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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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