting hosts is higher than in singly infected hosts but is lower than the sum.

The constraints outlined in (i)–(iv) are derived via theoretical and empirical results. One of the key conceptual ideas in evolutionary biology to help explain the occurrence of parasite polymorphism (i.e., virulence polymorphism, infection polymorphism) in natural systems is the occurrence of “specificity costs” where parasites adapted to one particular host genotype (i.e., better able to infect or exploit a particular host) necessarily exhibit reduced fitness on the other host genotypes. In the absence of these trade-offs, one would expect (all things being equal) a single parasite genotype to emerge. Typically, however, numerous parasite genotypes are found in host populations. Differential infectivity and virulence has been demonstrated in a small number of animal parasite systems (e.g., Decaestecker et al., 2003; Little et al., 2006).

We first examine the possible evolutionary consequences of the host–parasite interaction under the three host life-history strategies listed in Table 2. Consider the scenario in which a new parasite strain (e.g., strain 2) is trying to invade a population where a wild strain (e.g., strain 1) is already established. Based on Results 4 and 5, we suspect that the competitive ability of the strain 2 is determined by the invasion reproductive number  $\mathcal{R}_2^1$ , not its basic reproductive number  $\mathcal{R}_2$ . Therefore, we assume that natural selection will favor the parasite strain that maximizes its invasion reproductive number  $\mathcal{R}_2^1$  under particular virulence constraints. For example, in Fig. 8 we have used the following constraint for  $(\delta_{a2}, \delta_{b2})$ :

$$\frac{\delta_{a2}}{\delta_{a1}} + \frac{\delta_{b2}}{\delta_{b1}} = c \tag{15}$$

( $c$  for constant,  $c > 0$ ). Eq. (15) represents the straight line in Fig. 8. Let  $(\delta_{a2}^*, \delta_{b2}^*)$  denote the optimal virulence pair

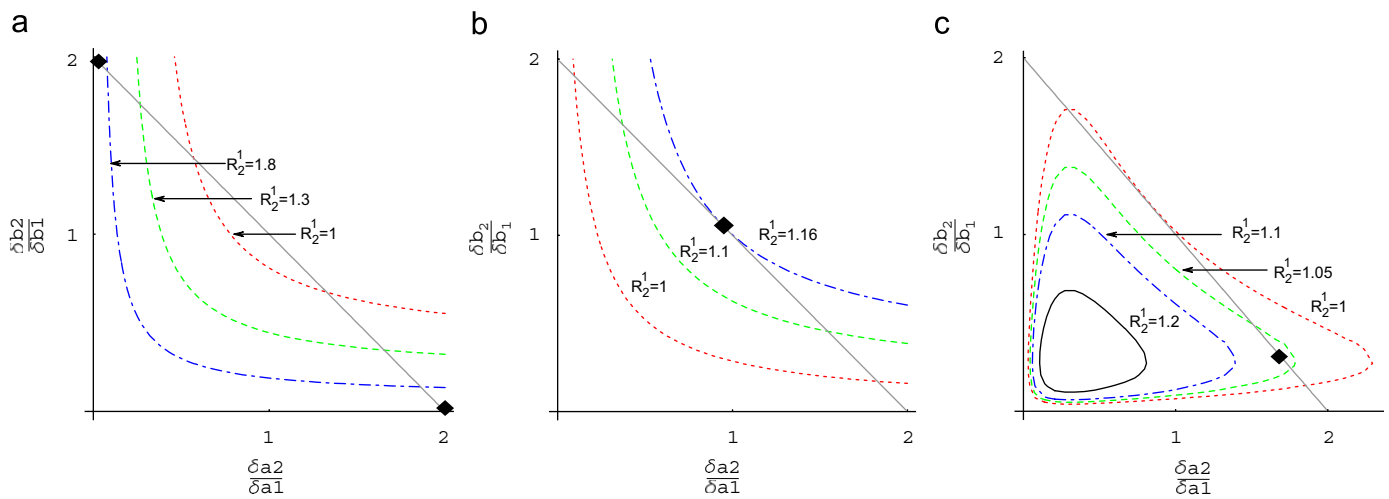


Fig. 8. Contour plot of  $\mathcal{R}_2^1$  as a function of  $(\frac{\delta_{a2}}{\delta_{a1}}, \frac{\delta_{b2}}{\delta_{b1}})$ . A diamond represents a pair of values of  $\delta_{a2}$  and  $\delta_{b2}$  for which  $\mathcal{R}_2^1$  is maximized under the constraint  $\frac{\delta_{a2}}{\delta_{a1}} + \frac{\delta_{b2}}{\delta_{b1}} = 2$ . It shows that, for the chosen set of parameter values,  $\mathcal{R}_2^1$  is maximized at (a) two extreme points in the tolerance case, (b) a single point at which  $\delta_{a2}$  and  $\delta_{b2}$  are similar in the control case, or (c) a single point at which  $\delta_{a2}/\delta_{a1}$  is much larger than  $\delta_{b2}/\delta_{b1}$  in the threshold case. Note that in the case (c) curves corresponding to large  $\mathcal{R}_2^1$  values do not intersect with the line  $\frac{\delta_{a2}}{\delta_{a1}} + \frac{\delta_{b2}}{\delta_{b1}} = 2$ .

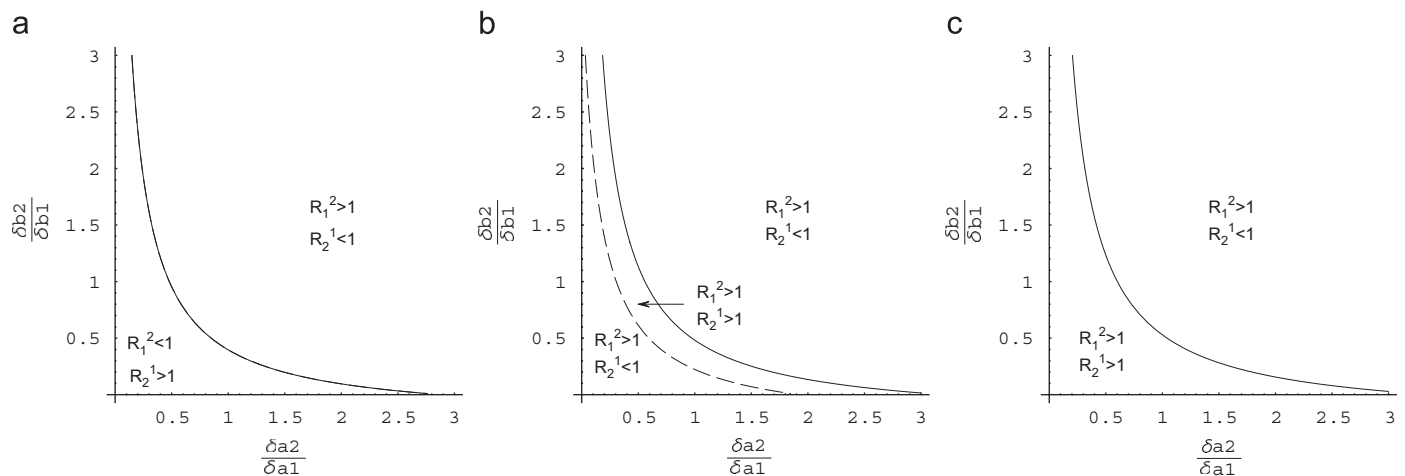


Fig. 9. This is for the tolerance case. Contour curves  $\mathcal{R}_1^2 = 1$  (dashed) and  $\mathcal{R}_2^1 = 1$  (solid) are plotted and the region of coexistence given by  $\mathcal{R}_2^1 > 1$  and  $\mathcal{R}_1^2 > 1$  is specified for  $\rho = 0, 0.0001$  and  $0.0002$ . It shows that the coexistence region increases with  $\rho$ .

which maximizes  $\mathcal{R}_2^1$ . Then  $(\delta_{a2}^*, \delta_{b2}^*)$  are given by the intersection point(s) of the line (15) and the level curve of  $\mathcal{R}_2^1$  with the largest value, which is represented by a diamond in Fig. 8. Parameter values used are the same as those in Fig. 4.

We observe in Fig. 8 that the three host defense mechanisms may lead to very different  $(\delta_{a2}^*, \delta_{b2}^*)$ . In the case of tolerance described in Table 2,  $\mathcal{R}_2^1$  is maximized when  $(\delta_{a2}^*, \delta_{b2}^*) = (0, c\delta_{b1})$  or  $(c\delta_{a1}, 0)$ , i.e., the virulence is the highest in one type of hosts and lowest in the other (Fig. 8(a)). This pattern could ultimately result in the selection of parasites that preferentially infect one host type over another, allowing for the emergence of specialist parasite strategies. In the control case, both  $\delta_{a2}^*$  and  $\delta_{b2}^*$  are positive and have an intermediate value with similar magnitudes (Fig. 8(b)), suggesting possible selection for more generalist strategies. In the threshold case, both  $\delta_{a2}^*$

and  $\delta_{b2}^*$  are again positive but one may have a much larger value than another (Fig. 8(c)). Clearly, this is intermediate between the last two cases. In fact, it will resemble more the tolerance case if  $e_2$  is small while it will resemble more the control case if  $e_2$  is large.

Next, we examine the variation in invasion conditions and coexistence regions when the coinfection rate is varied. For simplicity we assume that all coinfection rates are equal, i.e.,  $\rho'_{a1} = \rho'_{a2} = \rho'_{b1} = \rho'_{b2} = \rho$ . For each graph in Fig. 9, we again fix the virulence of parasite strain 1 ( $\delta_{a1}$  and  $\delta_{b1}$ ) and plot  $\mathcal{R}_i^j$  as a function of the virulence of parasite strain 2 ( $\delta_{a2}$  and  $\delta_{b2}$ , or equivalently,  $\frac{\delta_{a2}}{\delta_{a1}}$  and  $\frac{\delta_{b2}}{\delta_{b1}}$ ). The curves determined by  $\mathcal{R}_1^2 = 1$  and  $\mathcal{R}_2^1 = 1$  are drawn, which identify three possible regions representing coexistence ( $\mathcal{R}_1^2 > 1$  and  $\mathcal{R}_2^1 > 1$ ) or competitive exclusion ( $\mathcal{R}_i^j > 1$  and  $\mathcal{R}_j^i < 1, i \neq j$ ). When there is no coinfection (i.e.,  $\rho = 0$ ), only one parasite strain will survive and persist, and

coexistence does not occur (Fig. 9(a)). When the coinfection rate becomes positive and increases (Fig. 9(b), (c)), the region of coexistence ( $\mathcal{R}_1^2 > 1$  and  $\mathcal{R}_2^1 > 1$ ) appears and expands. It also suggests that coexistence is more likely to occur when the ratios,  $\frac{\delta_{a2}}{\delta_{a1}}$  and  $\frac{\delta_{b2}}{\delta_{b1}}$ , are small, which means that parasite strain 2 has a lower virulence in both types of hosts. The parameter values used in this figure are  $d_{ki} = d = 250$ ,  $c_{ki} = c = 150$ ,  $\Lambda_a = 150$ ,  $\Lambda_b = 120$ ,  $\rho_{a1} = \rho_{b1} = 6 \times 10^{-5}$ ,  $\rho_{a2} = \rho_{b2} = 5 \times 10^{-5}$ ,  $\mu = 1$ ,  $\delta_{a1} = \delta_{b1} = 1$ ,  $\delta_{a2} = \delta_{b2} = 1.1$ .

For the control case, the region of coexistence also increases with the coinfection rate  $\rho$ , which is similar to the case of tolerance (see Fig. 10). However, due to the correlation between  $c_{ki}$  and  $\delta_{ki}$  (see (13)), it shows that coexistence is more likely to occur when the ratios,  $\frac{\delta_{a2}}{\delta_{a1}}$  and  $\frac{\delta_{b2}}{\delta_{b1}}$ , are large, which means that parasite strain 2 has a higher virulence in both types of hosts. This is opposite to the case of tolerance. Values of other parameters are the same as in Fig. 9 with  $\phi = 150$ .

Finally, Fig. 11 is for the threshold case (see (14)). We observe again that the coexistence region increases with the coinfection rate  $\rho$ , which is the same as the last two cases. However, unlike in the tolerance or control case, coexistence is now possible only for intermediate values of virulence for both parasite strains and both host types. Other parameter values are the same as in Fig. 9 with  $e_1 = 160$  and  $e_2 = 0.1$ .

Figs. 9–11 illustrate the influence of coinfection in the outcomes of the host–parasite interaction. In these figures, we have assumed that the parasite reproduction rates in coinfecting hosts ( $d_{ki}$ ) are equal for both parasite strains and both types of hosts. We can also examine the effect when we vary  $d_{ki}$  which reflects the heterogeneity in differential capacity of parasites to infect and exploit different host types. Experimental evidence has demonstrated that significant reproductive differences can occur in particular parasite strains when they occur in coinfecting hosts of different genetic backgrounds (de Roode et al., 2004).

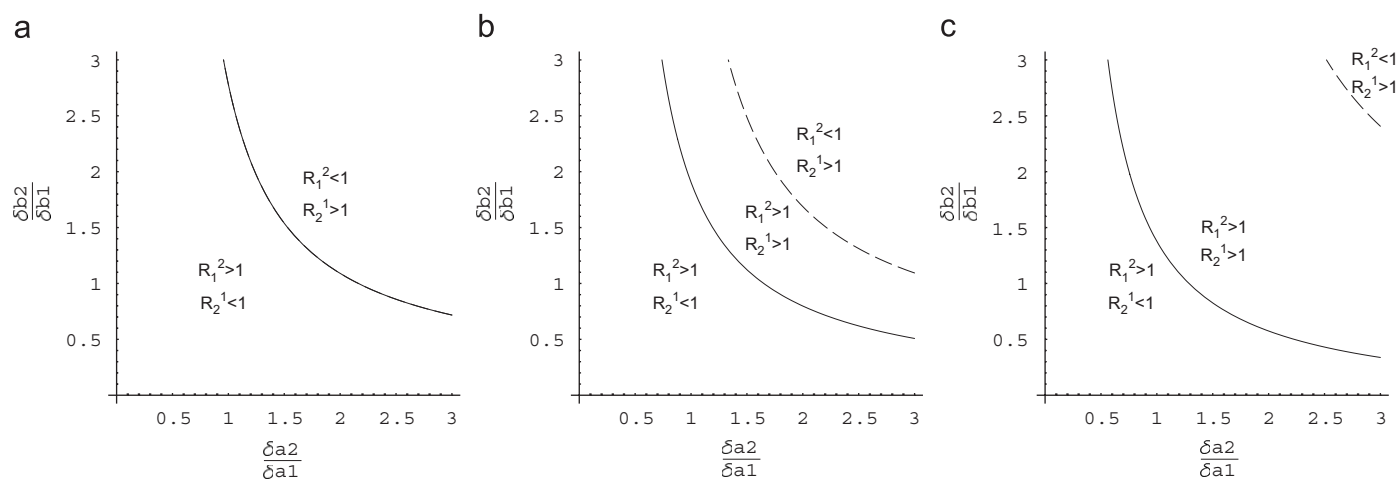


Fig. 10. This is for the control case. It seems to be similar to the tolerance case that the coexistence region increases with  $\rho$ .

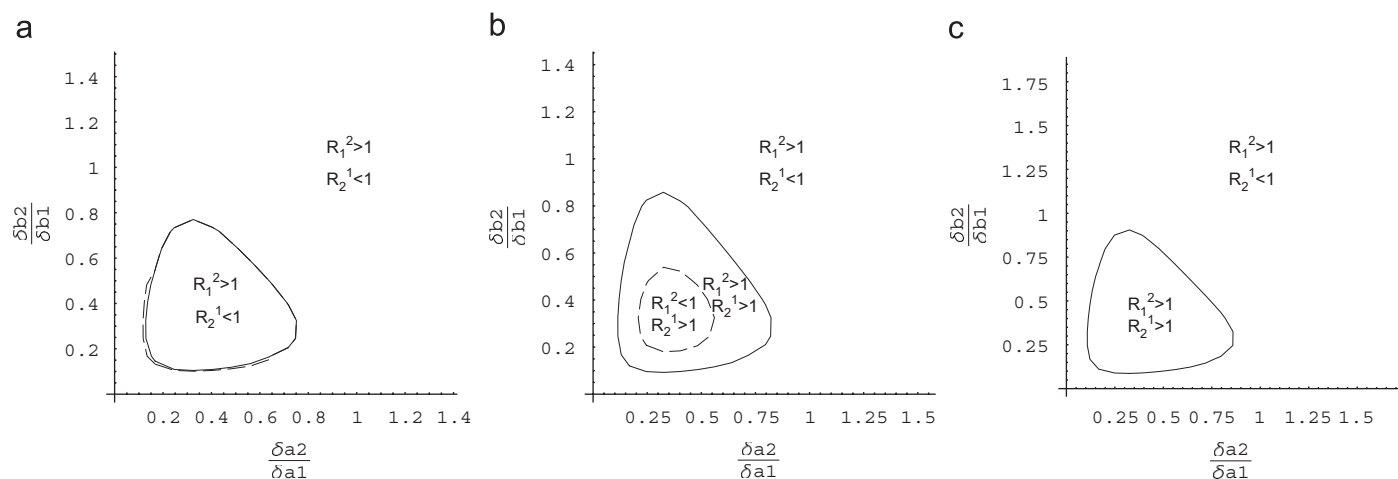


Fig. 11. This is for the threshold case. The shapes of the curves  $\mathcal{R}_i^j$  are very different from the last two cases, while the coexistence region is still increasing with  $\rho$ .

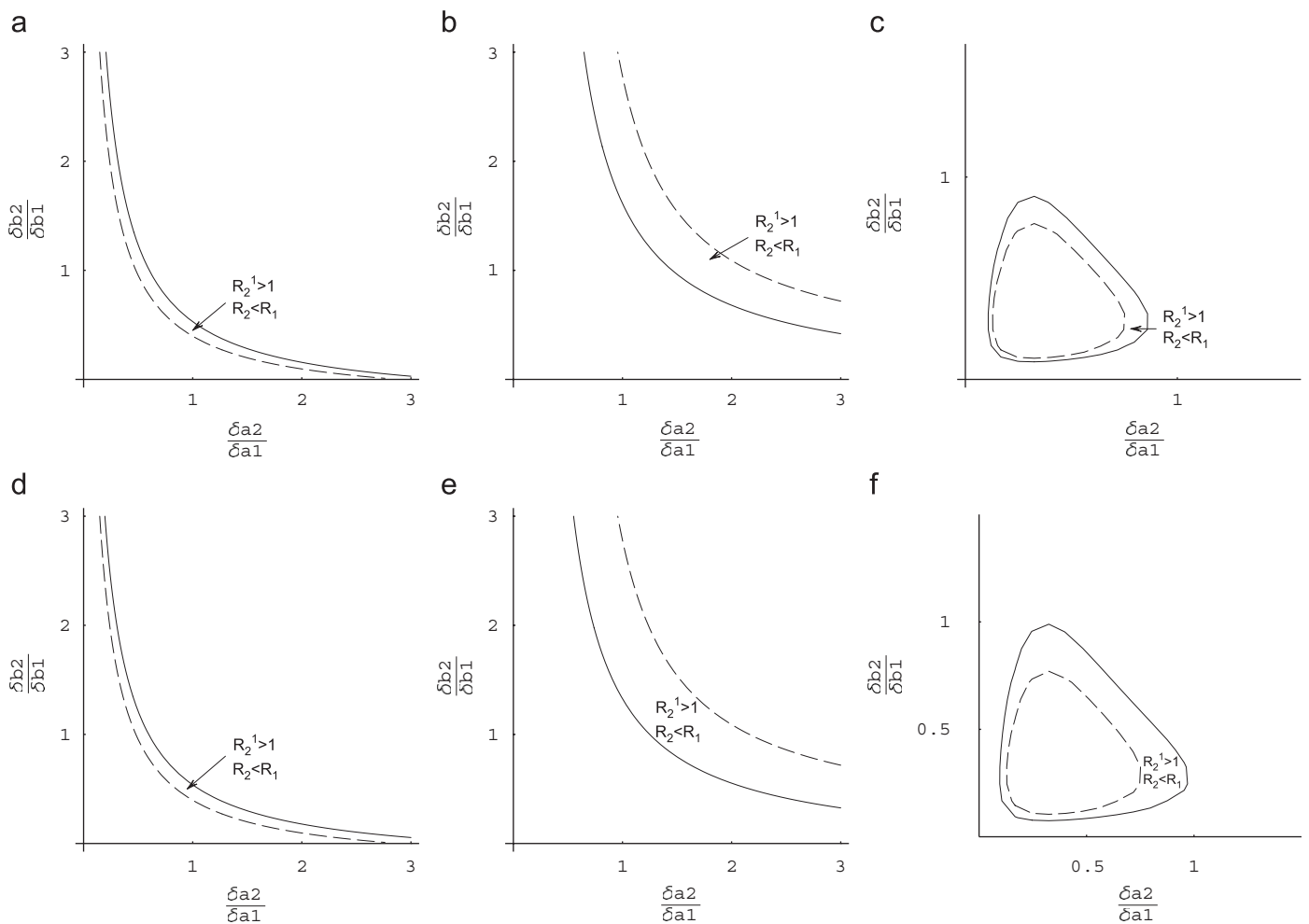


Fig. 12.  $\rho = 2 \times 10^{-5}$  in all figures. For (a) and (b),  $d_{a1} = d_{a2} = 200$ ,  $d_{b2} = 320 = 4d_{b1}$ . For (c) and (d),  $d_{a1} = d_{a2} = \phi\delta_{a12}$ ,  $d_{b2} = 1.6(\phi\delta_{b12}) = 4d_{b1}$ , where  $\phi = 150$ . In (e) and (f),  $d_{a1} = d_{a2} = e_1\delta_{a12}/(e_2 + \delta_{a12})$ ,  $d_{b2} = 1.6(e_1\delta_{b12}/(e_2 + \delta_{b12})) = 4d_{b1}$ . Other parameters are the same as in Figs. 9–11.

In Fig. 12 we consider a case where parasites demonstrate similar reproduction in coinfecting hosts of type  $a$  while parasite strain 2 specializes on (i.e., better exploits) host type  $b$ , which leads to the condition  $d_{a1} = d_{a2}$  and  $d_{b2} > d_{b1}$ . For the purpose of comparison, we assume for (a)–(c) that  $d_{b2} = d_{b1}$ , but for (d)–(f) we assume that  $d_{b2} = 4d_{b1}$  with the constraint that  $d_{b2} + d_{b1}$  is unchanged. The coinfection rate  $\rho$  is fixed at the same positive value for (a)–(f). To make it transparent of the role of host heterogeneity, we use other parameters such that  $R_2 < R_1$ . We are interested in the region  $\Omega$  determined by  $R_2 < R_1$  and  $R_2^1 > 1$  (i.e., the region between the solid and dashed curves shown in Fig. 12) in which coinfection is required for parasite strain 2 to survive. We examine how this region will change due to the heterogeneity described above. In the case of tolerance, ((a) and (d)), the magnitude of the invasion region  $\Omega$  does not differ based on host heterogeneity. Under the control ((b) and (e)) and threshold ((c) and (f)) scenarios, the invasion region  $\Omega$  expands (although not dramatically) if infection heterogeneity occurs in the system.

## 5. Discussion

Understanding the establishment and transmission of parasitic organisms is essential for predicting the manifestation and spread of disease. Unfortunately, acquisition of the empirical data necessary for such analysis is limited by both temporal and financial constraints. Mathematical models have been employed to circumvent these issues and their utilization has broadened our knowledge of the evolutionary outcomes that can occur between hosts and parasites. In this study we assessed the evolutionary dynamics in an interaction that included multiple strains of host, of parasite, and the potential for coinfection by different parasite strains.

Not surprisingly, in the case where the two parasite strains are not specialized on different hosts and coinfection was not permitted in our study, the parasite strain with the highest basic reproductive rate ( $R_0$ ) excluded those expressing lower values. In the case where coinfection was permitted, parasite strains with lower  $R_0$  could coexist in the population, but only under particular conditions, namely when rates of coinfection were above particular

thresholds. Under these circumstances, even parasite strains with  $\mathcal{R}_0$  values less than 1 could invade and persist in the population. In biological systems this could occur via facilitation where the infection of hosts by one parasite strain enhances the probability of infection by other parasite strains. There is substantial empirical support for this phenomenon at the species level (Christensen et al., 1987). For example, the trematode species, *Austrobilharzia terrigalensis*, is only able to infect its host snail (*Valcumnus australis*) if the snail has been previously infected by other trematode species (Appleton, 1983). Less evidence exists for infection facilitation within a species due to a lack of tools required for genotype-level detection. However, some empirical work has demonstrated that parasite strains can co-occur within hosts suggesting that facilitation may be occurring in host–parasite systems (Eppert et al., 2002).

Our results in this paper demonstrate the possible effect of coinfection on parasite persistence. To make this transparent, we have considered in Result 4 the case where the two-parasite strains do not specialize on different host types. If, however, each parasite strain specializes on one type of host, then coexistence may be possible even if there is no coinfection and, e.g.,  $\mathcal{R}_1 > \mathcal{R}_2$  (see Regoes et al., 2000; Li et al., 2003).

In this study, reductions in coinfection rates prevented parasite strain  $i$  from invading host populations even in circumstances where  $\mathcal{R}_i > 1$  (Result 4). In biological systems, this pattern may be generated through a number of processes involving parasites and hosts. Direct competition between parasite species and between strains of parasite within species is one explanation that has been well documented in a number of systems (Davies et al., 2002; Paul et al., 2002; Gower and Webster, 2004; Sandland et al., 2007). In these cases, parasites may (1) physically interfere with each other (Loker, 1994), (2) attempt to sequester more nutrients than their competitors (Davies et al., 2002), or (3) produce allelopathic substances to suppress the competitive ability of other parasites (Sandland and Goater, 2000). Also, successful coinfection could be reduced via host defense responses that respond asymmetrically to different parasite strains (de Roode et al., 2004).

Miller et al. (2005) assessed the effects of two host defensive strategies on the evolution of host susceptibility and resistance. In the case of tolerance, hosts reduced parasite pathogenicity without influencing the growth rate of the parasite. This could arise by reducing host immune responses which can cause damage to not only the parasite, but the host as well. Alternatively, control may arise when hosts actively suppress parasite reproduction through defense mechanisms. Results demonstrated that host strategies were indeed important for determining evolutionary outcomes. However, this study was performed from the perspective of host evolution. In our study, we incorporated the scenarios outlined in Miller et al. (2005) (tolerance and control) and also investigated a third

process (threshold), but assessed the evolutionary responses of parasites under these scenarios in the presence and absence of coinfection between parasite strains (see Fig. 8). These results demonstrated how host life-history decisions in combination with coinfection can influence the evolution of either parasite specificity or generalist parasite strategies.

Finally, this work also demonstrated how coinfection and life-history strategies interact with host variability to influence parasite evolution. For tolerant hosts, increasing exploitation (parasite reproduction) in particular coinfecting hosts did not alter the magnitude of the invasion region, whereas under both control and threshold scenarios, the capacity for strain 2 parasites to invade expanded with the inclusion of host heterogeneity (see Figs. 9–12). In all cases, in the absence of coinfection, the parasite strain with the higher  $\mathcal{R}_i$  persisted in the population and the other strain was driven to extinction. Introducing coinfection into the models altered the evolutionary dynamics of the system, often allowing for the coexistence of parasite strains; however, the shape and the magnitude of the coexistence regions varied based on life-history strategies employed by hosts. These results suggest that host life-history decisions in combination with coinfection can have important implications for the persistence of parasite strains. Thus, the results from our model (1) in combination with empirical patterns demonstrate the important role that coinfection may play in the establishment of parasite strains within host populations.

Through a unified model for coinfection and superinfection, Mosquera and Adler (1998) concluded that coinfection tends to favor higher virulence and support greater coexistence than their single-infection model. In addition, the authors assume that coinfection by less virulent parasite strains is impossible. Furthermore, work by Regoes et al. (2000) showed that the evolution of parasite specialists or generalists depended on trade-offs in virulence between different host types. Like the work by Mosquera and Adler, our results demonstrate that coexistence between parasite strains can depend on coinfection. However, unlike their work, coinfection was decoupled from virulence in our study. This is an important difference, and one that has biological ramifications, especially in light of the fact that empirical research has demonstrated coinfection between less and more virulent parasite strains (de Roode et al., 2004; Gower and Webster, 2004). Moreover, we found that host strategies were also important for the degree of host specialization expressed by parasites, as opposed to virulence (Regoes et al., 2000).

We need to point out here that, although our model in this study is a microparasite transmission model, it is also useful for assessing the dynamics of macroparasite systems (e.g., schistosome parasites which use an indirect life cycle). Even though there is no direct inclusion of parameters specifically associated with a second host species, we can, in essence, include the effects of this host by altering parameters such as  $\rho_{ki}$ ,  $\rho'_{ki}$ ,  $c_{ki}$  and  $d_{ki}$ . For example, if

the reproductive rate of a particular parasite genotype is high (high  $c_{ki}$ ) in Species  $a$ , but is low in Species  $b$  (the next host in the life cycle), we can account for this by reducing  $\rho_{ki}$  which equates to subsequent reductions in the infection rate of Species  $a$  after passage through the other host.

Understanding the evolution and persistence of parasite strains is crucial for predicting disease patterns in natural systems. Yet very little is known about the degree to which coinfection interacts with host attributes to determine evolutionary outcomes. Results from this work demonstrate that combinations of host life-history strategies and coinfection levels can be important for parasite evolution, both in terms of the persistence of parasite strains and for the evolution of their tendencies toward specialism and/or generalism.

**Acknowledgments**

We thank the reviewer for very helpful comments and suggestions which gratefully improved the presentation of the paper. This research is partially supported by NSF grant DMS-0314575.

**Appendix A. Proof of Result 1**

The Jacobian of the system (1) at  $E_0$  has the following block form

$$J(E_0) = \begin{pmatrix} M_1 & * & * & * \\ 0 & M_2 & * & * \\ 0 & 0 & M_3 & * \\ 0 & 0 & 0 & M_4 \end{pmatrix},$$

where “\*” represent a matrix that does not affect the proof, and

$$M_1 = \begin{pmatrix} -\mu & 0 \\ 0 & -\mu \end{pmatrix},$$

$$M_2 = \begin{pmatrix} \rho_{a1}c_{a1}\hat{S}_a - (\mu + \delta_{a1}) & \rho_{a1}c_{b1}\hat{S}_a \\ \rho_{b1}c_{a1}\hat{S}_b & \rho_{b1}c_{b1}\hat{S}_b - (\mu + \delta_{b1}) \end{pmatrix},$$

$$M_3 = \begin{pmatrix} \rho_{a2}c_{a2}\hat{S}_a - (\mu + \delta_{a2}) & \rho_{a2}c_{b2}\hat{S}_a \\ \rho_{b2}c_{a2}\hat{S}_b & \rho_{b2}c_{b2}\hat{S}_b - (\mu + \delta_{b2}) \end{pmatrix},$$

$$M_4 = \begin{pmatrix} -(\mu + \delta_{a12}) & 0 \\ 0 & -(\mu + \delta_{b12}) \end{pmatrix},$$

where  $\hat{S}_k = \Lambda_k/\mu$  for  $k = a, b$ . All eigenvalues of  $M_1$  and  $M_4$  are negative. Let  $\lambda_1^*$  denote the dominant eigenvalue of the positive matrix

$$H_1 = \begin{pmatrix} \frac{\rho_{a1}c_{a1}\hat{S}_a}{\mu + \delta_{a1}} & \rho_{a1}c_{b1}\hat{S}_a \\ \rho_{b1}c_{a1}\hat{S}_b & \frac{\rho_{b1}c_{b1}\hat{S}_b}{\mu + \delta_{b1}} \end{pmatrix}.$$

Using the results in Diekmann and Heesterbeek (2000) we know that all eigenvalues of  $M_2$  have a negative real part if and only if  $\lambda_1^* < 1$ , and at least one eigenvalue of  $M_2$  has a positive real part if and only if  $\lambda_1^* > 1$ . From  $\hat{S}_k = \Lambda_k/\mu$  it is easy to check that

$$\lambda_1^* = \mathcal{R}_1.$$

We can show in a similar way that  $M_3$  has all eigenvalues with a negative real part if and only if  $\mathcal{R}_2 < 1$ , and at least one eigenvalue with a positive real part if and only if  $\mathcal{R}_2 > 1$ . It follows that  $E_0$  is l.a.s. if  $\mathcal{R}_0 < 1$  and unstable if  $\mathcal{R}_0 > 1$ . This completes the proof.  $\square$

**Appendix B. Proof of Result 2**

*Global stability of  $E_0$ .* The stability of the parasite-free equilibrium  $E_0$  in the single-infection model (4) is determined by the eigenvalues of matrix  $M_2$  in Appendix A. Therefore, the local stability of the equilibrium follows directly from the appendix. Notice that the equations for  $S_k$  are always less than the equations

$$\dot{S}_k = \Lambda_k - \mu S_k, \quad k = a, b.$$

These two equations together with the equations for  $I_{k1}$  in system (4) consist of a monotone dynamic system. By the comparison theorem, solutions of system (4) is dominated by those of the monotone system, which are attracted to  $E_0$  if  $\mathcal{R}_1 < 1$ . Therefore,  $E_0$  is globally attractive for the system (4) and hence globally asymptotically stable if  $\mathcal{R}_1 < 1$ .

*Existence of  $\bar{U}$ .* The components of an interior equilibrium  $\bar{U}$  satisfy the equations

$$\Lambda_a - \rho_{a1}\bar{P}_1\bar{S}_{a1} - \mu\bar{S}_{a1} = 0, \tag{16}$$

$$\Lambda_b - \rho_{b1}\bar{P}_1\bar{S}_{b1} - \mu\bar{S}_{b1} = 0, \tag{17}$$

$$\rho_{a1}\bar{P}_1\bar{S}_{a1} - (\mu + \delta_{a1})\bar{I}_{a1} = 0, \tag{18}$$

$$\rho_{b1}\bar{P}_1\bar{S}_{b1} - (\mu + \delta_{b1})\bar{I}_{b1} = 0, \tag{19}$$

$$\bar{P}_1 = c_{a1}\bar{I}_{a1} + c_{b1}\bar{I}_{b1}. \tag{20}$$

From (16) and (18), we have

$$\Lambda_a - (\mu + \delta_{a1})\bar{I}_{a1} - \mu \frac{(\mu + \delta_{a1})\bar{I}_{a1}}{\rho_{a1}\bar{P}_1} = 0,$$

and hence

$$\bar{P}_1 = \frac{\mu(\mu + \delta_{a1})\bar{I}_{a1}}{\rho_{a1}\chi} \quad \text{where } \chi = \Lambda_a - (\mu + \delta_{a1})\bar{I}_{a1}. \tag{21}$$

Using (20) and (21) we get

$$\bar{I}_{b1} = \frac{\mu(\mu + \delta_{a1}) - c_{a1}\rho_{a1}\chi}{c_{b1}\rho_{a1}\chi} \bar{I}_{a1}. \tag{22}$$

From (19), (20) and (21) we have

$$\bar{S}_a = \frac{\chi}{\mu},$$

$$\bar{S}_b = \frac{\mu + \delta_{b1}}{\rho_{b1}c_{b1}\mu(\mu + \delta_{a1})} (\mu(\mu + \delta_{a1}) - \rho_{a1}c_{a1}\chi). \tag{23}$$

All components of  $\bar{U}$  except  $\bar{I}_{a1}$  were expressed in terms of  $\bar{I}_{a1}$ . Substitution of (21)–(23) into (17) yields

$$A_b\chi - \frac{\mu + \delta_{b1}}{\rho_{a1}c_{b1}}(\mu(\mu + \delta_{a1}) - \rho_{a1}c_{a1}\chi)\bar{I}_{a1} - \frac{\mu + \delta_{b1}}{\rho_{b1}c_{b1}(\mu + \delta_{a1})}(\mu(\mu + \delta_{a1}) - \rho_{a1}c_{a1}\chi)\chi = 0, \quad (24)$$

which can be rewritten as the following equation for  $x = \bar{I}_{a1}$ :

$$f(x) = A_2x^2 + A_1x + A_0 = 0, \quad (25)$$

where

$$A_2 = (\mu + \delta_{a1})c_{a1}(\rho_{a1} - \rho_{b1}), \quad (26)$$

$$A_1 = \mu(\mu + \delta_{a1}) \left[ 1 - \mathcal{R}_1 - \frac{\rho_{b1}}{\rho_{a1}} + \frac{A_a c_{a1}}{\mu(\mu + \delta_{a1})}(\rho_{b1} - \rho_{a1}) \right], \quad (27)$$

$$A_0 = A_a\mu(\mathcal{R}_1 - 1). \quad (28)$$

Symmetrically we can obtain the following equation that  $\bar{I}_{b1}$  satisfies:

$$g(x) = B_2x^2 + B_1x + B_0 = 0, \quad (29)$$

where

$$B_2 = (\mu + \delta_{b1})c_{b1}(\rho_{b1} - \rho_{a1}), \quad (30)$$

$$B_1 = \mu(\mu + \delta_{b1}) \left[ 1 - \mathcal{R}_1 - \frac{\rho_{a1}}{\rho_{b1}} + \frac{A_b c_{b1}}{\mu(\mu + \delta_{b1})}(\rho_{a1} - \rho_{b1}) \right], \quad (31)$$

$$B_0 = A_b\mu(\mathcal{R}_1 - 1). \quad (32)$$

We separately discuss the existence of  $\bar{U}$ .

*Case i.* Suppose that  $\rho_{a1} = \rho_{b1}$ . Then  $A_2 = 0$ , and from Eq. (25) we can easily obtain the expression for  $\bar{I}_{a1}$  and hence all components of  $\bar{U}$  as follows:

$$\bar{S}_a = \frac{A_a}{\mu \mathcal{R}_1}, \quad \bar{S}_b = \frac{A_b}{\mu \mathcal{R}_1}, \quad \bar{P}_1 = \frac{\mu(\mathcal{R}_1 - 1)}{\rho_{a1}},$$

$$\bar{I}_{a1} = \left( \frac{A_a}{\mu + \delta_{a1}} \right) \left( \frac{\mathcal{R}_1 - 1}{\mathcal{R}_1} \right), \quad \bar{I}_{b1} = \left( \frac{A_b}{\mu + \delta_{b1}} \right) \left( \frac{\mathcal{R}_1 - 1}{\mathcal{R}_1} \right). \quad (33)$$

Obviously,  $\bar{U}$  exists uniquely if and only if  $\mathcal{R}_1 > 1$ .

*Case ii.* Suppose that  $\rho_{a1} < \rho_{b1}$ . Then  $A_2 < 0$ , and hence  $f(x)$  is concave down. Note that

$$f\left(\frac{A_a}{\mu}\right) = \frac{\delta_{a1}}{\mu^2} A_a^2 c_{a1}(\rho_{a1} - \rho_{b1}) - A_a(\mu + \delta_{a1}) \frac{\rho_{b1}}{\rho_{a1}} - A_a \delta_{a1}(\mathcal{R}_1 - 1).$$

If  $\mathcal{R}_1 > 1$ ,  $f\left(\frac{A_a}{\mu}\right) < 0$  and  $f(0) > 0$ . Therefore,  $f(x)$  has a unique zero point  $\bar{I}_{a1}$  in the interval  $(0, A_a/\mu)$ . Actually  $\bar{I}_{a1} < A_a/(\mu + \delta_{a1})$  since  $f(A_a/(\mu + \delta_{a1})) < 0$ . From (22), (24) and (29), it follows that the corresponding  $\bar{I}_{b1}$  is in the interval  $(0, A_b/(\mu + \delta_{b1}))$ . Therefore, if  $\mathcal{R}_1 > 1$ , the model (4) admits a unique positive equilibrium which is biologically meaningful. From the global stability of the

parasite-free equilibrium we can exclude the existence of a positive equilibrium if  $\mathcal{R}_1 < 1$ .

*Case iii.* In the case of  $\rho_{a1} > \rho_{b1}$ ,  $B_2 < 0$  and hence  $g(x)$  is concave down. By the same arguments as in Case ii, the unique existence of  $\bar{U}$  can be followed.

Combining the above discussion, we have the existence and uniqueness of  $\bar{U}$ .

*Stability conditions for  $\bar{U}$ .* The stability of the positive equilibrium  $\bar{U}$  is determined by the eigenvalues of the Jacobian matrix:

$$J(\bar{U}) = \begin{pmatrix} -\rho_{a1}\bar{P}_1 - \mu & 0 & -\rho_{a1}c_{a1}\bar{S}_{a1} & -\rho_{a1}c_{b1}\bar{S}_{b1} \\ 0 & -\rho_{b1}\bar{P}_1 - \mu & -\rho_{b1}c_{a1}\bar{S}_{b1} & -\rho_{b1}c_{b1}\bar{S}_{b1} \\ \rho_{a1}\bar{P}_1 & 0 & \rho_{a1}c_{a1}\bar{S}_{a1} - \mu_{\delta_{a1}} & \rho_{a1}c_{b1}\bar{S}_{a1} \\ 0 & \rho_{b1}\bar{P}_1 & \rho_{b1}c_{a1}\bar{S}_{b1} & \rho_{b1}c_{b1}\bar{S}_{b1} - \mu_{\delta_b} \end{pmatrix},$$

where  $\mu_{\delta_a} = \mu + \delta_{a1}$ ,  $\mu_{\delta_b} = \mu + \delta_{b1}$ . The characteristic equation is given by

$$\lambda^4 + C_1\lambda^3 + C_2\lambda^2 + C_3\lambda + C_4 = 0,$$

where

$$C_1 = 2\mu + \mu_{\delta_a} + \mu_{\delta_b} + \bar{P}_1\rho_{a1} + \bar{P}_1\rho_{b1} - c_{a1}\rho_{a1}\bar{S}_a - c_{b1}\rho_{b1}\bar{S}_b,$$

$$C_2 = \mu^2 + 2\mu\mu_{\delta_a} + 2\mu\mu_{\delta_b} + \mu_{\delta_a}\mu_{\delta_b} + \mu\bar{P}_1\rho_{a1} + \mu_{\delta_a}\bar{P}_1\rho_{a1} + \mu_{\delta_b}\bar{P}_1\rho_{a1} + \mu\bar{P}_1\rho_{b1} + \mu_{\delta_a}\bar{P}_1\rho_{b1} + \mu_{\delta_b}\bar{P}_1\rho_{b1} + \bar{P}_1^2\rho_{a1}\rho_{b1} - 2c_{a1}\mu\rho_{a1}\bar{S}_a - c_{a1}\mu_{\delta_b}\rho_{a1}\bar{S}_a - c_{a1}\bar{P}_1\rho_{a1}\rho_{b1}\bar{S}_a - 2c_{b1}\mu\rho_{b1}\bar{S}_b - c_{b1}\mu_{\delta_a}\rho_{b1}\bar{S}_b - c_{b1}\bar{P}_1\rho_{a1}\rho_{b1}\bar{S}_b,$$

$$C_3 = \mu^2\mu_{\delta_a} + \mu^2\mu_{\delta_b} + 2\mu\mu_{\delta_a}\mu_{\delta_b} + \mu\mu_{\delta_a}\bar{P}_1\rho_{a1} + \mu\mu_{\delta_b}\bar{P}_1\rho_{a1} + \mu_{\delta_a}\mu_{\delta_b}\bar{P}_1\rho_{a1} + \mu\mu_{\delta_a}\bar{P}_1\rho_{b1} + \mu\mu_{\delta_b}\bar{P}_1\rho_{b1} + \mu_{\delta_a}\mu_{\delta_b}\bar{P}_1\rho_{b1} + \mu_{\delta_a}\bar{P}_1^2\rho_{a1}\rho_{b1} + \mu_{\delta_b}\bar{P}_1^2\rho_{a1}\rho_{b1} - c_{a1}\mu^2\rho_{a1}\bar{S}_a - 2c_{a1}\mu\mu_{\delta_b}\rho_{a1}\bar{S}_a - c_{a1}\mu\bar{P}_1\rho_{a1}\rho_{b1}\bar{S}_a - c_{a1}\mu_{\delta_b}\bar{P}_1\rho_{a1}\rho_{b1}\bar{S}_a - c_{b1}\mu^2\rho_{b1}\bar{S}_b - 2c_{b1}\mu\mu_{\delta_a}\rho_{b1}\bar{S}_b - c_{b1}\mu\bar{P}_1\rho_{a1}\rho_{b1}\bar{S}_b - c_{b1}\mu_{\delta_a}\bar{P}_1\rho_{a1}\rho_{b1}\bar{S}_b,$$

$$C_4 = \mu^2\mu_{\delta_a}\mu_{\delta_b} + \mu\mu_{\delta_a}\mu_{\delta_b}\bar{P}_1\rho_{a1} + \mu\mu_{\delta_a}\mu_{\delta_b}\bar{P}_1\rho_{b1} + \mu_{\delta_a}\mu_{\delta_b}\bar{P}_1^2\rho_{a1}\rho_{b1} - c_{a1}\mu^2\mu_{\delta_b}\rho_{a1}\bar{S}_a - c_{a1}\mu\mu_{\delta_b}\bar{P}_1\rho_{a1}\rho_{b1}\bar{S}_a - c_{b1}\mu^2\mu_{\delta_a}\rho_{b1}\bar{S}_b - c_{b1}\mu\mu_{\delta_a}\bar{P}_1\rho_{a1}\rho_{b1}\bar{S}_b.$$

Using Eqs. (16)–(19) rewrite  $C_1$  as

$$C_1 = 2\mu + \rho_{a1}c_{b1}\bar{S}_a \frac{I_{b1}}{I_{a1}} + \rho_{b1}c_{a1}\bar{S}_b \frac{I_{a1}}{I_{b1}} + \bar{P}_1\rho_{a1} + \bar{P}_1\rho_{b1},$$

and  $C_4$  as

$$C_4 = \mu^2\mu_{\delta_a}\mu_{\delta_b} \left( 1 - c_{a1} \frac{\rho_{a1}\bar{S}_a}{\mu_{\delta_a}} - c_{b1} \frac{\rho_{b1}\bar{S}_b}{\mu_{\delta_b}} \right) + \mu\mu_{\delta_a}\bar{P}_1\rho_{a1}(\mu_{\delta_b} - c_{b1}\rho_{b1}\bar{S}_b) + \mu\mu_{\delta_b}\bar{P}_1\rho_{b1}(\mu_{\delta_a} - c_{a1}\rho_{a1}\bar{S}_a) + \mu_{\delta_a}\mu_{\delta_b}\bar{P}_1^2\rho_{a1}\rho_{b1} = \mu^2\mu_{\delta_a}\mu_{\delta_b} \left( 1 - \frac{c_{a1}I_{a1}}{\bar{P}_1} - \frac{c_{b1}I_{b1}}{\bar{P}_1} \right) + \mu\mu_{\delta_a}\bar{P}_1\rho_{a1}\rho_{b1}c_{a1}\bar{S}_b \frac{I_{a1}}{I_{b1}}$$

$$\begin{aligned} & + \mu\mu_{\delta_b}\bar{P}_1\rho_{b1}\rho_{a1}c_{b1}\bar{S}_a\frac{I_{b1}}{I_{a1}} + \mu_{\delta_a}\mu_{\delta_b}\bar{P}_1^2\rho_{a1}\rho_{b1} \\ & = \mu\mu_{\delta_a}\bar{P}_1\rho_{a1}\rho_{b1}c_{a1}\bar{S}_b\frac{I_{a1}}{I_{b1}} + \mu\mu_{\delta_b}\bar{P}_1\rho_{b1}\rho_{a1}c_{b1}\bar{S}_a\frac{I_{b1}}{I_{a1}} \\ & \quad + \mu_{\delta_a}\mu_{\delta_b}\bar{P}_1^2\rho_{a1}\rho_{b1}. \end{aligned}$$

Notice that  $C_1 > 0$  and  $C_4 > 0$ . From Routh–Hurwitz theorem, it follows that the interior equilibrium  $\bar{U}$  is stable if

$$C_1 C_2 - C_3 > 0, \quad C_1 C_2 C_3 - C_3^2 - C_1^2 C_4 > 0. \quad (34)$$

In this paper, parameter values we take in all numerical simulations satisfy the above conditions, i.e.,  $\bar{U}$  is stable.

In the case of  $\rho_{a1} = \rho_{b1}$ , the expressions for the coefficients are given by

$$\begin{aligned} C_1 &= 2\mu\mathcal{R}_1 + \frac{1}{\mathcal{R}_1} \left( \frac{\mu_{\delta_b}c_{a1}A_a\rho}{\mu\mu_{\delta_a}} + \frac{\mu_{\delta_a}c_{b1}A_b\rho}{\mu\mu_{\delta_b}} \right), \\ C_2 &= 2\mu\mathcal{R}_1(\mu_{\delta_a} + \mu_{\delta_b}) + \mu^2\mathcal{R}_1^2 - \rho(c_{a1}A_a + c_{b1}A_b)(1 + 1/\mathcal{R}_1), \\ C_3 &= \mu^2\mathcal{R}_1^2(\mu_{\delta_a} + \mu_{\delta_b}) + \mu\mu_{\delta_a}\mu_{\delta_b}(\mathcal{R}_1 - 1) - (c_{a1}A_a + c_{b1}A_b)\mu\rho, \\ C_4 &= \mu^2\mu_{\delta_a}\mu_{\delta_b}\mathcal{R}_1(\mathcal{R}_1 - 1). \quad \square \end{aligned}$$

### Appendix C. Calculation of $\mathcal{R}_2^1$

Using the same notation as in van den Driessche and Watmough (2002), the vector for the rate of new infections (by parasite strain 2),  $\mathcal{F}(x)$ , and the vector for the rate of transfer of hosts,  $\mathcal{V}(x)$ , are, respectively,

$$\begin{aligned} \mathcal{F}(x) &= \begin{pmatrix} \rho_{a2}P_2\bar{S}_a \\ \rho_{b2}P_2\bar{S}_b \\ \rho'_{a2}P_2\bar{I}_{a1} \\ \rho'_{b2}P_2\bar{I}_{b1} \end{pmatrix}, \\ \mathcal{V}(x) &= \begin{pmatrix} \rho'_{a1}P_1I_{a2} + (\mu + \delta_{a2})I_{a2} \\ \rho'_{b1}P_1I_{b2} + (\mu + \delta_{b2})I_{b2} \\ -\rho'_{a1}P_1I_{a2} + (\mu + \delta_{a12})I_{a12} \\ -\rho'_{b1}P_1I_{b2} + (\mu + \delta_{b12})I_{b12} \end{pmatrix}, \end{aligned}$$

where  $\bar{S}_a$ ,  $\bar{S}_b$ ,  $\bar{I}_{a1}$  and  $\bar{I}_{b1}$  are the corresponding components in  $\bar{E}$  given by (33) in the case  $\rho_{a1} = \rho_{b1}$ . Let

$$\begin{aligned} \mathcal{V}^-(x) &= \begin{pmatrix} \rho'_{a1}P_1I_{a2} + (\mu + \delta_{a2})I_{a2} \\ \rho'_{b1}P_1I_{b2} + (\mu + \delta_{b2})I_{b2} \\ (\mu + \delta_{a12})I_{a12} \\ (\mu + \delta_{b12})I_{b12} \end{pmatrix}, \\ \mathcal{V}^+(x) &= \begin{pmatrix} 0 \\ 0 \\ \rho'_{a1}P_1I_{a2} \\ \rho'_{b1}P_1I_{b2} \end{pmatrix}, \end{aligned}$$

then  $\mathcal{V} = \mathcal{V}^- - \mathcal{V}^+$ . The derivatives of  $\mathcal{F}$  and  $\mathcal{V}$  at  $x_0 = 0$  are, respectively,

$$\begin{aligned} F = D\mathcal{F}(0) &= \begin{pmatrix} \rho_{a2}c_{a2}\bar{S}_a & \rho_{a2}c_{b2}\bar{S}_a & \rho_{a2}d_{a2}\bar{S}_a & \rho_{a2}d_{b2}\bar{S}_a \\ \rho_{b2}c_{a2}\bar{S}_b & \rho_{b2}c_{b2}\bar{S}_b & \rho_{b2}d_{a2}\bar{S}_b & \rho_{b2}d_{b2}\bar{S}_b \\ \rho'_{a2}c_{a2}\bar{I}_{a1} & \rho'_{a2}c_{b2}\bar{I}_{a1} & \rho'_{a2}d_{a2}\bar{I}_{a1} & \rho'_{a2}d_{b2}\bar{I}_{a1} \\ \rho'_{b2}c_{a2}\bar{I}_{b1} & \rho'_{b2}c_{b2}\bar{I}_{b1} & \rho'_{b2}d_{a2}\bar{I}_{b1} & \rho'_{b2}d_{b2}\bar{I}_{b1} \end{pmatrix} \\ &= \begin{pmatrix} \rho_{a2}\bar{S}_a \\ \rho_{b2}\bar{S}_b \\ \rho'_{a2}\bar{I}_{a1} \\ \rho'_{b2}\bar{I}_{b1} \end{pmatrix} (c_{a2}, c_{b2}, d_{a2}, d_{b2}), \end{aligned}$$

and from (33)

$$V = D\mathcal{V}(0) = \begin{pmatrix} T_{a2} & 0 & 0 & 0 \\ 0 & T_{b2} & 0 & 0 \\ -\rho'_{a1}\bar{P}_1 & 0 & T_{a12} & 0 \\ 0 & -\rho'_{b1}\bar{P}_1 & 0 & T_{b12} \end{pmatrix},$$

where

$$T_{k2} = \rho'_{k1}\bar{P}_1 + \mu + \delta_{k2}, \quad T_{k12} = \mu + \delta_{k12}, \quad k = a, b. \quad (35)$$

Clearly, all eigenvalues of  $V$  are positive. Hence, all conditions (A1)–(A5) in van den Driessche and Watmough (2002) can be verified. It follows that  $\mathcal{R}_2^1$  is given by the dominant eigenvalue of the matrix  $FV^{-1}$ . Notice that

$$V^{-1} = \begin{pmatrix} \frac{1}{T_{a2}} & 0 & 0 & 0 \\ 0 & \frac{1}{T_{b2}} & 0 & 0 \\ \frac{\rho'_{a1}\bar{P}_1}{T_{a2}T_{a12}} & 0 & \frac{1}{T_{a12}} & 0 \\ 0 & \frac{\rho'_{b1}\bar{P}_1}{T_{b2}T_{b12}} & 0 & \frac{1}{T_{b12}} \end{pmatrix}$$

and

$$\begin{aligned} FV^{-1} &= \begin{pmatrix} \rho_{a2}\bar{S}_a \\ \rho_{b2}\bar{S}_b \\ \rho'_{a2}\bar{I}_{a1} \\ \rho'_{b2}\bar{I}_{b1} \end{pmatrix} \\ &\quad \times \left( \frac{c_{a2}}{T_{a2}} + \frac{d_{a2}\rho'_{a1}\bar{P}_1}{T_{a2}T_{a12}}, \frac{c_{b2}}{T_{b2}} + \frac{d_{b2}\rho'_{b1}\bar{P}_1}{T_{b2}T_{b12}}, \frac{d_{a2}}{T_{a12}}, \frac{d_{b2}}{T_{b12}} \right). \end{aligned}$$

Therefore,  $\mathcal{R}_2^1$  is equal to the only non-zero eigenvalue of  $FV^{-1}$ , i.e.,

$$\mathcal{R}_2^1 = \sum_{k=a,b} \left( \rho_{k2}\bar{S}_k \left( \frac{c_{k2}}{T_{k2}} + \frac{d_{k2}\rho'_{k1}\bar{P}_1}{T_{k2}T_{k12}} \right) + \rho'_{k2}\bar{I}_{k1} \frac{d_{k2}}{T_{k12}} \right), \quad (36)$$

which is exactly the same as the formula given in (7). Moreover, since all conditions (A1)–(A5) in van den



Driessche and Watmough (2002) hold,  $x_0$  is l.a.s. if  $\mathcal{R}_2^1 > 1$  and unstable if  $\mathcal{R}_2^1 < 1$ .

#### Appendix D. Stability of the boundary equilibrium $\bar{E}$

The Jacobian of the system (1) at  $\bar{E}$  has the following block form

$$J(\bar{E}) = \begin{pmatrix} J(\bar{U}) & * \\ 0 & F - V \end{pmatrix},$$

where  $J(\bar{U})$ ,  $F$  and  $V$  are given in Appendices B and C, and the block  $*$  is of no interests. Since  $\bar{U}$  is assumed to be stable for the system (4), the spectral bound  $s(J(\bar{U})) < 0$ . The stability of  $\bar{E}$  is determined by the spectral bound  $s(F - V)$ . According to Diekmann and Heesterbeek (2000, Chap. 6),  $s(F - V) < 0$  is equivalent to  $s(FV^{-1}) < 1$ . Notice that  $s(FV^{-1}) = \mathcal{R}_2^1$  (see Appendix C). The equilibrium is stable if  $\mathcal{R}_2^1 < 1$  and unstable if  $\mathcal{R}_2^1 > 1$ .

#### References

- Anderson, R.M., May, R.M., 1981. The population dynamics of microparasites and their invertebrate hosts. *Phil. Trans. R. Soc. Lond.* 291, 451–524.
- Anderson, R.M., May, R.M., 1982. Coevolution of hosts and parasites. *Parasitology* 85, 411–426.
- Appleton, C.C., 1983. Studies on *Austroilharzia terrigalensis* (Trematoda: Schistosomatidae) in the Swan estuary, Western Australia: frequency of infection in the intermediate host population. *Int. J. Parasitol.* 13, 51–60.
- Beck, K., Keener, J.P., Ricciardi, P., 1984. The effects of epidemics on genetic evolution. *J. Math. Biol.* 19, 79–94.
- Boots, M., Bowers, R.G., 1999. Three mechanisms of host resistance to microparasites—avoidance recovery and tolerance—show different evolutionary dynamics. *J. Theor. Biol.* 201, 13–23.
- Bowers, R.G., Boots, M., Begon, M., 1994. Life-history trade-offs and the evolution of pathogen resistance: competition between host strain. *Proc. R. Soc. Lond. B* 257, 247–253.
- Bremermann, H.J., Pickering, J., 1983. A game-theoretical model of parasite virulence. *J. Theor. Biol.* 100, 411–426.
- Christensen, N.O., Nansen, P., Fagbemi, B.O., Monrad, J., 1987. Heterologous antagonistic and synergistic interactions between helminths and protozoans in concurrent infection of mammal hosts. *Parasitol. Res.* 73, 387–410.
- Davies, C.M., Fairbrother, E., Webster, J.P., 2002. Mixed strain schistosome infections of snails and the evolution of parasite virulence. *Parasitology* 124, 31–38.
- de Roode, J.C., Culleton, R., Cheesman, S.J., Carter, R., Read, A.F., 2004. Host heterogeneity is a determinant of competitive exclusion or coexistence in genetically diverse malaria infections. *Proc. R. Soc. Lond. B* 271, 1073–1080.
- Decaestecker, E., Vergote, A., Ebert, D., Meester, L.D., 2003. Evidence for strong host clone–parasite species interactions in the daphnia microparasite system. *Evolution* 57, 784–792.
- Diekmann, O., Heesterbeek, J.A.P., 2000. *Mathematical Epidemiology of Infectious Diseases: Model Building, Analysis and Interpretation*. Wiley, New York, p. 365.
- Eppert, A., Lewis, F.A., Grzywacz, C., Coura-Filho, P., Caldas, I., Minchella, D.J., 2002. Distribution of schistosome infections in molluscan hosts at different levels of parasite prevalence. *J. Parasitol.* 88 (2), 232–236.
- Frank, S.A., 1992. A kin selection model for the evolution of virulence. *Proc. R. Soc. Lond. B* 250, 195–197.
- Gower, C.M., Webster, J.P., 2004. Fitness of indirectly transmitted pathogens: restraint and constraint. *Evolution* 58 (6), 1178–1184.
- Levin, B.R., 1982. Evolution of parasites and hosts. In *Population Biology of Infectious Diseases*. Springer, New York.
- Li, J., Ma, Z., Blythe, S.P., Carlos, C.-C., 2003. Coexistence of pathogens in sexually-transmitted disease models. *J. Math. Biol.* 47, 547–568.
- Little, T.J., Watt, K., Ebert, D., 2006. Parasite–host specificity: experimental studies on the basis of parasite adaptation. *Evolution* 60, 31–38.
- Loker, E.S., 1994. On being a parasite in an invertebrate host: a short survival course. *J. Parasitol.* 80, 728–747.
- May, R.M., Anderson, R.M., 1979. Population biology of infectious disease II. *Nat. Lond.* 280, 455.
- May, R.M., Anderson, R.M., 1990. Parasite–host coevolution. *Parasitology* 100, S89–S101.
- Miller, M.R., White, A., Boots, M., 2005. The evolution of host resistance: tolerance and control as distinct strategies. *J. Theor. Biol.* 236, 198–207.
- Minchella, D.J., Loverde, P.T., 1981. A cost of early reproductive effort in the snail *Biomphalaria glabrata*. *Am. Nat.* 118, 876–881.
- Minchella, D.J., 1985. Host life history variation in response to parasitism. *Parasitol.* 90, 205–216.
- Mosquera, J., Adler, F.R., 1998. Evolution of virulence: a unified framework for coinfection and superinfection. *J. Theor. Biol.* 195, 293–313.
- Nowak, M.A., May, R.M., 1994. Superinfection and the evolution of parasite virulence. *Proc. R. Soc. Lond. B* 255, 81–89.
- Paul, R.E., Nu, V., Krettli, A.U., Brey, P.T., 2002. Interspecific competition during transmission of two sympatric malaria parasite species to the mosquito vector. *Proc. R. Soc. Lond. B* 269, 2551–2557.
- Regoes, R.R., Nowak, M.A., Bonhoffer, S., 2000. Evolution of virulence in a heterogeneous host population. *Evolution* 54 (1), 64–71.
- Sandland, G.J., Goater, C.P., 2000. Development and intensity dependence of *Ornithodiplostomum ptychocheilus* metacercariae in fathead minnows (*Pimephales promelas*). *J. Parasitol.* 86, 1056–1060.
- Sandland, G.J., Minchella, D.J., 2003a. Costs of immune defense: an enigma wrapped in an environmental cloak? *Trends Parasitol.* 19, 571–574.
- Sandland, G.J., Minchella, D.J., 2003b. Effects of diet and *Echinostoma revolutum* infection on energy allocation patterns in juvenile *Lymnaea elodes* snails. *Oecologia* 134, 479–486.
- Sandland, G.J., Minchella, D.J., 2004. Life-history plasticity in hosts exposed to differing resources and parasitism. *Can. J. Zool.* 82, 1672–1677.
- Sandland, G.J., Rodgers, J.K., Minchella, D.J., 2007. Interspecific antagonism and virulence in hosts exposed to two parasite species. *J. Invertebr. Pathol.*, in press, doi:10.1007/s00436-007-0593-9.
- Tanaka, M.M., Feldman, M.W., 1999. Theoretical considerations of cross-immunity, recombination and the evolution of new parasitic strains. *J. Theor. Biol.* 198, 145–163.
- van den Driessche, P., Watmough, J., 2002. Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission. *Math. Biosci.* 180, 29–48.