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Transmission–virulence trade-offs in vector-borne diseases

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ABSTRACT

Though it is commonly supposed that there is a trade-off between virulence and transmission, there is little data and little insight into what it should look like. Here, we consider the specific case of vector-borne parasites (inspired by human malaria) and analyse an embedded model to understand how specific life-cycle aspects may affect this trade-off. First, we find that, for such parasites, the transmission function may have an S-shape. Second, we find that the trade-off obtained for vector-borne parasites is less sensitive to parameter variations than the trade-off obtained for directly transmitted parasites. Third, we find that other parasite traits, such as the conversion from replicative to infective stages, could have important epidemiological implications. Finally, we compare the effect of treatments targeting either the asexual or the sexual parasite life-stage.

1. Introduction

Most models for the evolution of parasite virulence assume that it is governed by a trade-off between transmission and parasite-induced mortality (Ewald, 1994). However, doubt has been cast on the universal validity of this basic assumption (Levin and Bull, 1994; Ebert and Bull, 2003). Though at some level there *should* be a relationship between parasite reproduction and negative effects experienced by the host (otherwise we would hesitate to call the parasite a parasite), these negative effects are not necessarily expressed as additional mortality. Moreover, these negative effects, whatever they are, could depend on parasite exploitation and transmission strategies in a variety of ways (morbidity, anaemia, sterilisation).

Vector-borne parasites differ in a number of ways from the simple setting assumed in most models for the evolution of virulence. The most significant of these ways is that these parasites do not transmit through direct contact but require transmission via an intermediate host (the vector). Many parasites fall into this category, including several protozoa such as *Plasmodium* parasites (the cause of malaria, see below) or *Leishmania*. Many of these parasite infections are structured populations, where replication and transmission are carried out by different functional forms. There exists some support for a trade-off relationship between virulence and transmission in some vector-borne diseases (Mackinnon and Read, 1999b; Davies et al., 2001) but, as for most diseases (Lipsitch and Moxon, 1997), the evidence is scarce.

Several theoretical studies have explored vector-borne parasite virulence evolution. An argument based on a classical trade-off assumption predicts intermediate or high virulence for vector-borne diseases. For instance, for indirectly transmitted parasites that use a mosquito to disperse, maintaining the main host in good health is less necessary (Ewald, 1983). Also, having a sexual life-stage could introduce a greater variability in virulence levels. Day (2002) uses an epidemiological model to study the importance of the contact rate (the rate at which a parasite gets a transmission opportunity). By assuming that this rate is constant for vector-borne diseases (because mosquitoes take care of the transmission), he shows that, under some conditions, Ewald's (1983) predictions are verified. Finally, Gandon (2004) developed a general framework to study multi-host parasites. He studies the case of vector-borne diseases and finds that differences in host immunisation could lead to higher levels of virulence. Other models on vector-borne parasites usually involve malaria. Several models consider its within-host dynamics (for a review, see Molineaux and Dietz (1999)) but their purpose is usually to

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fit a given set of experimental data and typically they do not link within-host and epidemiological dynamics. To our knowledge, there have been no theoretical studies on the trade-off between transmission and virulence for malaria though studying the trade-off emergence for particular host–parasite interactions might be crucial (Ebert and Bull, 2003).

In a previous study (Alizon and Van Baalen, 2005), we found that a trade-off relationship between transmission and virulence robustly emerges from within-host dynamics. We also found that although such trade-off curves tend to be convex, their precise shape depends sensitively on model parameters. This implies that the evolutionary stable level of virulence (ESV), *i.e.* the optimal virulence, can strongly depend on the characteristics of the host–parasite interaction (*e.g.* life-cycle, parameter values). It also suggests that small phenotypical or genotypical variations among hosts and parasites are sufficient to blur the trade-off relationship. This model is a variation of the so-called 'embedded model' approach, in which a model for within-host dynamics is combined with a larger-scale epidemiological model (for reviews, see Alizon and van Baalen (in press); Mideo et al. (in press)). Inspired by malaria, we therefore study an extension of our earlier model (Alizon and Van Baalen, 2005) in which parasites alternate between two host species. We also assume that parasites are able to reproduce in both hosts, which means we are focusing on biological transmission (as opposed to mechanical transmission where the vector only carries the parasite). We will often refer to malaria for illustrative purposes, but several parasite species could fit this model (for instance protozoa such as *Leishmania*).

About Plasmodium falciparum

P. falciparum is one of the four species causing human malaria, which kills around 2 million people each year. Though it is a major cause of human death (3.1% of world mortality in 2002 was due to malaria, Anker and Schaaf (2002)), in the mortality sense malaria cannot be classified as a very virulent disease as most infected adults recover from the disease or survive a relatively long time (Boyd, 1949). That is, the human host, at least the adults (children being much less immunised), does not seem to be an important component among the factors that constrain malaria evolution. The majority of deaths caused by malaria seems to be due to a naive immune system (World Health Organization, 2003). This would explain why malaria mostly kills children from 6 months to 5 years, who are building their immunity, and foreigners, because their immune systems are not familiar with malaria (Carter and Mendis, 2002).

The parasite life-cycle alternates between two host types: mosquitoes of the genus *Anopheles* and humans. An infected mosquito injects sporozoites when biting a human. This asexual form gives birth to merozoites that undergo clonal reproduction within the red blood cells (RBC) of the human host. Sometimes, infected RBCs produce sexual forms, called gametocytes (male or female). A mosquito that bites a human infected by *P. falciparum* may ingest some of these gametocytes. These ingested sexual stages may then, after going through a series of stages, settle in the salivary glands of the mosquito, which then becomes infective.

Experimental results suggest that a higher gametocyte density is linked with higher infectivity to mosquitoes (Taylor and Read, 1997; Mackinnon and Read, 1999b; Drakeley et al., 1999; Schall, 2000). Gametocyte production is thus crucial in determining the parasite's reproductive success. Surprisingly, gametocytes only constitute a few percent of the circulating parasites (Eichner et al., 2001). Thus one may ask why gametocytogenesis is so slow (Taylor and Read, 1997; Mideo and Day, 2008).

Table 1
List of the notations used

Notation	Default value	Description
φ	v	Parasite within-host growth rate
m	v	Parasite conversion rate
x_1	v	Density of asexual parasites
x_2	v	Density of sexual parasites
y	v	Lymphocyte density
σ_1	1	Killing rate of asexual parasites by the lymphocytes
σ_2	0.1	Killing rate of sexual parasites by the lymphocytes
b	0.01	Lymphocyte base-line production rate
c_1	0.1	Proliferation rate of lymphocytes activated by asexuals
c_2	0.01	Proliferation rate of lymphocytes activated by sexuals
δ	1	Lymphocyte mortality rate
R_0	v	Parasite basic reproduction ratio
α	v	Virulence, *i.e.* infected host mortality due to the infection
β	v	Transmission rate of the parasite
γ	v	Host recovery
S	v	Density of susceptible hosts
a	10	Transmission constant
M	v	Number of sexual parasites in a mosquito blood-meal
μ	0.1	Host natural death rate
u_1	0.05	Deleterious effect of a asexual (replicating) parasites
u_2	0.05	Deleterious effect of a sexual (non-replicating) parasites
w	0.01	Lymphocyte detrimental effect

Variables are indicated with a v and constants are indicated by their default values.

2. The model

2.1. Parasite within-host dynamics

We first focus on the processes taking place inside the main host. This within-host model is derived from our previous model for persistent infections (Alizon and Van Baalen, 2005). An important modification is that we distinguish two within-host stages of parasites: a stage that can replicate within the host (comparable to merozoites, the asexual stage of *Plasmodium*) and a stage that can be transmitted (comparable to the gametocytes, the sexual life-stage of *Plasmodium* which can be taken up by mosquitoes). Their densities are respectively denoted x_1 and x_2. Both life-stages are recognised and killed by the same lymphocytes (with density y) but with different successes, and while the former reproduces asexually, only the latter can be transmitted. Koella and Antia (1995) developed a similar model but for acute infections. The parasite within-host dynamics are described by the following two equations

$$\begin{aligned} \frac{\mathrm{d}x_1}{\mathrm{d}t} &= (\varphi(1-m) - \sigma_1 y)\, x_1 \\ \frac{\mathrm{d}x_2}{\mathrm{d}t} &= \varphi\, m\, x_1 - \sigma_2\, y\, x_2 \end{aligned} \tag{1}$$

where φ is the parasite intrinsic per capita growth rate, σ_1 the killing rate of asexual parasites by the immune system, σ_2 the killing rate of sexual parasites by the immune system and m the conversion rate of the parasites (*i.e.* for malaria the proportion of RBC that develop into gametocytes). This set of equations can be easily rendered dimensionless, however, in order to be able to carry out our analysis, we will measure x_1 and x_2 in terms of absolute numbers of parasites in the host. All the symbols used are summarised in Table 1.

Considering the specific case of malaria, one could expect gametocytes (x_2) to be targeted by specific components of the immune system but empirical evidence suggests that in fact they only suffer from cross-immunity with the merozoites (for an overview, see Buckling and Read (2001)). Also, one might ask why a framework for persistent infections can be applied to malaria. The reason is that empirical evidence shows that *Plasmodium* infections can persist for several years, depending on the host and on the parasite species (Mackinnon and Read, 2004b). Old