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# Interactions among virulence, coinfection and drug resistance in a complex life-cycle parasite

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ABSTRACT

Motivated by relatively recent empirical studies on *Schistosoma mansoni*, we use a mathematical model to investigate the impacts of drug treatment of the definitive human host and coinfection of the intermediate snail host by multiple parasite strains on the evolution of parasites' drug resistance. Through the examination of evolutionarily stable strategies (ESS) of parasites, our study suggests that higher levels of drug treatment rates (which usually tend to promote monomorphism as the evolutionary equilibrium) favor parasite strains that have a higher level of drug resistance. Our study also shows that whether coinfection of intermediate hosts affects the levels of drug resistance at ESS points and their stability depends on the assumptions on the cost of parasites paid for drug resistance, coinfection functions and parasites' reproduction within coinfected hosts. This calls for more empirical studies on the parasite.



## 1. Introduction

Coevolutionary dynamics between hosts and parasites are dictated by specific host attributes, parasite attributes, and their surrounding environment. Oftentimes, theoretical investigations incorporate host features such as resistance or tolerance into their models, whereas virulence is commonly identified as a key parasite attribute. Although there are numerous descriptions of virulence across biological disciplines, in evolutionary ecology it is typically defined as the reduction in host fitness generated by parasitic infection. In mathematical modeling, it is often approximated by the parasite-induced instantaneous death rate of infected host organisms (Bull, 1994; Read, 1994; Frank, 1996). In this study, we focus on host–parasite systems which involve a parasite with complex life cycle such as that of *Schistosoma mansoni*.

Traditionally, theoretical studies on the evolution of virulence have assumed positive associations between virulence and parasite replication rate, and between parasite replication rate and transmission success (Anderson and May, 1981; Frank, 1992, 1996; Bull, 1994; Mackinnon and Read, 1999). These trade-off assumptions underlie the prediction that selection should favor high virulence in parasite strains or species (Bonhoeffer and Nowak, 1994; Nowak and May, 1994; van Baalen and Sabelis, 1995; Mosquera and Adler, 1998). Most of the theoretical studies have considered host–parasite systems with one host type and a single strain of parasites. When multiple host types and more parasite strains are considered, different evolutionary outcomes of host–parasite interactions may emerge, especially if coinfection within a single host is possible (see, for example, May and Nowak, 1995; Mackinnon and Read, 1999; Gandon et al., 2001; de Roode et al., 2004; Huijben et al., 2010; Yang et al., in press). In these cases, the trade-off relationships between parasite virulence and other life history characteristics can be influenced by the interaction between multiple host types and parasite strains. As the benefit of increasing virulence may be nullified by the degree of host damage and corresponding reductions in parasite fitness, it is assumed that, all things being equal, selection will favor an optimal balance between parasite exploitation and transmission success, the direction and magnitude of which will be dictated by a suite of genetic and environmental factors.

Interactions between hosts and parasites may become more complex if environments change within host organisms. It is quite common for parasite strains or species to co-occur within their hosts (e.g., Minchella et al., 1995; Ebert and Mangin, 1997; Davies et al., 2002; de Roode et al., 2004; Hastings, 2006; Sandland et al., 2007). This can lead to competition among parasites and the subsequent emergence of strains or species utilizing particular virulence strategies. For example, empirical work by Ebert and

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Mangin (1997) suggested that parasite coinfection and within-host competition resulted in selection for low-virulence strains of the microparasite, *Glugoides intestinalis*, in its water flea host (*Daphnia magna*) while the work done by de Roode et al. (2004) shows that selection for high or low virulence of malaria parasites depends on host genotypes. These empirical results in combination with accumulating theoretical studies (e.g., Claessen and de Roos, 1995; van Baalen and Sabelis, 1995; Mosquera and Adler, 1998; Gandon et al., 2001; Zhang et al., 2007) suggest that coinfections can alter our views of virulence evolution such as the one mentioned earlier that models predict evolution to high virulence (Read and Taylor, 2001). This work focuses mainly on the impact of coinfection of the intermediate snail host and drug treatment of human hosts on the evolution of *schistosome* drug resistance and virulence to the intermediate host.

It has been well-documented that anti-parasite treatment programs targeting human hosts can result in the emergence of resistant parasite strains. Many recent studies have focused on the evolution and spread of drug resistance (e.g., Hastings and D'Alessandro, 2000; Hastings and Watkins, 2006; Hastings, 2006; Wargo et al., 2007; Huijben et al., 2010; Chmielecki et al., 2011; Read et al., 2011). The main argument is that by killing drug sensitive pathogens, drug treatment reduces the intensity of both intrahost and interhost competitions between drug sensitive and resistant pathogens and hence increases subsequent transmission of surviving resistant pathogens from treated hosts. As a result, while intensive drug treatment can reduce the appearance of certain drug resistant parasites through mutations, it may also maximize the transmission and facilitate the evolution of surviving resistant pathogens. This calls for studies on optimal treatment strategy (e.g., Torella et al., 2010; Chmielecki et al., 2011; Read et al., 2011). The prevalence and evolution of resistance may also be constrained by natural selection and genetic recombination (Hastings, 2006 and the reference therein). Because drug treatments on coinfected hosts benefit resistant pathogens the most, all the studies mentioned above indicate that coinfection of human hosts can make a significant contribution to resistance spread and evolution. For parasites with complex life cycles, the fitness in one obligatory host may be associated with that in another obligatory host; and thus, the prevalence and evolution of drug resistance may be affected by coinfection of the intermediate hosts and intrahost ecology. In the context of *schistosome*, this study shows that coinfection of the intermediate snail host may have a significant influence on the coexistence of parasites with different levels of drug resistance.

*S. mansoni* is a macroparasite with an indirect life-cycle that uses mammals as definitive hosts and snails as intermediate hosts. Adult parasites within the definitive hosts mate and produce eggs, which will hatch into free-swimming miracidia in water. Miracidia can infect snails and transform into sporocysts. About four weeks after an infection, the infected snails begin to release free-swimming cercariae, which can penetrate human skin and develop into adult parasites (CDC, 2012). High genetic diversity has been reported for *schistosome* parasites within both definitive and intermediate hosts using molecular markers (e.g., Sire et al., 1999, 2001; Eppert et al., 2002; Curtis et al., 2002). Current evidence supports the view that selection for resistance to praziquantel (PZQ) may be occurring in *schistosome* populations and natural *schistosome* strains exhibit varying resistance to treatment with PZQ (Fallon and Doenhoff, 1994; Fallon et al., 1997; Ismail et al., 1999; Cioli, 2000; Webster et al., 2008; Melman et al., 2009; Lamberton et al., 2010). Treatment of human hosts and parasite resistance to the drug as well as possible associated costs for resistance may have significant influence in the parasite's evolutionary strategy. Although it is known from empirical studies that coinfection is common (an infected snail usually carries a number of parasites of different strains), it is not clear how often or when drug resistant mutants may appear.

A series of relatively recent empirical studies on the parasite (Davies et al., 2001; Gower and Webster, 2004, 2005; Webster et al., 2004, 2008) demonstrate that the parasite fitness in the definitive mouse host is strongly inversely correlated with that in the intermediate snail host, while the parasite's virulence and replication rate exhibit opposite associations: positive in the definitive host and negative in the intermediate host. These findings prompted us to investigate their impacts on the long-term evolutionary equilibrium of the parasite. In this work we built a mathematical model that includes an age-structure in the definitive human host, drug treatment on humans, parasites' drug resistance and virulence to the intermediate snail host. Again, the virulence is measured by the parasite-induced mortality in the snail host. Because the disease-induced mortality in humans is low, it is ignored in our model. Using the model with assumptions from empirical studies, we studied how human drug treatment programs and coinfection of the intermediate host affect the evolutionarily stable strategy of the parasite's drug resistance and virulence to the intermediate host.

In the next section we introduce the mathematical model and its limiting system which captures the same asymptotic behaviors as those of the original one. Some basic dynamical behaviors of the limiting system determined by the parasite's reproduction number are also presented in this section. Section 3 derives the invasion conditions for mutant parasite strains, which can be used to infer how a mutant parasite can maximize its fitness under the environment set by resident parasites. In Section 4, we study the impacts of drug treatments of human hosts and coinfections of intermediate snail hosts on the evolutionarily stable strategy of parasites. Finally, some related issues are discussed in Section 5.

## 2. The model

Because parasite transmission to human hosts and drug treatment programs are age-dependent (Fenwick and Webster, 2006), the model is structured by the chronological age of human hosts, which is denoted by $a$. Consider two parasite strains ($i=1,2$) with different drug resistance levels (characterized by $\theta \geq 1$ in later sections). Let $n(t,a)$ denote the number of human hosts of age $a$ at time $t$ and $p_i(t,a)$ denote the total number of adult parasites of strain $i$ carried by all human hosts of age $a$. Assume that adult parasites $p_i(t,a)$ may die naturally at a rate $\mu_p$, be killed by age-dependent drug treatments $\sigma(a)$ of human hosts at a rate $f_i(\sigma(a))$ (depending on the parasite strain $i$), or die due to the natural death of human hosts at a rate $\mu_h(a)$. A human host can acquire an adult parasite at a rate proportional to the number of larvae (cercariae) $C_i$ with proportionality constant $\beta_i(a)$, depending on the host age $a$. Because the mortality rate of humans due to schistosomiasis is low (e.g., Kheir et al., 1999), we simply assume that the per capita death rate of human hosts due to a parasite infection is negligible, equal to zero. Following the framework due to Anderson and May (1978) and Dobson (1985) (see Hadeler and Dietz, 1983 and Hadeler, 1984 for partial differential equations and the derivation in the case of one strain of parasites in Appendix A), we have the partial differential equations for the density functions $n$ and $p_i$:

$$\left(\frac{\partial}{\partial t}+\frac{\partial}{\partial a}\right)n(t,a) = -\mu_h(a)n(t,a),$$

$$\left(\frac{\partial}{\partial t}+\frac{\partial}{\partial a}\right)p_i(t,a) = \beta_i(a)n(t,a)C_i-(\mu_h(a)+\mu_p+f_i(\sigma(a))p_i(t,a), \qquad (1)$$

**Table 1**
Definitions of variables and parameters ($i=1,2$).

| | |
|---|---|
| $\mu_h(a)$ | Per capita natural death rate of human hosts at age $a$ |
| $\mu_p$ | Per capita natural death rate of adult parasites in human hosts |
| $f_i(\sigma(a))$ | Per capita death rate of adult parasites due to drug treatments $\sigma(a)$ of aged-$a$ human hosts |
| $\beta_i(a)$ | The transmission rate of a strain $i$ cercaria to aged-$a$ human hosts |
| $\Lambda_h$ | Recruitment rate of human hosts |
| $\Lambda_s$ | Recruitment rate of snail hosts |
| $\mu_s$ | Per capita natural death rate of snail hosts |
| $\rho_i$ | Infection rate of uninfected snail hosts by a strain $i$ parasite |
| $\rho_{ji}$ | Rate at which a snail host that was infected with strain $i$ parasites is infected by a parasite of strain $j$ ($j\neq i$); $\rho_{ij}=0$ if $i=j$ |
| $\eta$ | Efficiency of coinfection in intermediate snail hosts |
| $\delta_i$ | Per capita disease-induced death rate of singly infected hosts $I_i$ |
| $\delta_{12}$ | Per capita disease-induced death rate of co-infected hosts $I_{12}$ |
| $c_i$ | Releasing rate of infected snails $I_i$ |
| $c_i'$ | Rate at which co-infected snails $I_{12}$ release strain $i$ parasites |
| $\gamma_i$ | The reproduction rate of strain $i$ adult parasites in infected human hosts |
| $\theta_i$ | Drug-resistance level of strain $i$ parasites |

together with the boundary conditions $n(t,0)=\Lambda_h$ (birth rate of human hosts), $p_i(t,0)=0$ (humans are born uninfected), and initial conditions are $n(0,a)=n_0(a)$, $p_i(0,a)=p_{i0}(a)$ for given bounded functions with compact support. The parameters in the equations are listed in Table 1. The natural mortality of human host is considered because the model includes the demographic process (birth and natural death) so that the human population does not go to extinction when long-term dynamics (an evolutionary time scale) are considered. It is also assumed that the infection within a human host will persist as long as the adult parasites remain inside the host and continue to lay eggs, and that the mortality of parasites within the human host includes both a natural death rate and an extra death rate due to drug treatment.

For the population dynamics of the intermediate snail host, we include the possibility of coinfection of snails by different strains of parasites. Assume that the double infection can occur only after an infection by a single strain of parasites and that the order in which coinfection occurs is irrelevant (Gower and Webster, 2005). For simplicity, we do not allow coinfections with the same strain of parasites, i.e., the coinfection rates $\rho_{ij}=0$ if $i=j$ (Mosquera and Adler, 1998). Under these assumptions, the snail population can be divided into four epidemiological classes: uninfected snail hosts ($S$), hosts infected only by parasites of strain $i$ ($I_i$, $i=1, 2$), and hosts co-infected with both strains ($I_{12}$). Following an approach similar to that of Mosquera and Adler (1998), we can describe the population dynamics for the intermediate snail host using the following set of differential and integral equations:

$$\frac{d}{dt}S=\Lambda_s-(\rho_1M_1+\rho_2M_2)S-\mu_sS,$$

$$\frac{d}{dt}I_i=\rho_iM_iS-\rho_{ji}M_jI_i-(\mu_s+\delta_i)I_i,$$

$$\frac{d}{dt}I_{12}=\rho_{12}M_1I_2+\rho_{21}M_2I_1-(\mu_s+\delta_{12})I_{12},$$

$$M_i=\gamma_i\int_0^\infty p_i(t,a)\,da,\quad 1\le i\neq j\le 2. \tag{2}$$

Here, $M_i$ represents the number of free-swimming parasites (miracidia) of strain $i$ produced by adult parasites of strain $i$, $P_i=\int_0^\infty p_i(t,a)\,da$ at the per capita rate $\gamma_i$. All other parameters are defined in Table 1.

The connection of the system (2) to the equations for the variables $n$ and $p_i$ in the system (1) is through the parasite population (cercariae) $C_i$ by the following equation:

$$C_i=c_iI_i+c_i'I_{12},\quad i=1,2, \tag{3}$$

which assumes that the number of strain $i$ cercariae is proportional to the number of snails infected by strain $i$ parasites (both singly infected and co-infected with the proportionality constants $c_i$ and $c_i'$, respectively).

Combining Eqs. (1)–(3) we have the following full model

$$\left(\frac{\partial}{\partial t}+\frac{\partial}{\partial a}\right)n(t,a)=-\mu_h(a)n(t,a),$$

$$\left(\frac{\partial}{\partial t}+\frac{\partial}{\partial a}\right)p_i(t,a)=\beta_i(a)n(t,a)C_i-(\mu_h(a)+\mu_p+f_i(\sigma(a))p_i(t,a),$$

$$\frac{d}{dt}S=\Lambda_s-(\rho_1M_1+\rho_2M_2)S-\mu_sS,$$

$$\frac{d}{dt}I_i=\rho_iM_iS-\rho_{ji}M_jI_i-(\mu_s+\delta_i)I_i,$$

$$\frac{d}{dt}I_{12}=\rho_{12}M_1I_2+\rho_{21}M_2I_1-(\mu_s+\delta_{12})I_{12},$$

$$C_i=c_iI_i+c_i'I_{12},\quad M_i=\gamma_i\int_0^\infty p_i(t,a)\,da,\ 1\le i\neq j\le 2, \tag{4}$$

with the initial and boundary conditions:

$$n(t,0)=\Lambda_h,\quad n(0,a)=n_0(a),\quad p_i(t,0)=0,\quad p_i(0,a)=p_{i0}(a),\ i=1,2.$$

We need to point out that in the model (4), we have ignored coinfection in the human host. This is mainly because there is little empirical information about the competition of different strains of parasites within infected definitive hosts. There is also an issue associated with mating of adult parasites within human hosts for sexual production of the parasites (Xu et al., 2005; Castillo-Chavez et al., 2008). These considerations will make the analysis of the model extremely difficult.

To study the dynamics of the system (4) on the evolutionary (long) time scale, we can simplify the mathematical analysis by ignoring the transient dynamics and considering only the limiting system which captures the asymptotical behaviors of system (4). We show in Appendix B that the limiting system of (4) is given by

$$\frac{d}{dt}S=\Lambda_s-(\rho_1M_1+\rho_2M_2)S-\mu_sS,$$

$$\frac{d}{dt}I_i=\rho_iM_iS-\rho_{ji}M_jI_i-\mu_{si}I_i,$$

$$\frac{d}{dt}I_{12}=\rho_{12}M_1I_2+\rho_{21}M_2I_1-\mu_{s12}I_{12},$$

$$M_i=\int_0^\infty (c_iI_i(t-a)+c_i'I_{12}(t-a))R_{hi}(a)\,da,\quad i,j=1,2,\ i\neq j, \tag{5}$$

together with given initial value $S(0)=S^0$ and initial functions $I_i^0(s)$ and $I_{12}^0(s)$ for $s\le 0$. In the system (5), we have used the following short-hand notations:

$$\mu_{si}=\mu_s+\delta_i,\quad \mu_{s12}=\mu_s+\delta_{12},\quad \pi_h(a)=e^{-\int_0^a\mu_h(w)\,dw},$$

$$\mu_{hi}(a)=\mu_h(a)+\mu_p+f_i(\sigma(a)),\quad \pi_{hi}(a,\tau)=e^{-\int_a^{a+\tau}\mu_{hi}(w)\,dw},$$

$$R_{hi}(\tau)=\Lambda_h\gamma_i\int_0^\infty \beta_i(a)\pi_h(a)\pi_{hi}(a,\tau)\,da,\quad \mathcal{R}_{hi}=\int_0^\infty R_{hi}(\tau)\,d\tau.$$

These notations have clear biological meanings. For example, $\pi_h(a)$ is the survival probability of human hosts of age $a$ while $\pi_{hi}(a,\tau)$ is the survival probability of an adult parasite in a human host of age $a+\tau$ who was infected $\tau$ time units ago (i.e., $\tau$ is the infection age of the host). Therefore, $R_{hi}(\tau)$ gives the total number

of strain $i$ miracidia produced by adult parasites within all human hosts with infection age $\tau$ due to one cercaria, and $\mathcal{R}_{hi}$ gives the total number of strain $i$ miracidia produced by adult parasites in all human hosts due to one cercaria.

Notice that susceptible snail hosts with the population level fixed at $\Lambda_s/\mu_s$ totally release $\Lambda_s\rho_i c_i/\mu_s\mu_{si}$ number of cercariae due to one miracidium. The basic reproduction number of strain $i$ parasites is given by

$$\mathcal{R}_i = \frac{\Lambda_s\rho_i c_i}{\mu_s\mu_{si}}\mathcal{R}_{hi}. \tag{6}$$

It is shown in Appendix C that when only a single strain of parasites (e.g., strain $i$) is present in the population, the population dynamics is determined completely by the basic reproduction number $\mathcal{R}_i$. That is, the disease-free equilibrium is globally asymptotically stable if $\mathcal{R}_i<1$, and it is unstable if $\mathcal{R}_i>1$, in which case a unique endemic equilibrium exists and is stable.

These results for the reduced system with a single strain of parasites will be helpful for the study of invasion by a mutant strain of parasites and the evolutionary outcomes of parasite strains. In the next section, we will focus the limiting system (5) and derive the invasion reproduction number (invasion fitness) and investigate the evolution of parasites' traits.

## 3. Invasion condition

In this section, we derive conditions under which a mutant strain of parasites can prosper and invade in a resident parasite population when a small number of mutants are introduced into the population. For this analysis, we assume that the resident parasite population has established itself at an equilibrium. This equilibrium will correspond to a positive equilibrium in a reduced system in which only one parasite strain is considered, but will correspond to a boundary equilibrium in the full system (5) in which both parasite strains are considered. Then, whether or not an invasion by the mutant strain is successful can be determined either by considering when the boundary equilibrium of the full system (5) is unstable or by conducting an invadability analysis based on information about the boundary equilibrium and the invasion reproduction number. The latter approach seems to be more biologically motivated than the former one (Bowers and Turner, 1997; Bowers, 2000).

There are three possible boundary equilibria of system (5), the parasite-free equilibrium:

$$Q_0=(\Lambda_s/\mu_s,0,0,0),$$

the equilibrium at which only strain 1 is present:

$$Q_1=(S_1^*,I_1^*,0,0) \quad \text{which exists if and only if } \mathcal{R}_1>1,$$

and the equilibrium at which only strain 2 is present:

$$Q_2=(S_2^*,0,I_2^*.0) \quad \text{which exists if and only if } \mathcal{R}_2>1,$$

The expressions for the equilibrium population levels, $S_i^*$ and $I_i^*$, are given in (26) in Appendix C, and $\mathcal{R}_i$ are given in (6). It is shown in Appendix D that the parasite-free equilibrium $Q_0$ is stable if $\mathcal{R}_i<1$ for both $i=1, 2$, and it is unstable if either $\mathcal{R}_1>1$ or $\mathcal{R}_2>1$. We assume in this section that both $\mathcal{R}_1$ and $\mathcal{R}_2$ are greater than 1 so that both of the boundary equilibria $Q_1$ and $Q_2$ exist.

Next, we derive the invasion conditions via the invadability analysis. Consider strain 1 parasites as the residents, whose population level has already stabilized at the equilibrium level $Q_1=(S_1^*,I_1^*,0,0)$, and strain 2 parasites as the invaders. We need to determine the average reproduction number of a typical invader in the environment set by the equilibrium $Q_1$. Note that a typical invader cercaria can produce miracidia in the number $\mathcal{R}_{h2}$ through the definitive human host. These miracidia can infect snails and consequently generate cercariae via two potential paths: (i) by infecting the uninfected snails $S_1^*$ and (ii) by co-infecting the infected snails $I_1^*$. In path (i), the number of snails infected by the miracidia $\mathcal{R}_{h2}$ is given by $\rho_2\mathcal{R}_{h2}S_1^*$. These infected snails may or may not become co-infected by resident parasites. Suppose that an infected snail (by an invader miracidium) remains singly infected for an average time $T_2$ and co-infected for an average time $T_{12}$. Then the probability that the infected snail dies while being singly infected is $\mu_{s2}T_2$, and the probability of dying while being co-infected is $\mu_{s12}T_{12}$. Therefore,

$$\mu_{s2}T_2+\mu_{s12}T_{12}=1. \tag{7}$$

Notice that the average time $T_2$ can be determined directly by the total rate $\mu_{s2}+\rho_{12}c_1\mathcal{R}_{h1}I_1^*$ (at which infected snails $I_2$ leave the class $I_2$ either dying or being co-infected), i.e.,

$$T_2=\frac{1}{\mu_{s2}+\rho_{12}c_1\mathcal{R}_{h1}I_1^*}. \tag{8}$$

Then $T_{12}$ can be determined from (7) as

$$T_{12}=\frac{\rho_{12}c_1\mathcal{R}_{h1}I_1^*}{\mu_{s2}+\rho_{12}c_1\mathcal{R}_{h1}I_1^*}\frac{1}{\mu_{s12}}. \tag{9}$$

Therefore, when the number of susceptible snails available to invading miracidia is $S_1^*$, a typical invader cercaria can reproduce the following number of cercariae:

$$(c_2T_2+c_2'T_{12})\rho_2\mathcal{R}_{h2}S_1^*. \tag{10}$$

In path (ii), the number of snails infected by resident parasites is $I_1^*$. These infected snails can be co-infected by the invading miracidia $\mathcal{R}_{h2}$ produced by adult parasites due to one invader cercaria, and remain being co-infected for an average time $1/\mu_{s12}$. Thus, through path (ii) a typical invader cercaria can reproduce the following number of cercariae:

$$\frac{c_2'\rho_{21}\mathcal{R}_{h2}I_1^*}{\mu_{s12}}. \tag{11}$$

Therefore, from (10) and (11) with $T_2$ and $T_{12}$ being replaced by (8) and (9), the total reproduction number of an invader cercaria is given by

$$\mathcal{R}_{21}=\frac{c_2\,\rho_2\mathcal{R}_{h2}S_1^*}{\mu_{s2}+\rho_{12}c_1\mathcal{R}_{h1}I_1^*}+\frac{\rho_{12}c_1\mathcal{R}_{h1}I_1^*c_2'\rho_2\mathcal{R}_{h2}S_1^*}{(\mu_{s2}+\rho_{12}c_1\mathcal{R}_{h1}I_1^*)\mu_{s12}}+\frac{c_2'\rho_{21}\mathcal{R}_{h2}I_1^*}{\mu_{s12}}. \tag{12}$$

It is clear from the deduction of $\mathcal{R}_{21}$ that if $\mathcal{R}_{21}>1$, a small number of invaders can start a growing population and hence the invasion will be successful in the environment $Q_1$ set by the residents. Therefore, the quantity $\mathcal{R}_{21}$ can be used as a measure of the fitness of invading parasites. We call $\mathcal{R}_{21}$ the invasion reproduction number (or invasion fitness) for strain 2 parasites.

From the symmetry between the two parasite strains, we can derive an invasion reproduction number $\mathcal{R}_{12}$ for the parasites of strain 1:

$$\mathcal{R}_{12}=\frac{c_1\rho_1\mathcal{R}_{h1}S_2^*}{\mu_{s1}+\rho_{21}c_2\mathcal{R}_{h2}I_2^*}+\frac{\rho_{21}c_2\mathcal{R}_{h2}I_2^*c_1'\rho_1\mathcal{R}_{h1}S_2^*}{(\mu_{s\,1}+\rho_{21}c_2\mathcal{R}_{h2}I_2^*)\mu_{s12}}+\frac{c_1'\rho_{12}\mathcal{R}_{h1}I_2^*}{\mu_{s12}}, \tag{13}$$

which determines whether or not strain 1 parasites can invade the population of strain 2 parasites.

The results given below show that the invasion reproduction numbers $\mathcal{R}_{21}$ and $\mathcal{R}_{12}$ actually determine the stability of the equilibria $Q_1$ and $Q_2$, respectively. The proof of the first result is given in Appendix D.

**Result 1.** Let $\mathcal{R}_{21}$ be as defined in (12). The equilibrium $Q_1$ is stable if $\mathcal{R}_{21}<1$ and it is unstable if $\mathcal{R}_{21}>1$.

**Result 2.** Let $\mathcal{R}_{12}$ be as defined in (13). The equilibrium $Q_2$ is stable if $\mathcal{R}_{12}<1$ and unstable if $\mathcal{R}_{12}>1$.

These results allow us to use the invasion reproduction numbers $\mathcal{R}_{ij}$ $(i,j=1,2,i\neq j)$ to investigate the evolutionarily stable strategies for parasite's traits.

## 4. Evolution of parasites

For the study of evolution of parasites presented in this section, we have chosen the approach of adaptive dynamics (for other applications of this approach, see Metz et al., 1996; Geritz et al., 1997, 1998). We focus on the long-term evolutionary equilibrium of the parasite's resistance to drug and virulence to the intermediate host. The adaptive dynamics approach allows for the decouple of the ecological/epidemiological and evolutionary time scales by assuming that mutations are rare and ecological/epidemiological dynamics of the population reaches its asymptotical state before some new mutants appear (Gandon and Day, 2009). This assumption leads to an evolutionary analysis simply based on the mutants' fitness in the environment prescribed by the resident population, and hence significantly simplify the mathematical analysis. This approach does not consider any genetic details related to parasites' traits (which are often unknown) and hence circumvents the intricacies of Mendelian inheritance (Geritz et al., 1998). However, it has been shown that the approach can produce compatible predictions in comparison with other genetic methods (see Geritz et al., 1998 and the reference therein). It is worthwhile to point out that the actual evolutionary changes in parasites' mean fitness may be studied using the approach proposed by Gandon and Day (2009).

In our evolutionary analysis, the measure we use for mutants's (invasion) fitness is the invasion reproduction number $\mathcal{R}_{21}$ as given in (12). For ease of presentation, we replace the subscripts $i=1,2$ for parasite strains by $i=r,m$ ($r$ for a resident strain and $m$ for a mutant strain), and use the following notation for $\mathcal{R}_{21}$:

$$\mathcal{R}(m,r)=\frac{c_m\rho_m\mathcal{R}_{hm}S_r^*}{\mu_{sm}+\rho_{rm}c_r\mathcal{R}_{hr}I_r^*}+\frac{\rho_{rm}c_r\mathcal{R}_{hr}I_r^*c'_m\rho_m\mathcal{R}_{hm}S_r^*}{(\mu_{sm}+\rho_{rm}c_r\mathcal{R}_{hr}I_r^*)\mu_{srm}}+\frac{c'_m\rho_{mr}\mathcal{R}_{hm}I_r^*}{\mu_{srm}}. \tag{14}$$

According to Result 1, if $\mathcal{R}(m,r)>1$ ($<1$), then the mutant strain can invade successfully and prosper (can not invade) in the population of a resident strain. A strategy $r^*$ is an evolutionarily singular strategy if the gradient $d\mathcal{R}(m,r)/dm$ is zero at $m=r=r^*$ (e.g., Metz et al., 1996; Geritz et al., 1997, 1998). An evolutionarily singular strategy $r^*$ is stable if $\mathcal{R}(m,r^*)$ is maximized at $m=r^*$, where it equals 1. The parasite strain with ESS as a resident strain can not be out-competed by invaders of other strains.

Our assumptions on parasites' trade-offs, which will be reflected by functional relationships between model parameters, are mostly based on empirical studies (e.g., Davies et al., 2001, 2002; Sturrock, 2001; Gower and Webster, 2004, 2005; Massara et al., 2004; Webster et al., 2004, 2008). These trade-off assumptions will allow us to investigate how drug treatments of human hosts and coinfection of the intermediate host affect the ESS in terms of the parasite's drug resistance and virulence to the intermediate host. Assume that the level of drug resistance of parasites is characterized by the parameter $\theta_i\geq 1$. The effect of resistance is reflected in the reduced parasite killing rate $f_i(\sigma(a))\leq\sigma(a)$, where $\sigma(a)$ is the age-dependent drug treatment rate. A simple example of the function $f_i$, as used in Xu et al. (2005) and Castillo-Chavez et al. (2008), could be

$$f_i(\sigma(a))=\frac{\sigma(a)}{\theta_i}.$$

For a drug resistant parasite strain $i$, it is assumed that $\theta_i>1$ due to the fact that drug sensitive parasite strains are less fit than resistant strains in the presence of human drug treatments. For presentation purposes, the results described in this section are for the case of constant (i.e., age-independent) drug treatment rate $\sigma$. The case of age-dependent treatment $\sigma(a)$ will be discussed in Section 5. We also assume that high drug resistance is associated with low reproduction rates $\gamma_i$ in the definitive host (Webster et al., 2008) and describe the rate $\gamma_i$ by a decreasing function:

$$\gamma_i=\gamma(\theta_i)=\gamma_0\overline{\gamma}(\theta_i),\quad i=1,2,$$

where $\gamma_0>0$ is a constant. We will consider three types of functions for $\overline{\gamma}(\theta)$: linear, convex–concave and concave. See Fig. 1 (right) for the shapes of these functions.

Field studies show that the risk of *schistosome* infection depends on the age of the definitive human hosts and the age of peak infection also varies according to the prevalence level of the disease (Homeida et al., 1988; WHO, 1989; Sturrock, 2001; Massara et al., 2004; Deribe et al., 2011). For ease of numerical simulations we consider the parasites' transmission rate $\beta_i(a)$ to be a piece-wise function of age $a$:

$$\beta_i(a)=\begin{cases}\beta_i y_j & \text{if } 10(j-1)<a\leq 10j,\quad j=1,2,\ldots,7,\\ 0 & \text{if } a>70.\end{cases}$$

Here, the constant $\beta_i$ represents the background transmission rate of strain $i$ parasites, and the multipliers $y_j$ have fixed values dependent on the age group $j$. Fig. 1(left) shows the multipliers $y_j$ versus age $a$ that we used in numerical simulations.

For the infection rates of snail hosts, we assume that the rates for single infection and coinfection are different. The rates of single infections $\rho_i$ are equal to a constant, i.e,

$$\rho_1=\rho_2=\rho_0.$$

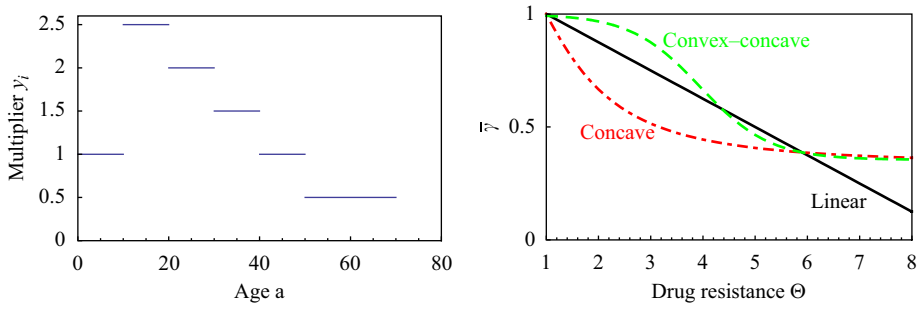


**Fig. 1.** The left figure is a plot of multipliers $y_i$ versus the age of human hosts. The parasites' transmission rate $\beta_i(a)$ to human hosts is given by the product of $y_j$ and a background transmission rate $\beta_i$. The figure on the right is a plot of the function $\overline{\gamma}(\theta)$ versus the drug resistance level $\theta$ for the reproduction rate of adult parasites in human hosts $\gamma_i=\gamma_0\overline{\gamma}$. In numerical simulations, $\overline{\gamma}(\theta)=(9-\theta)/8$ for the linear trade-off, $\overline{\gamma}(\theta)=(0.55+1/(8e^{1.5\theta-8}+1))/1.55$ for the convex–concave trade-off, and $\overline{\gamma}(\theta)=4/3-\theta^2/(2+\theta^2)$ for the concave trade-off and $\gamma_0=9000$ per year.

However, the coinfection rates $\rho_{ij}$ ($i,j=1,2, i\neq j$) are assumed to be an increasing function of the difference in levels of drug resistance $|\theta_1-\theta_2|$ (Gower and Webster, 2005). Here we simply assume that the coinfection rates of snail hosts take the following form:

$$\rho_{12}=\rho_{21}=\rho(x)=\eta\rho_0\frac{x^n}{0.2+x^n}, \tag{15}$$

where $x=|\theta_1-\theta_2|$ and $\eta$ measures the relative efficiency of coinfections (cf. Levin and Pimentel, 1981), which allows us to study how coinfections affect the ESS. The parameter $n$ determines whether $\rho_{ij}$ is differentiable with respect to $\theta_2$ at $\theta_2=\theta_1$. We will present the evolutionary results for differentiable and non-differentiable coinfection functions separately in two subsections.

Note that $\beta_i$ represents the infection rate of the definitive host and $c_i$ is the parasite (cercariae) production rate. From the formula for the invasion reproduction number $\mathcal{R}(m,r)$ (which is expressed in terms of $\mathcal{R}_h$), we notice that $\beta_i$ and $c_i$ always appear in the product form $\beta_i c_i$ in $\mathcal{R}(m,r)$. Although empirical studies (Davies et al., 2001; Gower and Webster, 2004) show that the parasite virulence $\delta_i$ is negatively correlated to $c_i$ and positively correlated to $\beta_i$, it is not clear how the product $\beta_i c_i$ changes with $\delta_i$. To simplify the analysis, we assume a trade-off between $\delta_i$ and the product $\beta_i c_i$ denoted by

$$c_i\beta_i=T_{c\beta}(\delta_i),\quad i=1,2, \tag{16}$$

where $T_{c\beta}(\delta)$ is a function which can be either an increasing or a decreasing function of $\delta$.

For the case of coinfection, depending on how coinfection may affect the reproduction $c_i'$ in comparison to $c_i$ for parasite strain $i$, there are three possible relationships between the products $c_i'\beta_i$ and $c_i\beta_i$ ($i=1,2$) which can be described by

$$c_1'\beta_1+c_2'\beta_2=\xi(c_1\beta_1+c_2\beta_2) \tag{17}$$

with $\xi$ being smaller than, greater than, or equal to 1. For ease of reference, we introduce the definitions: the case of $\xi\geq 1$ is referred to as *facilitation*, whereas the case of $\xi<1$ is referred to as *competitive suppression*. As for the trade-off between reproduction and virulence of parasites within coinfected snail hosts, based on the finding that low virulent strains can have competitive advantages over high virulent strains within the intermediate host (Gower and Webster, 2005) we assume the following links between $c_i'\beta_i$ and $\delta_j$:

$$c_i'\beta_i\propto\frac{\delta_j}{\delta_1+\delta_2},\quad 1\leq i\neq j\leq 2, \tag{18}$$

with the proportionate constant equal to $\xi(c_1\beta_1+c_2\beta_2)=\xi[T_{c\beta}(\delta_1)+T_{c\beta}(\delta_2)]$. That is, combining (17) and (18) we have

$$c_i'\beta_i=\xi[T_{c\beta}(\delta_1)+T_{c\beta}(\delta_2)]\frac{\delta_j}{\delta_1+\delta_2},\quad 1\leq i\neq j\leq 2. \tag{19}$$

We are now ready to discuss the ESS of the parasites and identify optimal levels of drug resistance ($\theta$) and virulence ($\delta$). Denote a singular strategy by $r^*=(\theta^*,\delta^*)$. Then it satisfies

$$\left.\frac{\partial\mathcal{R}(m,r)}{\partial\delta_m}\right|_{m=r}=0,\quad \left.\frac{\partial\mathcal{R}(m,r)}{\partial\theta_m}\right|_{m=r}=0. \tag{20}$$

From the first equation, together with the constraint on coinfection of snail hosts, $\rho_{ij}=0$ for $i=j$, it follows that

$$\frac{d(c_m\beta_m)}{d\delta_m}=\frac{c_m\beta_m}{\mu_{sm}},$$

from which the virulence $\delta^*$ can be obtained. Note that $c_m\beta_m/\mu_{sm}$ is positive. Thus, this $\delta^*$ exists only if the product $c_m\beta_m$, as a trade-off function of virulence $\delta_m$, is an increasing function and $\delta^*$ is evolutionarily stable if $c_m\beta_m$ is a concave function. As in the case of directly transmitted diseases (e.g., Pugliese, 2002; Svennungsen and Kisdi, 2009), one can study how the shape of the trade-off function $c_m\beta_m$ and/or an increase in snail mortality (due to snail control efforts) affect the virulence $\delta^*$ to snail hosts.

The ESS resistance level $\theta^*$ can be calculated by substituting the value of $\delta^*$ into the second equation of (20) in the case where the coinfection rates $\rho_{ij}$ given in (15) is differentiable with respect to $\theta_2$ at $\theta_2=\theta_1$ (e.g., $n=2$). The evolutionary stability and convergence of the ESS point will be examined by the second derivatives of the invasion reproduction number $\mathcal{R}$ and pairwise invadability plots (PIP) (Metz et al., 1996; Geritz et al., 1997, 1998). In the case where the coinfection rates $\rho_{ij}$ is not differentiable (e.g, $n=1$), we substitute the value of $\delta^*$ into the expression (14) of $\mathcal{R}$ and then directly use PIP to study the ESS resistance $\theta^*$.

The above analysis can help to guide numerical simulations for identifying the ESS. Consider the case in which $T_{c\beta}(\delta)$ (see (16)) is an increasing function of the form:

$$T_{c\beta}(\delta)=c_0\beta_0\frac{1.5\delta^2}{0.5\delta_0^2+\delta^2},$$

where $c_0$, $\beta_0$ and $\delta_0$ are constants. Then, for biologically reasonable parameter values (see the caption of Fig. 2), $\delta^*$ can be computed and is equal to 2.873, which is smaller than the background virulence value 3.5. In this case, the coinfection efficiency $\eta$ and drug treatment rate $\sigma$ have no impact on $\delta^*$. In the following we separately present our results according to the differentiability of the coinfection functions $\rho_{ij}$.

### 4.1. Differentiable coinfection functions

In the case when the coinfection rates $\rho_{ij}$ (given in (15) for $n=2$) are differentiable, numerical simulations and PIPs (see Fig. 2) show that there exists an evolutionarily convergent ESS $\theta^*$. That is, in evolutionary time the drug resistance level $\theta^*$ tends to be approached.

To introduce PIPs, let us consider the case of the linear trade-off curve $\gamma(\theta)$ (see Fig. 1 for trade-off curves). When there is no coinfection (i.e., $\eta=0$) (Fig. 2A), any resident strain of parasites with drug resistance $\theta$ less than the ESS $\theta^*$ can be invaded by some more drug-resistant strains, not by any less resistant strain. Any resident strain with drug resistance level $\theta>\theta^*$ can be invaded by less resistant strains. Only $\theta^*$ is not invadable and thus it is evolutionarily convergent and stable. In this case, $\theta^*$ is the evolutionary endpoint (in the sense of evolutionary convergence and stable stability) and dimorphism or polymorphism is not possible. Fig. 2B is for the case of facilitation ($\xi\geq 1$) and when coinfections are allowed (i.e., $\eta>0$). It illustrates that the ESS $\theta^*$ is invadable and hence evolutionarily unstable. In this case, an initially monomorphic population will become dimorphic or even polymorphic, and the ESS $\theta^*$ is called a branching point. Fig. 2C is for the case of competitive suppression ($\xi<1$), and it shows that the ESS $\theta^*$ is evolutionarily stable and hence is an evolutionary endpoint.

When the trade-off curve $\gamma$ is linear, the PIPs reveal the following observations (Fig. 2A–D). The first observation is that variations in the coinfection efficiency $\eta$ or in $\xi$ do not affect the drug resistance level $\theta^*$ at ESS (see Fig. 2A–C). However, high coinfection efficiencies ($\eta$) and reproduction ($\xi\geq 1$) can alter the evolutionary stability of $\theta^*$ and hence make it more likely to have dimorphism or polymorphism (Fig. 2B). Our numerical simulations also show that, in the case of competitive suppression ($\xi<1$), an increase in the coinfection efficiency $\eta$ or a decrease

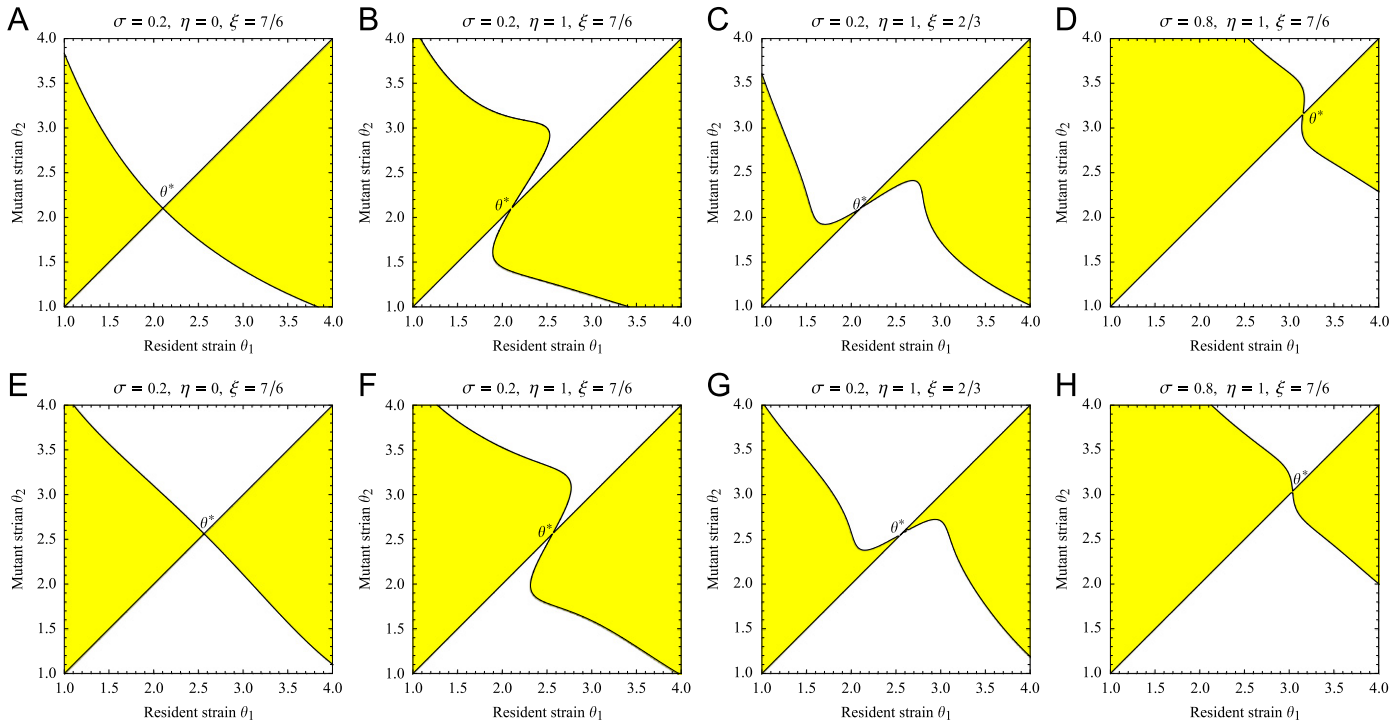


**Fig. 2.** Pairwise invadability plots (PIP) when the coinfection function $\rho_{ij}$ given in (15) is differentiable ($n=2$) with respect to $\theta_2$ at $\theta_2=\theta_1$. The invasion fitness $\mathcal{R}(m,r)$ is greater than 1 in the shaded regions and less than 1 in the unshaded regions. A–D are for the linear trade-off function $\gamma(\theta)$ while E–H are for the convex–concave trade-off function $\gamma(\theta)$. Except parameter values listed in the graphs, all others are $\Lambda_h=8$, $\mu_h=0.014$, $\Lambda_s=25$, $\rho_0=2\times10^{-9}$, $\mu_s=0.5$, $c_0=28\,000$, $\beta_0=0.000027$, $\delta_0=3.5$. The time unit of the parameters is per year and most of these parameter values are taken from Feng et al. (2004).

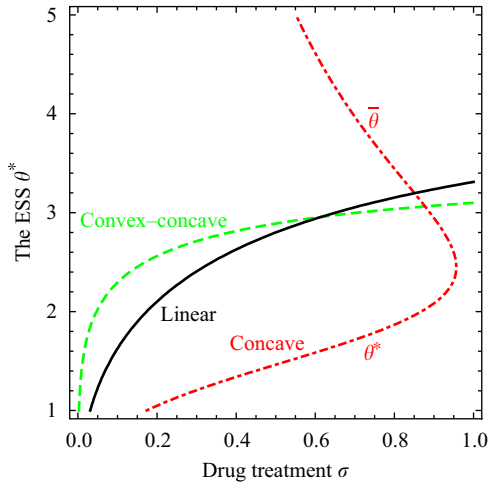


**Fig. 3.** Plot of the drug resistance level at the evolutionarily stable strategy (ESS) $\theta^*$ against the drug treatment rate $\sigma$ when the coinfection function $\rho_{ij}$ given in (15) is differentiable ($n=2$). The ESS $\overline{\theta}$ in the case of the concave trade-off curve $\gamma(\theta)$ is evolutionarily unstable, functioning as an evolutionary repeller. The parameter values are the same as in Fig. 2.

in $\xi$ tends to stabilize the ESS point $\theta^*$ and inhibit dimorphism as an evolutionary endpoint (e.g. Fig. 2C). The second observation is that if two strains exhibit facilitation within intermediate hosts ($\xi\geq1$), the drug treatment rate $\sigma$ tends to stabilize the ESS point $\theta^*$ and promote monomorphism as the final evolutionary result (Fig. 2B and D). In contrast, our simulations show that drug treatment does not change the stability of the ESS point in the case of competitive suppression $\xi<1$.

Similar observations can be made for the case of convex–concave trade-off (Fig. 2E–H). A noticeable difference between the linear and convex–concave trade-offs for low treatment rates (i.e., Fig. 2A–C versus E–G, or see Fig. 3) is that the resistance level $\theta^*$ at the ESS is higher in Fig. 2E–G. Recall that the convex–concave trade-off corresponds to a relatively lower cost for drug resistance (see Fig. 1). This suggests that even under moderate treatment rates, higher levels of drug resistance will still be likely to develop if the cost for drug resistance is low.

When the cost for drug resistance is relatively high as illustrated by the concave trade-off curve $\gamma$ shown in Fig. 1, there are usually two ESS points, denoted by $\theta^*$ and $\overline{\theta}$ and as shown in Fig. 4. The point $\overline{\theta}$ is evolutionarily unstable and divergent; and hence, it is unattainable and acts as an evolutionary repeller. The other point $\theta^*<\overline{\theta}$ is evolutionarily stable and convergent. Therefore, when a small variation in drug resistance is present, $\theta^*$ will be the final evolutionary endpoint. Fig. 4 also shows that when higher levels of drug resistance are allowed, the evolutionary result is expected to show either monomorphism of the strain with resistance $\theta^*$ or the most resistant strain (depending on the shape of $\gamma$). Again, these outcomes are the consequence of the specific feature associated with the trade-off function $\gamma(\theta)$ being concave (see Fig. 1). Notice from Fig. 1 that $\gamma$ decreases much more quickly with $\theta$ for $\theta<3.5$ than for $\theta>3.5$. This is, higher costs will be expected for an increase in drug resistance when $\theta$ is small. Therefore, for smaller values of $\theta$, an optimal resistance $\theta^*$ will likely to be at an intermediate level ($\theta^*<2.5$, see Fig. 3). On the other hand, when $\theta$ is large (greater than the critical level $\overline{\theta}$), due to the moderate cost the parasite may also develop higher levels of resistance.

From our numerical experiments we also noticed that the coinfection parameters $\eta$, $\xi$ and the treatment rate $\sigma$ have little impact on the evolutionary stability of the ESS $\theta^*$, implying that the structure of one stable and one unstable ESS is persistent.

### 4.2. Non-differentiable coinfection functions

When the coinfection functions $\rho_{ij}$ are not differentiable (see (15) for $n=1$), we use the linear trade-off $\gamma$ to illustrate the

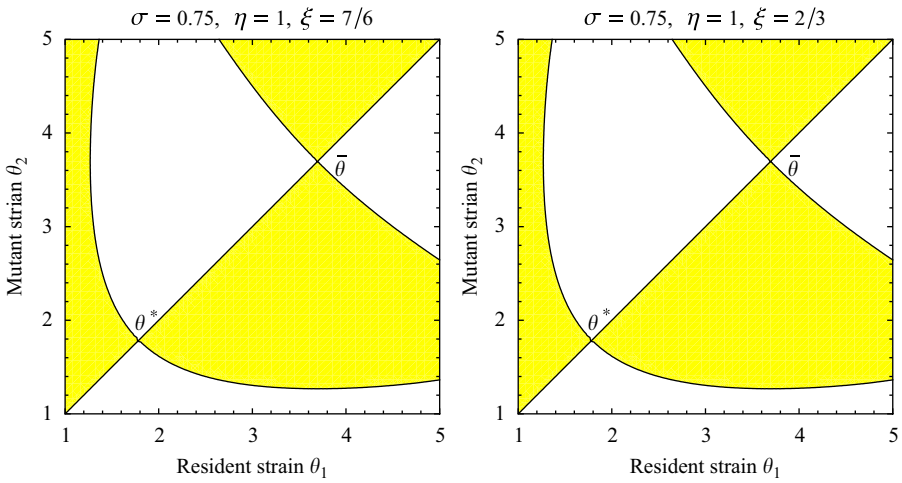


**Fig. 4.** Pairwise invadability plots (PIP) in the case of the concave trade-off $\gamma(\theta)$ and the differentiable coinfection function $\rho_{ij}$ given in (15) ($n$=2). Notations are as in Fig. 2 with the EES $\bar{\theta}$ being evolutionarily unstable and acting as a repeller. Numerical studies show that the treatment rate $\sigma$ and the coinfection efficiency $\eta$ have little impact on the stability of the ESS $\theta^*$. Parameters are the same as in Fig. 2 except those listed in the figures.

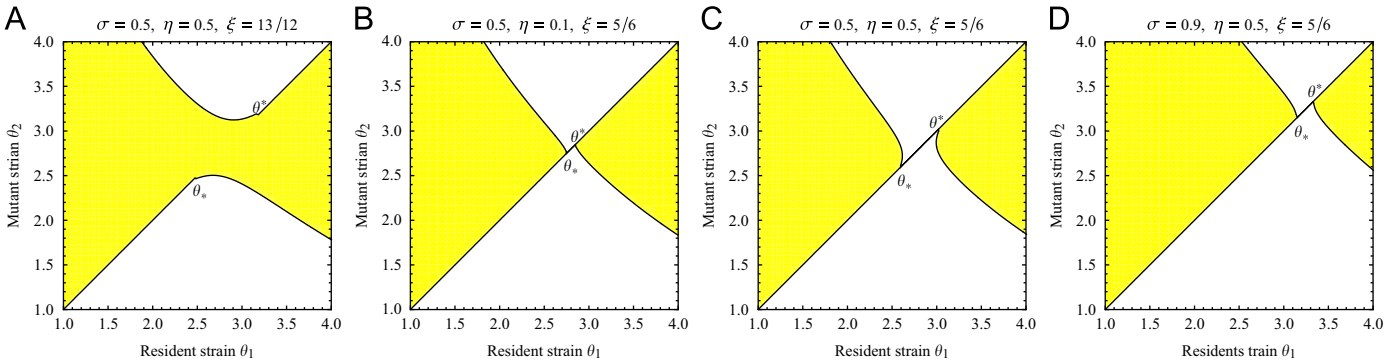


**Fig. 5.** Similar to the PIP plots in Fig. 2 but for the case of a linear trade-off function $\gamma(\theta)$ and a non-differentiable coinfection function $\rho_{ij}$. In this case, there are two ESS points, $\theta_*$ and $\theta^*$. Both $\theta_*$ and $\theta^*$ are evolutionarily attainable either from left or from right. But they may or may not prevent an invasion by mutant strains (see explanations in the text). The plot in A is for the case of $\xi \geq 1$, and plots in B–D are for the case of $\xi < 1$ with different values of $\eta$ or $\sigma$. Parameters are the same as in Fig. 2 except those specified on the graphs.

evolution of drug resistance. Unlike in the previous cases in which there is only a single ESS point, there are now two ESS points, which we denote by $\theta_*$ and $\theta^*$ as shown in Fig. 5. We observe from the plots in Fig. 5 that if a resident parasite strain has a drug resistance level below $\theta_*$, then it can be invaded by any parasite strain that has a higher level of drug resistance. If a resident strain has a resistance level above $\theta^*$, then it can be invaded by any parasite strain that has a lower resistant level. Therefore, $\theta_*$ and $\theta^*$ are evolutionarily convergent and attainable either from left or from right.

Fig. 5A is for the case of $\xi > 1$ (competitive facilitation). It illustrates that all strategies between $\theta_*$ and $\theta^*$ are invadable. Hence, the evolutionary outcome can be dimorphism or even polymorphism with drug resistance levels being in the range $[\theta_*,\theta^*]$. In contrast, monomorphism is expected for the case of $\xi < 1$ (competitive suppression) as demonstrated in Fig. 5B–D. Fig. 5B and C is for different values of the coinfection efficiency $\eta$. It shows in Fig. 5B that a resident strain with resistance level $\theta \in [\theta_*,\theta^*]$ is capable of preventing an invasion by mutant strains, and hence the evolutionary outcome can be a monomorphism with a resistance level in $[\theta_*,\theta^*]$. As $\eta$ increases (Fig. 5C), $\theta_*$ and $\theta^*$ can become invadable. Fig. 5C and D compares the outcomes for different values of $\sigma$ (drug treatment), and they show that an increase in $\sigma$ tends to stabilize $\theta_*$ and $\theta^*$.

In Fig. 6, we examine how the length of the interval $[\theta_*,\theta^*]$ may depend on other factors such as $\eta$ and $\sigma$. The curves in Fig. 6 show the changes of the ESS points $\theta_*$ and $\theta^*$ with $\eta$ (A and C) or $\sigma$ (B and D). For both the case $\xi > 1$ (A and B) and the case $\xi < 1$ (C and D), it shows that the interval $[\theta_*,\theta^*]$ increases with $\eta$ but decreases with $\sigma$ (except for very small $\sigma$). All parameter values are the same as in Fig. 2 except those listed on the graphs.

## 5. Discussion

Traditionally, theoretical studies on the evolution of pathogens assume positive associations between virulence and parasite replication rate, and between parasite replication rate and transmission success (Anderson and May, 1981; Frank, 1992, 1996; Bull, 1994; Mackinnon and Read, 1999). However, relatively recent empirical work demonstrated that the reproductive success of *schistosomes* in the definitive mouse host was strongly inversely related to the reproductive success in the intermediate snail host (Davies et al., 2001; Gower and Webster, 2004; Webster et al., 2008). Moreover, parasite reproductive output from snails was negatively correlated with both virulence (within snails) and transmission success to mice. These findings were both unexpected and exciting as they differed from the predictions emerging from traditional virulence theory (e.g., Frank, 1992, 1996; Bull, 1994). Motivated by these findings, we developed a mathematical model that includes both coinfections of snail hosts and parasites' drug resistance in human hosts. Armed with the

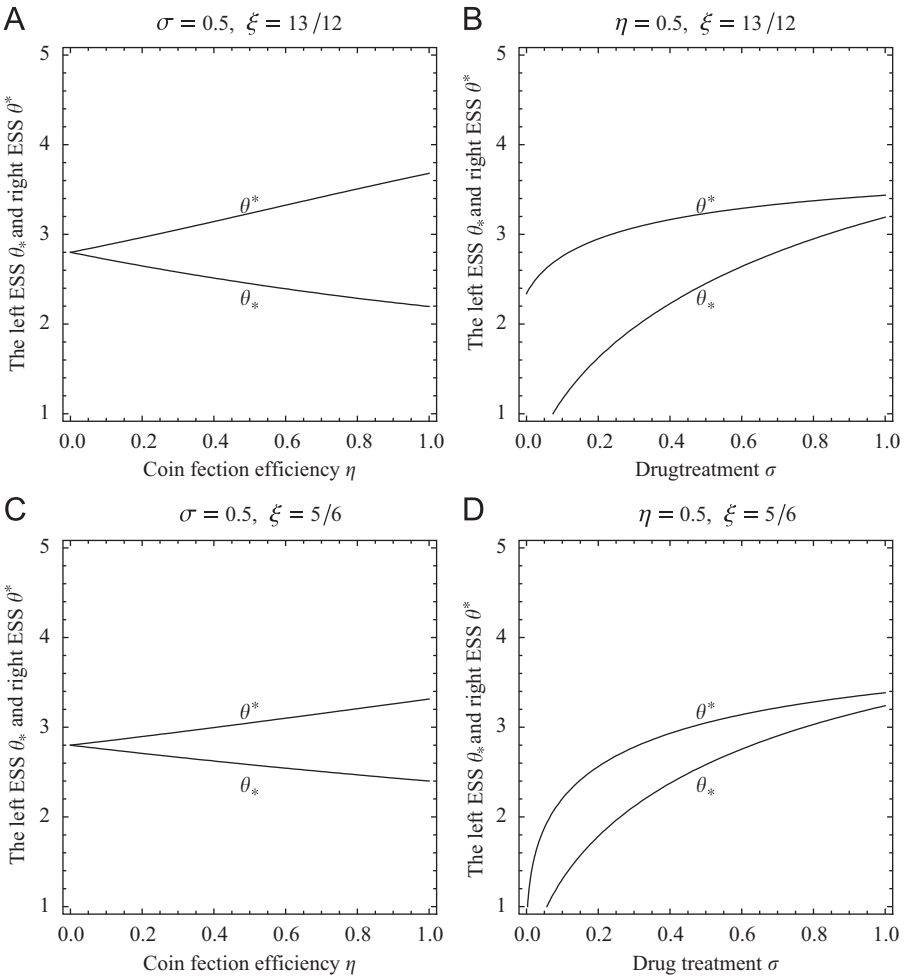


**Fig. 6.** Plots of the ESS points ($\theta_*$ and $\theta^*$) versus $\eta$ (A and C) or $\sigma$ (B and D) in the case of a linear trade-off function $\gamma(\theta)$ and a non-differentiable coinfection function $\rho_{ij}$. A and B illustrate the case of facilitation ($\xi > 1$), whereas C and D for the cases of competitive suppression ($\xi < 1$). We observe that the length of the interval $[\theta_*,\theta^*]$ increases with $\eta$ but decreases with $\sigma$ (except for very small $\sigma$). All parameter values are the same as in Fig. 2 except those listed on the graphs.

assumptions mainly based on a series of empirical studies (Chan et al., 1995; Davies et al., 2001; Gower and Webster, 2004, 2005; Webster et al., 2008), we investigated the impacts of human drug treatments and coinfections of intermediate snail hosts on the evolutionarily stable strategy (ESS) of *schistosome* drug resistance $\theta$ and the virulence $\delta$ to the intermediate snail host.

Our results suggest that the impact of human drug treatments ($\sigma$) and coinfections of intermediate hosts (represented by the parameter $\eta$ in the analysis) on ESS points may depend on other factors, three of which are discussed here. The first factor concerns the level of cost for parasites' resistance to the drug (described by the function $\gamma(\theta)$). Relatively low and high costs are represented by convex–concave, linear and concave curves, respectively (see Fig. 1). The second factor is the relationship between the coinfection rates $\rho_{ij}$ and the difference in drug resistance levels $|\theta_2-\theta_1|$ (see (15)). Two scenarios based on the properties of the function in (15) are presented in Sections 4.1 and 4.2, which illustrated that the conclusions under these two scenarios can be dramatically different (more details are summarized below), which suggest the importance and need for field studies that can help determine accurate relationships between the factors such as coinfection rates and resistance levels. The third factor is related to whether the effect of coinfection on parasite reproduction is in the form of facilitation ($\xi \geq 1$) or competitive suppression ($\xi < 1$).

One of the main conclusions of this study is that when the cost for parasites' drug resistance is *low* ($\gamma(\theta)$ is linear or convex–concave), coinfection of the intermediate host ($\eta$) tends to destabilize the ESS point $\theta^*$ and promotes di- or polymorphism in the case of facilitation ($\xi \geq 1$), while stabilizing the ESS and promoting monomorphism in the case of competitive suppression ($\xi < 1$) (see Figs. 2 and 5). The role of drug treatment ($\sigma$) is very different. Although the ESS may be destabilized in the case of $\xi \geq 1$, $\sigma$ has little effect on the stability of the ESS in the case of $\xi < 1$. In contrast to the above, when the cost for resistance is relatively *high* ($\gamma(\theta)$ is concave), the outcomes are dramatically different in the sense that both coinfection ($\eta$) and treatment ($\sigma$) have very little impact on the stability of the ESS points (see Fig. 4).

It should be noted that the different outcomes mentioned above in terms of whether polymorphism or monomorphism will be expected are direct consequences of whether the parasites exhibit facilitation ($\xi \geq 1$) or competitive suppression ($\xi < 1$) within snail hosts. In the case of facilitation, coinfected snails release more parasites than singly infected snails; and thus, the parasites may improve their fitness by increasing the frequency of coinfection with other parasites with different levels of drug resistance. In the case of competitive suppression, the parasites do better in singly infected snail hosts; and thus, monomorphism is expected. Which strategies will be adopted by parasites may depend on specific host–parasite interactions. For example, the study on malaria parasites in Hastings (2006) shows that drug resistance rarely goes to fixation in a population under frequency-dependent competition. For *schistosome* parasites, empirical studies have shown that

snails exposed to mixed strains of parasites release more parasites than those exposed to a single strain of parasites (e.g., Davies et al., 2002). Therefore, *schistosome* parasites may exhibit facilitation within the intermediate host. Further empirical studies are needed to examine the drug sensitivity of the parasites.

Another conclusion in this study is about the effect of coinfection ($\eta$) and treatment ($\sigma$) on the ESS levels of drug resistance ($\theta^*$ and/or $\theta_*$). It may depend on model assumptions and parameter values. For example, we considered the second factor mentioned above and presented our results under two different assumptions on the coinfection function (15) (i.e., the relationship between the coinfection rates $\rho_{ij}$ and the level of drug resistance). We showed that while the coinfection efficiency ($\eta$) may have little effect on the level $\theta^*$ of drug resistance when the coinfection function in (15) is differentiable (see Section 4.1), the length of the ESS interval $[\theta_*,\theta^*]$ will depend on the magnitudes of $\eta$, $\xi$, and $\sigma$ (see Fig. 6). Other recent studies from different fields have suggested that coinfection may result in suppression of resistant pathogens (e.g., Hastings, 2006; Torella et al., 2010; Chmielecki et al., 2011; Read et al., 2011). The implication of the results in both our study and others is that whether or not and how the evolution of drug resistance will depend on coinfection and drug treatment may vary for different host–parasite systems, and that it is necessary to identify other relevant factors that may alter the predictions on the evolutionary trajectory.

We point out that, when considering the role of coinfections in our ESS analysis (see Section 4) we have focused mainly on coinfections in the intermediate snail hosts. Coinfections in human hosts may also be an important factor in the evolution and spread of parasites' drug resistance. It has been demonstrated that, in the presence of drug treatment, coinfections in human hosts can lead to a substantial competitive release of drug resistant parasites, which may accelerate the spread of drug resistance (e.g., Wargo et al., 2007; Huijben et al., 2010). As resistance spreads and coinfection frequently occurs, parasites' competition for resources may also constrain the prevalence of resistance because of the declining intrahost selection for resistance (Hastings, 2006). Given the fact that an infected snail often harbours a number of different parasite genotypes in the field (Sire et al., 1999; Eppert et al., 2002) and that mixed genotype infections lead to increased reproduction rates of the parasite (Davies et al., 2002), it is not clear whether or not the properties of ESS points can be affected if the parasites' competition for resources within snail hosts is incorporated in our model, especially when a trade-off may exist between parasites' competition ability in the intermediate snail host and other parasites' traits in the definitive human host. In the absence of these trade-offs, one might expect a lower level of $\theta^*$ based on the same argument as that for parasite competition within human hosts. For *schistosome* parasites, there also exists mating competition: males can pull paired females away from their partners although homospecific females are preferred (Cosgrove and Southgate, 2002). These competitions (within both human and snail hosts) have not been explicitly incorporated in our model. Further theoretical and empirical studies are needed in order to improve the model.

The evolutionary result of a parasite–host system usually depends on trade-offs between benefits and costs of the system (e.g., Boots and Haraguchi, 1999). It is even difficult to measure the shapes of trade-off curves due to lack of empirical data. In our numerical experiments, except for the trade-offs presented in Section 4 we also checked the evolutionary outcomes in the case of decreasing trade-off functions $T_{c\beta}(\delta)$. We found that these different trade-off assumptions do not bring any qualitative changes in the ESS $\theta^*$ except that the quantity of $\theta^*$ becomes much larger, which we believe is unrealistic.

Our model can be applied to study the impacts of age-dependent drug treatment programs (Colley et al., 2001; Fenwick et al., 2003). If drugs are distributed according to the infection risks of human hosts (e.g., given by the parasites' transmission rate $\beta_i(a)$), the model simulations show that the treatments usually result in a little higher drug resistance $\theta^*$ than those in the case of uniform (age-independent) treatments, acting as the role of higher uniform treatment rates. However, the drug resistance level at the ESS $\theta^*$ could be very low for treatment programs targeting at a specific age group of hosts like school-age children (Colley et al., 2001). This is because untreated patients functioning as refuges transmit drug sensitive parasites. A detailed study on the impacts of age-targeted treatment strategies will be presented elsewhere. Instead of age-targeted treatments one could study the effect of treatment strategies based on a threshold level of parasites within human hosts (i.e., symptomatic treatments). From the simulations we carried out under various scenarios of age-targeted treatments, we expect that symptomatic treatment tends to reduce the development of drug resistance (depending on the threshold level of parasites).

The parasite virulence considered in this study has been limited to intermediate hosts. We remark that although the virulence to human hosts is very low in terms of the disease mortality, it may be an interesting question to study when the morbidity caused by schistosomiasis is considered as a measure for parasite virulence. This question is relevant as the issue of drug resistance is clearly related to the high morbidity of the disease. To incorporate disease morbidity in the analysis presented in this paper, it may require the information about a stable endemic equilibrium of the model, which will be a very challenging task due to the complexity of the model. One way to do this is to first simplify our model by considering only the definitive host (i.e., ignoring the intermediate host). In any case, the main contribution of this study lies in its attempt to analyze a model which includes many details of the interaction between hosts and a parasite with a complex life cycle.

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## Appendix A. Derivation of Eq. (1)

The derivation of system (1) for two strains of parasites is the same as that for one strain of parasites. For writing convenience, we here consider one strain of parasites. Let $H(t,a,x)$ be the number of human hosts of age $a$ at time $t$, carrying $x$ adult parasites. Assume that the rate at which a human host acquires one adult parasite is proportional to the number $C$ of the larvae cercariae with proportionality constant $\beta(a)$, depending on the age $a$ of the host. Then parasites in a host may increase from $x-1$ to $x$ because of acquiring a new parasite at rate $\beta(a)C$, and decrease from $x+1$ to $x$ because of the natural death of one parasite at rate $\mu_p$, or being killed by drug treatments at rate $f(\sigma(a))$, where $\sigma(a)$ represents drug treatments. Of course, all parasites in a host die if the host dies. Human hosts die naturally at a rate $\mu_h(a)$ (note that the per capita death rate of human hosts due to one parasite infection is assumed to be zero). Following frameworks by Anderson and May (1978) (see also Dobson, 1985 for the case of ordinary differential equations and Hadeler and

Dietz, 1983; Hadeler, 1984 for the case of partial differential equations), we have the following infinite system of equations for $H(t,a,x)$

$$\left(\frac{\partial}{\partial t}+\frac{\partial}{\partial a}\right)H(t,a,x)=\beta(a)CH(t,a,x-1)+(\mu_p+f(\sigma))(x+1)H(t,a,x+1)$$
$$-(\beta(a)C+\mu_h+(\mu_p+f(\sigma))x)H(t,a,x) \quad (21)$$

for $x\geq 1$, and

$$\left(\frac{\partial}{\partial t}+\frac{\partial}{\partial a}\right)H(t,a,0)=(\mu_p+f(\sigma))H(t,a,1)-(\beta(a)C+\mu_h)H(t,a,0) \quad (22)$$

for $x=0$.

Let $n(t,a)$ denote the total number of human hosts of age $a$ at time $t$ and $p(t,a)$ denote the total number of adult parasites carried by human hosts of age $a$ at time $t$. Then

$$n(t,a)=\sum_{x=0}^{\infty}H(t,a,x), \quad p(t,a)=\sum_{x=1}^{\infty}xH(t,a,x).$$

Adding Eqs. (21) and (22) we have

$$\left(\frac{\partial}{\partial t}+\frac{\partial}{\partial a}\right)n(t,a)=-\mu_h n(t,a),$$

$$\left(\frac{\partial}{\partial t}+\frac{\partial}{\partial a}\right)p(t,a)=\beta(a)n(t,a)C-(\mu_h+\mu_p+f(\sigma))p(t,a),$$

which are the same as Eq. (1) (except the subindex $i$).

## Appendix B. Reduction to the limiting system

Note that the $n(t,a)$ equation in the model (4) is independent of other variables. Integrating the equation along characteristic lines, leads to

$$n(t,a)=\begin{cases}\Lambda_h\pi_h(a), & t\geq a,\\ n_0(a-t)\dfrac{\pi_h(a)}{\pi_h(a-t)}, & t<a\end{cases} \quad (23)$$

Substituting the expressions of $n(t,a)$ into the $p_i(t,a)$ equation and integrating the equation yields

$$p_i(t,a)=\begin{cases}\Lambda_h\int_0^a\beta_i(w)C_i(t+w-a)\pi_h(w)\dfrac{\pi_{hi}(a)}{\pi_{hi}(w)}\,dw, & t\geq a,\\ p_{i0}(a-t)\dfrac{\pi_{hi}(a)}{\pi_{hi}(a-t)}\\ \quad+\int_{a-t}^a\beta_i(w)C_i(t+w-a)n_0(a-t)\dfrac{\pi_{hi}(a)}{\pi_{hi}(w)}\dfrac{\pi_h(w)}{\pi_h(a-t)}\,dw, & t<a.\end{cases}$$

Denote the solution as

$$p_i(t,a)=\begin{cases}q_1(t,a), & t\geq a,\\ q_2(t,a), & t<a\end{cases} \quad (24)$$

Then

$$M_i=\gamma_i\int_0^{\infty}p_i(t,a)\,da=\gamma_i\int_0^t q_1(t,a)\,da+\gamma_i\int_t^{\infty}q_2(t,a)\,da.$$

Notice that the total population size of intermediate hosts is bounded by either $\Lambda_s/\mu_s$ or the initial population size. From the biological meanings of $\mu_h$, $\mu_{hi}$ and the initial functions $p_{i0}$, $n_0$, it follows that the last integral in the above formula goes to zero as $t\to\infty$. Thus, in the limit situation we have

$$\begin{aligned}M_i&=\gamma_i\int_0^{\infty}q_1(t,a)\,da\\ &=\gamma_i\int_0^{\infty}\Lambda_h\int_0^a\beta_i(w)C_i(t+w-a)\pi_h(w)\pi_{hi}(a)\pi_{hi}^{-1}(w)\,dw\,da\\ &=\gamma_i\Lambda_h\int_0^{\infty}\int_w^{\infty}\beta_i(w)C_i(t+w-a)\pi_h(w)\pi_{hi}(a)\pi_{hi}^{-1}(w)\,da\,dw\\ &=\gamma_i\Lambda_h\int_0^{\infty}\int_0^{\infty}\beta_i(w)C_i(t-a)\pi_h(w)\pi_{hi}(a+w)\pi_{hi}^{-1}(w)\,da\,dw\\ &=\gamma_i\Lambda_h\int_0^{\infty}C_i(t-a)\int_0^{\infty}\beta_i(w)\pi_h(w)\pi_{hi}(w+a)\pi_{hi}^{-1}(w)\,dw\,da\\ &=c_i\int_0^{\infty}I_i(t-a)R_{hi}(a)\,da+c_i'\int_0^{\infty}I_{12}(t-a)R_{hi}(a)\,da.\end{aligned}$$

Substituting the expression for $M_i$ into the $S$, $I_i$ and $I_{12}$ equation in model (4), we have the limiting system (5). From (23) and (24) and $C_i=c_iI_i+c_i'I_{12}$, we know that as $t\to\infty$,

$$n(t,a)\to\Lambda_h\pi_h(a),$$

$$p_i(t,a)\to\Lambda_h\int_0^a\beta_i(w)(c_iI_i(t+w-a)+c_i'I_{12}(t+w-a))\pi_h(w)\frac{\pi_{hi}(a)}{\pi_{hi}(w)}\,dw.$$

Therefore, the asymptotic behavior of $p_i(t,a)$ can be determined once the behaviors of $I_i(t)$ and $I_{12}(t)$ are determined. Thus, it is enough to study the limiting system (5) in order to investigate the equilibria of model (4) and their stabilities.

## Appendix C. Stability analysis of the single strain infection model

By setting the coinfection rates $\rho_{ij}=0$, which implies that $I_{12}=0$, one can obtain the single strain infection model from model (4) and its limiting system is given by

$$\frac{d}{dt}S=\Lambda_s-\rho_i\tilde{M}_iS-\mu_sS,$$

$$\frac{d}{dt}I_i=\rho_i\tilde{M}_iS-\mu_{si}I_i, \quad (25)$$

where $\tilde{M}_i=c_i\int_0^{\infty}I_i(t-a)R_{hi}(a)\,da$. Setting the right side of system (25) equal to zero, we have the disease-free equilibrium and an interior equilibrium:

$$E_0=(S^0,I_i^0)=\left(\frac{\Lambda_s}{\mu_s},0\right),$$

$$E_i=(S_i^*,I_i^*)=\left(\frac{\Lambda_s}{\mu_s}\frac{1}{\mathcal{R}_i},\frac{\Lambda_s}{\mu_{si}}\left(1-\frac{1}{\mathcal{R}_i}\right)\right), \quad (26)$$

if the reproductive number $\mathcal{R}_i>1$, where

$$\mathcal{R}_i=\frac{\Lambda_s\rho_ic_i\mathcal{R}_{hi}}{\mu_s\mu_{si}}.$$

**Claim 1.** *The disease-free equilibrium $E_0$ for the single strain model (25) is stable if $\mathcal{R}_i<1$ and unstable if $\mathcal{R}_i>1$. In the later case, there exists a unique endemic equilibrium $E_i$ which is stable. Moreover, $E_0$ is also a global attractor when $\mathcal{R}_i<1$, i.e., $\lim_{t\to\infty}(S(t),I_i(t))=E_0$ with $S(0)\geq 0, I_i(0)\geq 0$.*

**Proof.** Linearizing the system (25) at an equilibrium point $(\tilde{S},\tilde{I}_i)$ we can obtain a linear system for the perturbations of $S$ and $I_i$. For the linear system we look for the exponential solutions $z_0e^{\lambda t}$ and end up with an eigenvalue problem $J_1z_0=0$. Here $z_0$ is a constant two-dimensional vector and the matrix $J_1$ is given by

$$J_1=\begin{pmatrix}-\lambda-\mu_s-\rho_ic_i\mathcal{R}_{hi}\tilde{I}_i & -\rho_ic_i\hat{R}_{hi}\tilde{S}\\ \rho_ic_i\mathcal{R}_{hi}\tilde{I}_i & -\lambda-\mu_{si}+\rho_ic_i\hat{R}_{hi}\tilde{S}\end{pmatrix}. \quad (27)$$

Here, $\hat{R}_{hi}=\int_0^{\infty}R_{hi}(a)e^{-\lambda a}\,da$. Obviously, $\hat{R}_{hi}<\mathcal{R}_{hi}$ for $\lambda\geq 0$ and $(d/d\lambda)\hat{R}_{hi}<0$.

Stability of $E_0$. By evaluating the determinant of $J_1$ at the disease-free equilibrium $E_0$, we have the characteristic equation:

$$(\lambda+\mu_s)\left(\lambda+\mu_{si}-\rho_i c_i \hat{R}_{hi}\frac{\Lambda_s}{\mu_s}\right)=0. \tag{28}$$

That is, either $\lambda=-\mu_s$ or

$$g(\lambda)=\lambda+\mu_{si}-\rho_i c_i \hat{R}_{hi}\frac{\Lambda_s}{\mu_s}=0,$$

Note that $(d/d\lambda)\hat{R}_{hi}<0$. The function $g(\lambda)$ is an increasing function. Therefore $g(\lambda)$ has no positive real zeros if $(0)>0$ and one positive real zero if $g(0)<0$. Note that

$$g(0)=\mu_{si}-\rho_i c_i \mathcal{R}_{hi}\frac{\Lambda_s}{\mu_s}=\mu_{si}(1-\mathcal{R}_i).$$

Thus if $\mathcal{R}_i>1$, $g(0)<0$ and $g(\lambda)$ have a positive real zero, implying that $E_0$ is unstable. If $\mathcal{R}_i<1$, $g(0)>0$ and hence $g(\lambda)>0$ for $\lambda\geq 0$. Therefore, in order to obtain the stability of $E_0$ in the case of $\mathcal{R}_i<1$, we only need to show that $g(\lambda)$ has no complex zeros with nonnegative real parts. Suppose that $x\geq 0$ and

$$g(x+yi)=x+yi+\mu_i-\rho_i c_i\frac{\Lambda_s}{\mu_s}\int_0^\infty e^{-(x+yi)a}R_{hi}(a)\,da=0.$$

Then the real part of $g(x+yi)$ must equal to zero, i.e.

$$Re(g(x+yi))=x+\mu_{si}-\rho_i c_i\frac{\Lambda_s}{\mu_s}\int_0^\infty e^{-xa}\cos(ya)R_{hi}(a)\,da=0.$$

However, $Re(g(x+yi))\geq g(x)>0$, a contradiction. Thus, the function $g(\lambda)$ has no zero points with nonnegative real parts and hence $E_0$ is stable if $\mathcal{R}_i<1$.

Stability of $E_i$. Similarly, evaluating the determinant of $J_1$ at the endemic equilibrium $E_i$, we have the characteristic equation:

$$[\lambda+\mu_s+\rho_i c_i \mathcal{R}_{hi}I_i^*][\lambda+\mu_{si}-\rho_i c_i \hat{R}_{hi}S_i^*]+(\rho_i c_i)^2\hat{R}_{hi}\mathcal{R}_{hi}S_i^*I_i^*=0,\ i.e.,$$

$$(\lambda+\mu_s)(\lambda+\mu_{si})-\rho_i c_i \hat{R}_{hi}S_i^*(\lambda+\mu_s)+\rho_i c_i \mathcal{R}_{hi}I_i^*(\lambda+\mu_{si})=0. \tag{29}$$

Rewrite the equation as

$$\lambda+\mu_{si}-\rho_i c_i \hat{R}_{hi}S_i^*+\rho_i c_i \mathcal{R}_{hi}I_i^*\frac{\lambda+\mu_{si}}{\lambda+\mu_s}=0$$

and denote the left side by $F(\lambda)$. We need to show that $F(\lambda)$ has no zero points with nonnegative real parts when $\mathcal{R}_i>1$.

Note that $\mu_s\leq\mu_{si}$. When $\lambda\geq 0$,

$$F(\lambda)>\lambda+\mu_{si}-\rho_i c_i \hat{R}_{hi}S_i^*=\lambda+\mu_{si}-\rho_i c_i \hat{R}_{hi}\frac{\Lambda_s}{\mu_s\mathcal{R}_i}=h(\lambda).$$

The function $h(\lambda)$ is an increasing function and $h(0)=0$, implying that $h(\lambda)\geq 0$ for $\lambda\geq 0$. Therefore, $F(\lambda)$ has no nonnegative real zeros. Suppose that $x+yi$ is a complex zero point of $F(\lambda)$ with $x\geq 0$, i.e., $F(x+yi)=0$ with $x\geq 0$. Then the real part of $F(x+yi)$ must be zero,

$$Re(F(x+yi))=x+\mu_{si}-\rho_i c_i S_i^*\int_0^\infty e^{-xa}\cos(ya)R_{hi}(a)\,da + \rho_i c_i I_i^*\left[1+\frac{\delta_i(x+\mu_s)}{(x+\mu_s)^2+y^2}\right]=0.$$

Note that

$$0=Re(F(x+yi))>x+\mu_{si}-\rho_i c_i S_i^*\int_0^\infty e^{-xa}R_{hi}(a)\,da=h(x)\geq 0,$$

a contradiction. Thus, $F(\lambda)$ has no complex zeros with nonnegative real parts. Therefore, $E_i$ is stable if $\mathcal{R}_i>1$.

Global property: The solutions of system (25) with nonnegative initial conditions remain nonnegative, and

$$\frac{d}{dt}(S+I_i)=\Lambda_s-\mu_s S-(\mu_s+\delta_i)I_i\leq\Lambda_s-\mu_s(S+I_i).$$

Therefore, the supreme limit of $S(t)+I_i(t)$ is bounded by $\Lambda_s/\mu_s$. Let

$$S^\infty=\limsup_{t\to\infty}S(t),\quad I_i^\infty=\limsup_{t\to\infty}I_i(t).$$

Using Lemma A.20 in Thieme's book (2003), we can choose a sequence $t_n\to\infty$ such that $(d/dt)I_i(t_n)\to 0$ and $I_i(t_n)\to I_i^\infty$. From the $I_i$ equation in the system (25) it follows that

$$0\leq\rho_i c_i \mathcal{R}_{hi}I_i^\infty S^\infty-\mu_{si}I_i^\infty\leq\left(\rho_i c_i \mathcal{R}_{hi}\frac{\Lambda_s}{\mu_s}-\mu_{si}\right)I_i^\infty=\mu_{si}(\mathcal{R}_i-1)I_i^\infty.$$

Therefore, $I_{si}^\infty=0$ if $\mathcal{R}_i<1$. It follows that $\lim_{t\to\infty}(S(t),I_i(t))=(\Lambda_s/\mu_s,0)$. □

## Appendix D. Stability of equilibria $Q_i$

**Claim 2.** *The disease-free equilibrium $Q_0$ is stable with respect to the limiting system (5) if both reproductive numbers $\mathcal{R}_i$ ($i=1,2$) are less than 1. It is unstable if $\mathcal{R}_i>1$ for some $i=1,2$.*

**Proof.** As in Appendix C, linearizing system (5) at $Q_0$ and looking for exponential solutions of the linearized system we can obtain the characteristic equation:

$$(\lambda+\mu_s)\left(\lambda+\mu_{s1}-\rho_1 c_1 \hat{R}_{h1}\frac{\Lambda_s}{\mu_s}\right)(\lambda+\mu_{s12})\left(\lambda+\mu_{s2}-\rho_2 c_2 \hat{R}_{h2}\frac{\Lambda_s}{\mu_s}\right)=0.$$

From the analysis of the roots of Eq. (28), it follows that all the roots of the above equation have negative real parts and hence $Q_0$ is stable if $\mathcal{R}_i<1$, $i=1,2$. Otherwise, the characteristic equation has roots with positive real parts, implying that $Q_0$ is unstable. □

**Proof of Result 1.** The stability of the equilibrium $Q_1$ is governed by the roots of the characteristic equation for the model (5) at $Q_1$, which is given by the determinant of the matrix $J$ equal to zero, where

$$J=\begin{pmatrix}J_1 & *\\ 0 & J_2+J_3+id_\lambda\end{pmatrix},\quad J_2=\begin{pmatrix}-\mu_{s2}-\rho_{12}c_1I_1^*\mathcal{R}_{h1} & 0\\ \rho_{12}c_1I_1^*\mathcal{R}_{h1} & -\mu_{s12}\end{pmatrix},$$

$$J_3=\begin{pmatrix}\rho_2 c_2 S_1^*\hat{R}_{h2} & \rho_2 c_2' S_1^*\hat{R}_{h2}\\ \rho_{21}c_2I_1^*\hat{R}_{h2} & \rho_{21}c_2'I_1^*\hat{R}_{h2}\end{pmatrix},\quad id_\lambda=\begin{pmatrix}-\lambda & 0\\ 0 & -\lambda\end{pmatrix}, \tag{30}$$

where $J_1$ is the matrix given in (27) evaluated at $E_1$, and the block $*$ is of no interests. Therefore, the roots of the characteristic equation are roots of either

$$det(J_1)=0\quad\text{or } det(J_2+J_3+id_\lambda)=0.$$

From Claim 1 in Appendix C, we know that $E_1$ is stable if $\mathcal{R}_1>1$ and hence all the roots of the equation $det(J_1)=0$ have negative real parts. Thus, the stability of $Q_1$ is determined by the roots of the equation $det(J_2+J_3+id_\lambda)=0$, which can be simplified as

$$(\lambda+\mu_{s2}+\rho_{12}c_1I_1^*\mathcal{R}_{h1})(\lambda+\mu_{s12}-\rho_{21}c_2'I_1^*\hat{R}_{h2}) -\rho_2 S_1^*\hat{R}_{h2}(c_2(\lambda+\mu_{s12})+c_2'\rho_{12}c_1I_1^*\mathcal{R}_{h1})=0. \tag{31}$$

Consider the function $g(\lambda)=\lambda+\mu_{s12}-\rho_{21}c_2'I_1^*\hat{R}_{h2}$. The function $g(\lambda)$ is an increasing function and has the properties: $g(\lambda)>0$ for $\lambda\geq 0$ if $g(0)>0$ and $g(\lambda)$ has a non-negative real zero point (denoted $\lambda_0$) if $g(0)\leq 0$. From Eq. (31) it follows that the (real or complex) roots of the equation are not zero points of the function

$g(\lambda)$. Therefore we can rewrite the equation into

$$G(\lambda)=\lambda+\mu_{s2}+\rho_{12}c_1I_1^*\mathcal{R}_{h1}-\rho_2S_1^*(c_2(\lambda+\mu_{s12})+c_2'\rho_{12}c_1I_1^*\mathcal{R}_{h1})\frac{\hat{R}_{h2}}{g(\lambda)}=0.$$

Note that whenever $\lambda\geq 0$ and $g(\lambda)\neq 0$, we have

$$\frac{d}{d\lambda}\left(\frac{(\lambda+\mu_{s12})\hat{R}_{h2}}{g(\lambda)}\right)=\frac{1}{g^2(\lambda)}\left(-\rho_{12}c_2'I_1^*(\hat{R}_{h2})^2+(\lambda+\mu_{s12})^2\frac{d}{d\lambda}\hat{R}_{h2}\right)<0$$

$$\frac{d}{d\lambda}\left(\frac{\hat{R}_{h2}}{g(\lambda)}\right)=\frac{1}{g^2(\lambda)}\left((\lambda+\mu_{s12})\frac{d}{d\lambda}\hat{R}_{h2}-\hat{R}_{h2}\right)<0.$$

Therefore, $dG(\lambda)/d\lambda>0$ for $\lambda\geq 0$ whenever $G(\lambda)$ is well-defined. Thus $G(\lambda)$ is an increasing function either on $(\lambda_0,\infty)$ when $g(0)\leq 0$ or on $[0,\infty)$ when $g(0)>0$. $G(\lambda)$ also satisfies the limit properties:

$$\lim_{\lambda\to\lambda_0^+}G(\lambda)=-\infty,\quad \lim_{\lambda\to\infty}G(\lambda)=+\infty.$$

Therefore, $G(\lambda)$ has a positive real zero point if $g(0)\leq 0$ and hence the equilibrium $Q_1$ is unstable. The condition $g(0)\leq 0$ is equivalent to

$$\frac{\rho_{21}c_2'\mathcal{R}_{h2}I_1^*}{\mu_{s12}}\geq 1,$$

which is a sufficient condition for $\mathcal{R}_{21}>1$. In the case of $g(0)>0$, the sign of $G(0)$ determines whether $G(\lambda)$ has positive real zero points. That is, $G(\lambda)$ has a positive real zero point if $G(0)<0$ while $G(\lambda)$ has no positive real zeros if $G(0)>0$. Calculations show that the condition $G(0)<0$ $(>0)$ is equivalent to $\mathcal{R}_{21}>1$ $(<1)$. Therefore, $Q_1$ is unstable if $\mathcal{R}_{21}>1$.

To obtain the stability of $Q_1$ when $\mathcal{R}_{21}<1$ (i.e., $G(0)>0$), we only need to show that all complex roots of the equation $G(\lambda)=0$ have negative real parts. Suppose that $G(x+yi)=0$ with $x\geq 0$ when $G(0)>0$. Regarding $\lambda$ as a parameter, the matrix $J_3$ given in (30) is a matrix function, $J_3(\lambda)$. Recall that the zero points of the function $G(\lambda)$ are the roots of $det(J_2+J_3(\lambda)+id_\lambda)=0$. Therefore, $x+yi$ is an eigenvalue of the matrix $J_2+J_3(x+yi)$. The matrix $J_2+J_3(0)$ has positive off-diagonal elements and hence has a principal eigenvalue $\lambda_1$. That is, the spectral bound $s(J_2+J_3(0))$ of the matrix $J_2+J_3(0)$ is $\lambda_1$. Since the characteristic equation of $J_2+J_3(0)$ is given by the equation $G(\lambda)=0$ with $\hat{R}_{h2}$ replacing by $\mathcal{R}_{h2}$, it follows from the monotonicity of $G(\lambda)$ that $s(J_2+J_3(0))=\lambda_1<0$ when $G(0)>0$. Noting that $\int_0^\infty e^{-(x+yi)a}R_{h2}(a)\,da\leq\int_0^\infty e^{-xa}R_{h2}(a)\,da<\mathcal{R}_{h2}$ and applying the monotonicity of spectral bounds for matrices with nonnegative off-diagonal elements, we have the following inequality for spectral bounds:

$$\begin{aligned}0\leq x\leq s(J_2+J_3(x+yi))&\leq s(J_2+|J_3(x+yi)|)\leq s(J_2+J_3(x))\\&\leq s(J_2+J_3(0))<0,\end{aligned}$$

a contradiction. Therefore, the complex zero points of $G(\lambda)$ must have negative real parts and hence $Q_1$ is stable if $\mathcal{R}_{21}<1$. □

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