Dose-dependent infection rates of parasites produce the Allee effect in epidemiology

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In many epidemiological models of microparasitic infections it is assumed that the infection process is governed by the mass-action principle, i.e. that the infection rate per host and per parasite is a constant. Furthermore, the parasite-induced host mortality (parasite virulence) and the reproduction rate of the parasite are often assumed to be independent of the infecting parasite dose. However, there is empirical evidence against those three assumptions: the infection rate per host is often found to be a sigmoidal rather than a linear function of the parasite dose to which it is exposed; and the lifespan of infected hosts as well as the reproduction rate of the parasite are often negatively correlated with the parasite dose. Here, we incorporate dose dependences into the standard modelling framework for microparasitic infections, and draw conclusions on the resulting dynamics. Our model displays an Allee effect that is characterized by an invasion threshold for the parasite. Furthermore, in contrast to standard epidemiological models a parasite strain needs to have a basic reproductive rate that is substantially greater than 1 to establish an infection. Thus, the conditions for successful invasion of the parasite are more restrictive than in mass-action infection models. The analysis further suggests that negative correlations of the parasite dose with host lifespan and the parasite reproduction rate helps the parasite to overcome the invasion constraints of the Allee-type dynamics.

Keywords: dose effect; inoculum size; Allee effect; breakpoint; epidemiological model; microparasites

1. INTRODUCTION

Many key epidemiological processes, such as infection, host survival and fecundity, and within-host reproduction of a parasite have been found to depend on the parasite inoculum or the parasite dose to which the host is exposed. In macroparasitic infections it is usually observed that the parasite-induced effects on host fecundity, host survival and parasite reproduction rate within the host are negatively correlated with the parasite dose (Anderson & May 1982; Keymer 1982; Michael & Bundy 1989; Nie & Kennedy 1993; Ashworth *et al.* 1996). Many infection experiments suggest that the dynamics of microparasitic infections may also be subjected to strong dose-dependent effects (Dobson & Owen 1977; Diffley *et al.* 1987; Hochberg 1991; Agnew & Koella 1999; Little & Ebert 2000; McLean & Bostock 2000). Infection of *Daphnia magna* with the microparasitic bacterium *Pasteuria ramosa* and the fungus *Metschnikowiella biscuspidata*, for example, showed strong dose dependences of host mortality and fecundity, parasite reproduction within the host, and infection rate acting at every level of parasite dose (Ebert *et al.* 2000). Moreover, the potential importance of dose effects in microparasitic infections is well recognized in epidemiological studies (Aaby 1991; Glynn *et al.* 1994). Across macro- and microparasitic infections, one can observe the following general trends of these dose dependences: the infection rate is found to be an increasing function of the

parasite dose, usually sigmoidal in shape. Furthermore, parasitic virulence generally increases with the dose, whereas the reproduction rate of the parasite within the host tends to be negatively correlated with the parasite dose.

These correlations with parasite dose contain important information on the interaction between the parasite and the host, and are in conflict with assumptions typically made in epidemiological models. Commonly it is assumed that the infection rate depends on the product of the concentration of hosts and the concentration of parasites—the so-called *mass-action principle* (Hamer 1906). If the infection was appropriately described by a mass-action term one should not observe sigmoidal relationships between infection rate and parasite dose, but rather a merely saturating relationship. Furthermore, many epidemiological models assume that the virulence and within-host reproduction rate of the parasite are independent of the parasite dose—in discordance with the empirical evidence mentioned above.

In this paper, the observed dependence of infection rate, parasite virulence and reproduction on parasite dose are incorporated into the standard modelling framework for microparasitic infections (Anderson & May 1979, 1981, 1982; Levin & Pimentel 1981; May & Anderson 1983), and the resulting dynamics of the host–parasite system are studied.

In § 2, we shortly review the model of Anderson & May (1981) that serves as a reference model throughout the paper. In § 3, an infection term that is a sigmoidal function of the concentration of free parasites is incorporated. In

§ 4, a virulence term is considered that depends on the parasite concentration, and in § 5, we further assume that the within-host reproductive rate of the parasite is a decreasing function of the concentration of free parasites. It is found that a sigmoidal infection rate leads to the Allee effect, a phenomenon that is characterized by an invasion threshold for the parasite. Additionally, the parasite fitness required for invasion (as measured by the basic reproductive rate) is higher in a model with a sigmoidal infection rate than in models with a mass-action infection rate. Thus, invasion into a system with a sigmoidal infection rate requires both, a more abundant and a fitter parasite than in mass-action infection models. Moreover, we show that a negative correlation between the parasite dose and host lifespan as well as a negative correlation between parasite dose and its reproduction rate, act in favour of the parasite, facilitating its invasion.

2. STANDARD MODEL

As a reference model, we consider a version of a model that was proposed by Anderson & May (1981) to study the population dynamics of microparasitic infections. The model—henceforth referred to as the *standard model*—describes the interaction between susceptible hosts, x, infected hosts, y, and free parasites, v:

$$\dot{x} = \lambda - dx - \beta vx; \tag{2.1}$$

$$\dot{y} = \beta vx - (a + d)y; \tag{2.2}$$

$$\dot{v} = cy - uv. \tag{2.3}$$

The assumptions that underlie these equations are that susceptible hosts are born at a constant rate, λ, die at a density-dependent rate, dx, and are infected with a rate βxv. This infection term is based on the mass-action principle (Hamer 1906). Furthermore, infected hosts are assumed to die at a density-dependent rate $(a + d)y$ that is higher than the rate at which susceptible hosts die. The parameter a measures the virulence of the parasite, here defined as the contribution of the parasite to the mortality of the host. Finally, free parasites are released from infected hosts at the rate cy, and die at a rate uv. One aspect in which the model (2.1)–(2.3) and the original model by Anderson and May differs is that we assume a constant birth rate of susceptible hosts, λ, whereas Anderson and May assume a birth rate that depends on the total number of hosts, $N = x + y$. This simplification is commonly adopted (Nowak & May 1994; May *et al.* 1995) to avoid an unrealistic exponential growth of susceptible hosts in the absence of parasites. Furthermore, equation (2.3) describes the dynamics of free parasites, whereas in the original model by Anderson & May (1981) the dynamics of free parasites is not formulated explicitly.

The model has at most two equilibria: an unstable uninfected equilibrium given by $x_0 = \lambda/d$, $y_0 = 0$ and $v_0 = 0$, and a globally stable infected equilibrium given by $\hat{x} = [(a + d)u]/(\beta c)$, $\hat{y} = [\lambda/(a + d)] - du/(\beta c)$ and $\hat{v} = \{\lambda c/[(a + d)u]\} - d/\beta$. The basic reproductive rate (Dietz 1975, 1976; Anderson & May 1981, 1991; May & Anderson 1983; Bremermann & Thieme 1989; Diekmann *et al.* 1990) of the parasite is given by

$$R_0 = \frac{\lambda \beta c}{d(a + d)u}. \tag{2.4}$$

The basic reproductive rate contains important information about the population dynamics and the adaptive dynamics of this host–parasite system. First, the infected equilibrium exists only if the basic reproductive rate exceeds unity, $R_0 > 1$ (by 'existence' we mean that there is a positive equilibrium solution, $\hat{v}$). Second, the condition $R_0 > 1$ is necessary for successful parasite invasion. We would like to stress that it is a peculiarity of the present model that positivity of the equilibrium solution and invasion competence of the parasite are equivalent. In the following sections it will be shown that this does not always have to be the case. Third, it has been repeatedly shown that the evolutionary dynamics acts to maximize the basic reproductive rate (Anderson & May 1982; Bremermann & Thieme 1989; Diekmann *et al.* 1990).

In the present model, the rate at which susceptible hosts are infected, βvx, depends linearly on the concentration of free parasites. Moreover, the death rate of infected hosts, $(a + d)y$, and the rate at which parasites are released from infected hosts, cy, are assumed to be independent of the concentration of the free parasites. In § 3, these assumptions are relaxed and the resulting dynamics are compared with the dynamics of the standard model (2.1)–(2.3).

3. DOSE-DEPENDENT INFECTION

A nonlinear relationship between parasite dose and infection rate has been frequently observed in experiments (Ebert *et al.* 2000; McLean & Bostock 2000). We take the dose dependence of the infection rate into account by relaxing the mass-action assumption that is made in the standard model (2.1)–(2.3):

$$\dot{x} = \lambda - dx - x\beta(v); \tag{3.1}$$

$$\dot{y} = x\beta(v) - (a + d)y; \tag{3.2}$$

$$\dot{v} = cy - uv; \tag{3.3}$$

where the rate of infection per host, $\beta(v)$, is a sigmoidal function of the parasite concentration v:

$$\beta(v) = \frac{(v/\mathrm{ID}_{50})^\kappa}{1 + (v/\mathrm{ID}_{50})^\kappa}, \quad \kappa > 1. \tag{3.4}$$

Here, ID_{50} denotes the infectious dose at which 50% of the hosts are infected and κ measures the slope of the sigmoidal curve at ID_{50}. How far this specific infection term is justified on the basis of the observed dose dependence of the infection rate is discussed in § 5. In figure 1, $\beta(v)$ is plotted in comparison with the infection term of the standard model (2.1)–(2.3).

(a) *Equilibria*

Model (3.1)–(3.3) has at most three non-trivial equilibrium solutions. Two stable equilibria (uninfected and infected) are separated by one unstable equilibrium. The uninfected equilibrium is equivalent to that of the standard model (2.1)–(2.3). Approximations of the infected equilibria can be found in Appendix B. However, in contrast to the standard model (2.1)–(2.3), in the present model the uninfected equilibrium is locally stable. The local stability is due to the existence of the unstable equilibrium which lies 'between' the uninfected and stable, infected equilibrium, $x_0 > \check{x} > \hat{x}$, $\hat{y} > \check{y} > 0$ and $\hat{v} > \check{v} > 0$.
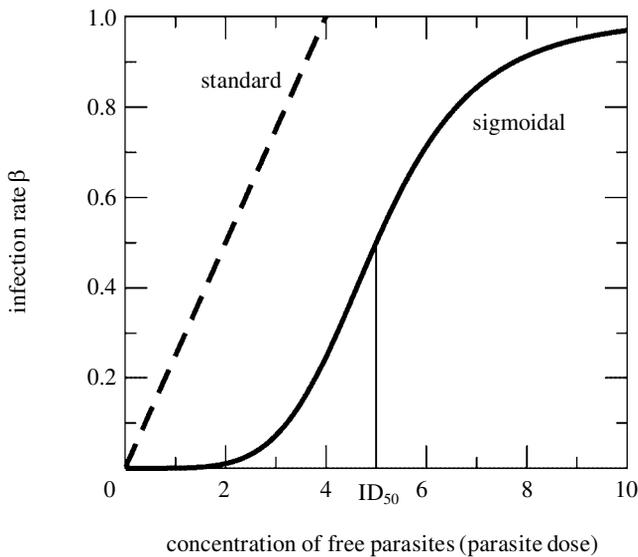
Figure 1. Infection rate as function of the parasite dose for model (3.1)–(3.3) (solid line) and the standard model (2.1)–(2.3) (dashed line). When comparing the two models, we choose our parameters so that the slopes at the ID_{50} are identical. Parameters: $ID_{50} = 5$; $\kappa = 5$.

It is interesting to note that $\tilde{v}$ and $\hat{v}$ are inversely related: $\tilde{v} = \{(dID_{50}^{\kappa})/[(1 + d)\hat{v}]\}^{1/(\kappa - 1)}$. The stable and the unstable infected equilibria exist if

$$\frac{\lambda c}{d(a + d)u ID_{50}}\left(\frac{(\kappa - 1)d}{1 + d}\right)^{1/\kappa} > 1. \qquad (3.5)$$

This criterion is analogous to the condition '$R_0 > 1$' in the standard model (2.1)–(2.3), and we refer to it as the *positivity condition of the equilibrium solution*. The derivation of the positivity condition can be found in Appendix A. Note that the positivity of the equilibrium solution does not imply that the parasite will be able to invade. Thus, unlike in the standard model (2.1)–(2.3), positivity of the equilibrium and invasion competence of the parasite are not equivalent here. This result seems to be a general pattern found in models with dose-dependent infection rates (Dushoff 1996). (The condition for successful parasite invasion will be discussed in § 3b.)

These three equilibria can be illustrated by considering a simplified version of model (3.1)–(3.3). If we assume that the dynamics of the parasite is substantially faster than that of the infected hosts, $u >> a$, the model can be reduced to

$$\dot{x} = \lambda - dx - \beta\left(\frac{cy}{u}\right)x; \qquad (3.6)$$

$$\dot{y} = \beta\left(\frac{cy}{u}\right)x - (a + d)y. \qquad (3.7)$$

The equilibrium solutions can be determined graphically by plotting the null clines (defined by $\dot{x} = 0$ and $\dot{y} = 0$) into the phase plane of the system. At the intersection points of the two null clines, $\dot{x} = 0$ and $\dot{y} = 0$ are simultaneously fulfilled. Thus, the intersections correspond to equilibrium solutions. In figure 2a, the null clines of the reduced model (3.6) and (3.7) and the basin of attraction of the uninfected equilibrium are plotted. Figure 2b shows the null clines of the reduced standard model (2.1)–(2.3).
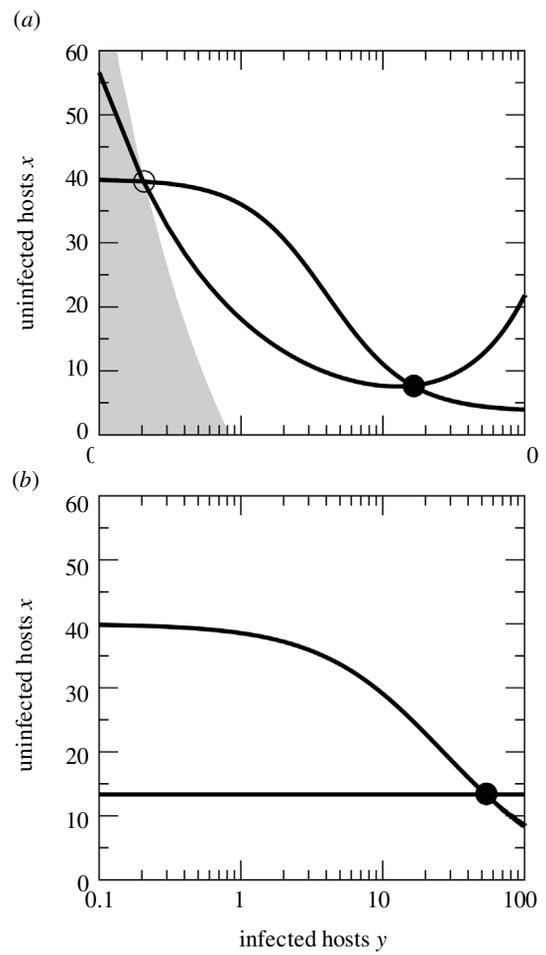

Figure 2. (a) Null clines of the reduced sigmoidal infection model (3.6) and (3.7). The white and black circles denote the unstable equilibrium (saddle point) and the stable infected equilibrium (stable focus), respectively. The shaded region marks the basin of attraction of the uninfected equilibrium. (b) Null clines of the standard model (2.1)–(2.3). Here, there is only one stable infected equilibrium. Parameters: $\lambda = 4$; $d = 0.1$; $u = 30$; $ID_{50} = 5$; $\kappa = 1.5$; $\beta = 0.015$; $c = 7.5$; and $a = 0.1$.

(b) *Allee effect*

The dynamics of model (3.1)–(3.3) are qualitatively different from the dynamics of the standard model (2.1)–(2.3). In order to invade the host population, the parasite must fulfil the condition

$$\frac{\lambda c}{d(a + d)u} \times \frac{\beta(v)}{v} > 1. \qquad (3.8)$$

Thus, in contrast to the standard model (2.1)–(2.3), invasion depends not only on the parameters, but also on the initial parasite concentration. In a simulation, we have determined the initial conditions for successful invasion of a parasite for the reduced model (3.6) and (3.7) (figure 2a). The threshold concentration that is needed by a parasite to invade the uninfected equilibrium is approximately given by $\{[d(a + d)uID_{50}^{\kappa}]/(\lambda c)\}^{1/(\kappa - 1)} = \tilde{v}$.

The threshold concentration decreases with decreasing ID_{50}, i.e. invasion is facilitated for highly infectious parasite strains. On the other hand, the threshold concentration increases for increasing parasite virulence, a. Thus, the invasion threshold is determined by the balance

between infectiousness and virulence of the parasite—a pattern which is familiar from early studies of the evolution of virulence, in which the balance between infectiousness and virulence was found to determine the invasion competence of the parasite via its effect on the basic reproductive rate (Anderson & May 1982).

The existence of an invasion threshold is typical for the so-called *Allee effect* that occurs when the abundance or frequency of a species is positively correlated with its growth rate (Stephens *et al.* 1999). For reviews on the importance of the Allee effect in ecology, and behavioural and conservation biology see Stephens & Sutherland (1999) and Courchamp *et al.* (1999). Although the relevance of the Allee effect for host–parasite systems has been noted earlier for sexually reproducing macroparasites (May 1977) its role in host–parasite interactions generally, i.e. also for asexually reproducing parasites and microparasites, has not been pointed out before.

(c) *Comparison with the standard model*

To what extent do the requirements that a successfully invading parasite has to meet differ from the respective requirements in the standard model? The requirements that the parasite population has to meet are more restrictive than those of the standard model (2.1)–(2.3) in two regards. First, in our model the outcome of the interaction between parasite and host depends on the initial concentration of the parasite, whereas in the standard scenario, any initial parasite concentration suffices to successfully establish an infection (as long as $R_0^{\text{standard}} > 1$). Second, the parasite fitness required for invasion (as measured by the basic reproductive rate) is higher than in the standard model (2.1)–(2.3) as will be shown next.

To be able to compare the results of the sigmoidal infection model (3.1)–(3.3) with those of the standard model (2.1)–(2.3), we need to relate the infection parameters of the two models. Since in the case of the sigmoidal infection model (3.1)–(3.3) the infection rate per parasite depends on the parasite concentration, we need to define a reference concentration at which the infection rates per parasite are equal in the two models. The definition of this reference concentration is somewhat arbitrary, but a natural choice is the ID_{50}. Around the ID_{50} the infection rate of the sigmoidal infection model (3.1)–(3.3) is approximately linear in the concentration of free parasites, and has a slope of *ca.* $\beta = \kappa/4ID_{50}^{\kappa}$. The sigmoidal infection model (3.1)–(3.3) can therefore be compared to a standard model (2.1)–(2.3) with infection rate, βxv (see figure 1). The specific choice of the ID_{50} as the reference parasite concentration for the comparison of the sigmoidal infection model with the standard model does not affect our results qualitatively.

The positivity condition (3.5) can now be rewritten in terms of the basic reproductive rate the parasite would have in the standard model (2.1)–(2.3), $R_0^{\text{standard}} = (\lambda\beta c)/[d(a + d)u]$, which leads to

$$R_0^{\text{standard}} > \frac{\kappa^2}{4}\left(\frac{1 + d}{(\kappa - 1)d}\right)^{(\kappa - 1)/\kappa} =: R_{\text{thres}}. \quad (3.9)$$

Unless the parameter κ that measures how sigmoid the infection rate is, is only slightly larger than 1, or the mortality of uninfected hosts is very large, the threshold basic reproductive rate, R_{thres}, is larger than 1. Thus, our analy-
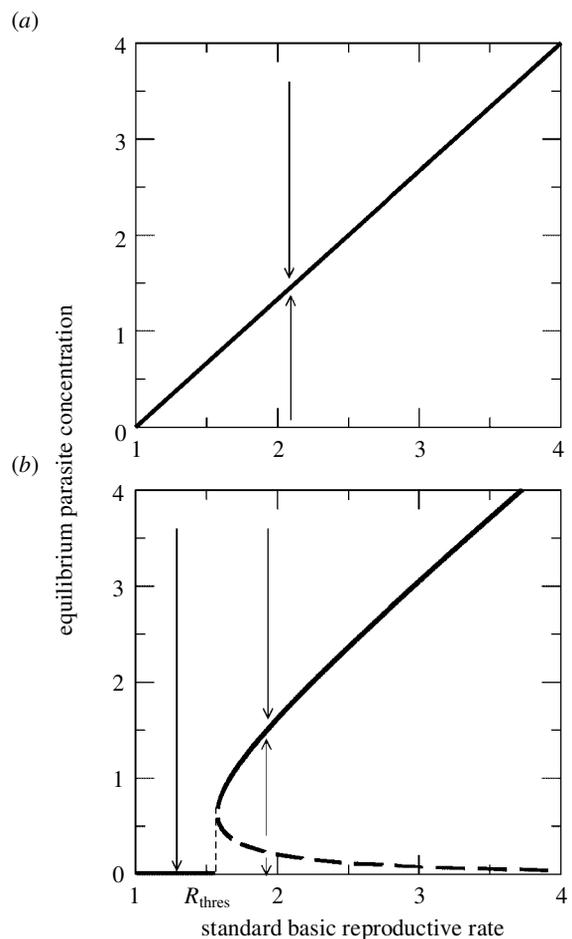

Figure 3. Equilibrium parasite concentration for different values of the basic reproductive rate, R_0^{standard}. (*a*) In the case of the standard model (2.1)–(2.3), there is one equilibrium if the basic reproductive rate exceeds unity. The parasite concentration at equilibrium increases linearly with the basic reproductive rate. (*b*) In the case of the sigmoidal infection model (3.1)–(3.3), two equilibrium solutions exist (solid and dashed lines) if the standard basic reproductive rate exceeds a higher threshold level, R_{thres}. For successful invasion, the parasite has to have a starting concentration that is higher than the unstable equilibrium parasite concentration (dashed line). R_{thres} and the unstable equilibrium represent the two additional difficulties that the parasite has to overcome to successfully invade system (3.1)–(3.3). The arrows in both plots indicate the direction of the change in parasite concentration in the ranges within which the parasite concentration is not at equilibrium. Parameters: $\lambda = 4$; $d = 0.1$; $u = 2$; $ID_{50} = 5$; $\kappa = 1.5$, i.e. $\beta = \kappa/(4ID_{50}) = 0.075$; $c = 7.5$; and $a = 0.1$.

sis suggests that the standard basic reproductive rate of the parasite may have to be substantially larger than unity to allow the existence of an infected equilibrium.

In summary, a dose-dependent infection rate is associated with a twofold disadvantage of the parasite: first, the Allee effect leads to an invasion threshold for the parasite, and second, the parasite fitness required for invasion may be higher. In figure 3, this twofold disadvantage is illustrated by plotting the equilibrium parasite concentration as a function of the standard basic reproductive rate, R_0^{standard}.
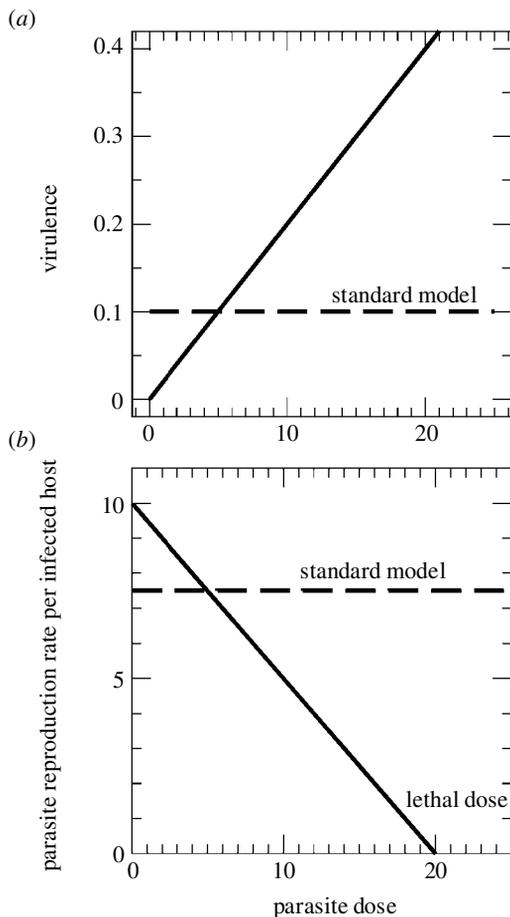
(a)

(b)

Figure 4. (*a*) Dose-dependent virulence as a function of the parasite dose. In the standard model (2.1)–(2.3), virulence is assumed to be constant (dashed line), whereas in model (4.1)–(4.3) we assume that the virulence is a linearly increasing function of the parasite dose (solid line). When comparing the two models, we assume that the virulences are identical at the parasite concentration of ID_{50}. Parameters: $ID_{50} = 5$; $a = 0.1$; and $\alpha = 0.02$. (*b*) Dose-dependent parasite reproduction rate as a function of the parasite dose. In the standard model (2.1)–(2.3), the reproduction rate is assumed independent of the parasite dose (dashed line), whereas in model (4.1)–(4.3) we assume that the reproduction rate of the parasite is a linearly decreasing function of the parasite dose (solid line). When comparing the two models, we assume that the reproduction rates are identical at the parasite concentration of ID_{50}. Parameters: $ID_{50} = 5$; $\bar{c} = 7.5$; $c_{max} = 10$; and $LD = 20$.

4. OTHER DOSE DEPENDENCES

(a) *Dose-dependent virulence*

The degree of parasite virulence is often observed to be positively related with the parasite dose (Ebert *et al.* 2000), whereas the standard model (2.1)–(2.3) and our sigmoidal infection model assumes constant parasite virulence, a. In this section, we investigate the consequences of such a positive correlation by substituting αvy for av into the equation of infected hosts of the sigmoidal infection model:

$$\dot{x} = \lambda - dx - x\beta(v); \tag{4.1}$$

$$\dot{y} = x\beta(v) - (\alpha v + d)y; \tag{4.2}$$

$$\dot{v} = cy - uv. \tag{4.3}$$

Figure 4*a* illustrates the dose-dependent virulence term

in comparison with the constant virulence that is assumed in the standard model (2.1)–(2.3).

This system has three non-trivial equilibria (uninfected, unstable and infected; see Appendix B), and displays the Allee effect as the model in § 3. The invasion threshold in the present model is given by $\hat{v} \approx [(d^2 u ID_{50}^\kappa)/(\lambda c)]^{1/(\kappa - 1)}$. Note that this invasion threshold is lower than in the model in the preceding section, i.e. invasion is facilitated when compared with the sigmoidal infection model (3.1)–(3.3).

To investigate whether the fitness of the parasite required for invasion (as measured by the parasite's basic reproductive rate) is higher than in the case of the mass-action infection model, the positivity condition for the present system (4.1)–(4.3) must be found. To that end, we define $R_0^{standard} = \lambda\beta c/[d(a + d)u]$ where $\beta = \kappa/(4ID_{50})$ as before (see figure 1), and $\bar{a} = \alpha ID_{50}$ (see figure 4*a*), i.e. we assume that the infection rate and virulence of model (4.1)–(4.3) and the standard model (2.1)–(2.3) are equivalent when the parasite concentration equals ID_{50}. The resulting positivity condition cannot be expressed analytically, but the threshold basic reproductive rate, R_{thres}, is always smaller than that derived in § 3. If the dose dependence is very pronounced R_{thres} may be even less than unity.

Thus, dose-dependent virulence facilitates parasite invasion in two respects: first, the invasion threshold of the Allee dynamics is lowered; and second, the parasite fitness required for invasion is lower than in model (3.1)–(3.3) with a sigmoidal infection rate only. Intuitively, the facilitation of parasite invasion is due to the fact that invading parasite populations have typically low frequencies, which, in the present model, result in low initial virulence. Figure 5 illustrates the twofold disadvantage of the parasite (compared with the standard model) but simultaneously shows that the invasion threshold and R_{thres} are smaller than in the sigmoidal infection model without dose-dependent virulence (3.1)–(3.3).

(b) *Dose-dependent parasite reproduction*

In this subsection, the dynamical consequences of a parasite reproduction rate that is negatively related with the parasite dose are discussed. To this end, $c_{max}(1 - v/LD)y$ is substituted for cy into the equation of infected hosts of the sigmoidal infection model (3.1)–(3.3), where LD denotes the lethal dose that immediately kills a host:

$$\dot{x} = \lambda - dx - x\beta(v); \tag{4.4}$$

$$\dot{y} = x\beta(v) - (a + d)y; \tag{4.5}$$

$$\dot{v} = c_{max}\left(1 - \frac{v}{LD}\right)y - uv. \tag{4.6}$$

Figure 4*b* shows the dose-dependent parasite reproduction rate in comparison with the dose-independent rate that is assumed in the standard model (2.1)–(2.3).

As before, this system has three non-trivial equilibria (see Appendix B), and displays the Allee effect. Here, the invasion threshold is smaller than that of the sigmoidal infection model (3.1)–(3.3): $v \approx [\{d(a + d)u ID_{50}^\kappa [1 - (ID_{50}/LD)]\}/(\lambda c)]^{1/(\kappa - 1)}$. Therefore, the parasite concentration required for invasion is lower than in the model (3.1)–(3.3), that considers a sigmoidal infection term only.
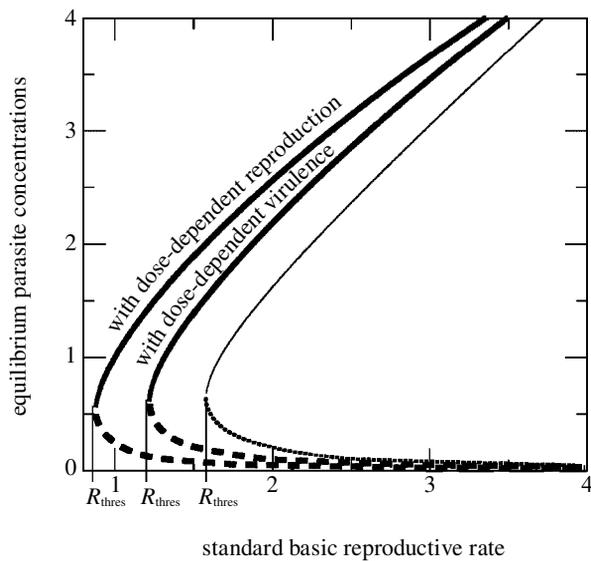
Figure 5. Equilibrium parasite concentration for different values of the basic reproductive rate, R_0^{standard}, for the sigmoidal infection model (3.1)–(3.3) (thin line), the model with dose-dependent virulence (4.1)–(4.3) and the model with dose-dependent reproduction (4.4)–(4.6). Dose-dependent virulence and reproduction terms reduce R_{thres} and the invasion thresholds (dashed lines) and thus facilitate invasion of the parasite. The amount of reduction in R_{thres} depends on the strength of the respective dose dependence. Parameters: $\lambda = 4$; $d = 0.1$; $u = 2$; $\text{ID}_{50} = 5$; $\kappa = 1.5$, i.e. $\beta = \kappa/(4\text{ID}_{50}) = 0.075$; $c_{\text{max}} = 10$; $\text{LD} = 20$, i.e. $\bar{c} = 7.5$; and $\alpha = 0.02$, i.e. $\bar{a} = 0.1$.

Regarding the parasite fitness required for invasion, the introduction of a dose-dependent reproduction rate leads to less severe restrictions on the basic reproductive rate of the parasite when compared with the sigmoidal infection model (3.1)–(3.3). Here, the standard basic reproductive rate is defined as $R_0^{\text{standard}} = (\lambda\beta\bar{c})/[d(a + d)u]$ where $\beta = \kappa/(4\text{ID}_{50})$ as before (see figure 1), and $\bar{c} = c_{\text{max}}[1 - (\text{ID}_{50})/\text{LD}]$ (see figure 4*b*), i.e. it is assumed that the infection rate and the parasite's reproduction rate of model (4.4)–(4.6) and the standard model (2.1)–(2.3) are equivalent when the parasite concentration equals ID_{50}. As in § 4a, the positivity condition and the minimum standard basic reproductive rate, R_{thres}, cannot be given analytically. However, R_{thres} is always smaller than in the sigmoidal infection model (3.1)–(3.3).

Thus, also a dose-dependent reproduction rate acts to facilitate parasite invasion, first, by reducing the invasion threshold, and second, by reducing the minimum basic reproductive rate, R_{thres}. The reduction of the invasion threshold and R_{thres} are illustrated in figure 5.

5. CONCLUSIONS

One of the oldest concepts in mathematical epidemiology is the so-called *mass-action principle* according to which the infection rate depends linearly on the densities of susceptible and infected hosts (Hamer 1906). This concept stems from chemical kinetics where the rate at which a reaction between two reagents takes place, is approxi-

mately linear in the concentrations of these reagents (Michaelis & Menten 1913). To assume mass-action kinetics is justified if one presupposes that the interacting populations are well mixed and replicate continuously.

In this paper, we substitute for the mass-action-type infection term by an infection rate that is a sigmoidal function of the parasite concentration. This substitution is motivated by various infection experiments (Agnew & Koella 1999; Little & Ebert 2000; Ebert *et al.* 2000; McLean & Bostock 2000) in which the infection probability was observed to increase sigmoidally with increasing parasite dose. The dynamics of the resulting model was compared to a mass-action infection model of Anderson & May (1981). As a consequence of a sigmoidal infection rate, the dynamics of the host–parasite system changes qualitatively, displaying the Allee effect—a phenomenon that is characterized by an invasion threshold for the parasite. Thus, parasite invasion is more difficult in models with sigmoidal infection rates than in mass-action infection models. The parasite population can establish an infection only if its founder population size exceeds this invasion threshold. Additionally, the parasite fitness required for invasion (as measured by its basic reproductive rate in the standard model (2.1)–(2.3)) is higher in a model with a sigmoidal infection rate than in a mass-action-type infection model. For successful invasion the parasite is required to have a basic reproductive rate that is substantially higher than unity, unlike in the standard model (2.1)–(2.3) in which the basic reproductive rate had to exceed unity by only a small amount.

We additionally considered terms for parasite virulence and reproduction rate which depend on the parasite concentration (Dobson & Owen 1977; Diffley *et al.* 1987; Aaby 1991; Hochberg 1991; Glynn *et al.* 1994; Agnew & Koella 1999; Ebert *et al.* 2000; Little & Ebert 2000; McLean & Bostock 2000), and thus are not constant, as is often assumed. Considering a positive correlation between the virulence of the parasite and its concentration, we obtained a lower invasion threshold for the parasite as with a sigmoidal infection rate only. Furthermore, the parasite fitness required for invasion is lower than in the sigmoidal infection model (3.1)–(3.3), and can be even lower than in the standard model (2.1)–(2.3). The same results hold for a parasite-reproduction term that is negatively correlated with parasite concentration. Thus, these correlations appear to be adaptive for the parasite, as they facilitate parasite invasion. However, this adaptionist explanation should be interpreted with caution since the observed relationships could be constrained by the physiology of the specific host–parasite interaction and thus may not be adaptable.

According to our analysis, the relationship between infection rate and parasite dose crucially affects the dynamics of the host–parasite system. If it is sigmoidal in shape—as assumed in the preceding sections—it produces the Allee effect. Since the sigmoidal shape concerns the change in slope of the relationship between the parasite dose and the infection rate, it represents a subtle property of a host–parasite system and thus has to be tested specifically. Existing data have to be re-assessed and new, specifically designed experiments may have to be conducted to determine whether, in a particular host–parasite sys-

tem, the infection rate per host is a sigmoidal function of the parasite dose. In systems where the infection rate turns out to be sigmoidal, one should also address the question of why the infection rate has a sigmoidal shape. A host immunity that prevents infection unless the host is challenged with high parasite concentrations represents a potential cause of the sigmoidal pattern.

Comparing the predictions of the sigmoidal infection model (3.1)–(3.3) with regard to the evolution of virulence to those of the standard model (2.1)–(2.3), it is clear that the evolutionary optimum does not differ between the two models. What does differ is the spectrum of sub-optimal parasite virulences that may be observed. In a host–parasite system that is governed by standard dynamics any parasite strain with $R_0^{\text{standard}} > 1$ will be able to invade the system, whereas in a system with a sigmoidal infection rate the restrictions on parasite invasion are more stringent, i.e. the parasite population faces stronger selection. Thus, the spectrum of observed virulences is expected to be narrower. This effect is weakened in systems that display any of the other dose dependences that are discussed here since these other dose dependences result in lower selection pressure on the parasite.

Alternatives to the mass-action-type infection term have been considered before (Wilson & Worcester 1945a,b; Severo 1969; Capasso & Serio 1978; Cunningham 1979; Liu et al. 1986, 1987). Some of the models in these studies display dynamical features similar to our sigmoidal infection model, i.e. an unstable equilibrium, and, as a consequence, an invasion threshold for the parasite (Severo 1969; Capasso & Serio 1978; Cunningham 1979; Liu et al. 1986, 1987). In these models however, unlike in our sigmoidal infection model (3.1)–(3.3), the alternative infection term is not a saturating function of the parasite concentration, and no explicit reference is made to the *Allee effect* as such. The main motivation of the these studies was to investigate the robustness of the predictions of standard epidemiological models by studying alternatives of the mass-action-type infection terms. Our motivation, in contrast, was to explore the consequences of a sigmoidal dose dependence of the infection rate as is frequently observed in host–parasite interaction.

The dose dependence in the incidence rates of infections has also been addressed before mostly in the context of macroparasitic infections (Macdonald 1965; May 1977; Aron 1983; Diekmann & Kretschmar 1991; Schweitzer & Anderson 1992; Schweitzer 1993; Dushoff 1996). These studies agree with ours with regard to the prediction of an invasion threshold for the parasite, although in these studies, except for the study by May (1977), the Allee effect is not mentioned explicitly. Since macroparasites often reproduce sexually, in some of the above-mentioned studies, the Allee effect was due to the difficulty of the sexually reproducing parasite to find a mate at low parasite abundances (Macdonald 1965; May 1977).

The main point of the current study is that the importance of the Allee effect is not confined to macroparasitic infections, nor to infections of sexually reproducing parasites. According to our analysis, a sufficient prerequisite for the Allee effect is a sigmoidal infection rate that is observed in a wide variety of host–parasite systems irrespective of their size and way of reproduction (Agnew &

Koella 1999; Ebert et al. 2000; Little & Ebert 2000; McLean & Bostock 2000).

APPENDIX A: POSITIVITY CONDITIONS

The sigmoidal infection model (3.1)–(3.3) has at most three non-trivial equilibrium solutions, two stable equilibria (uninfected and infected) separated by one unstable equilibrium. The positivity condition (3.5) under which the infected equilibria are positive and thus exist, can be derived as follows. The equilibrium conditions of the sigmoidal infection model (3.1)–(3.3) yield

$$\frac{\lambda \beta(v_{\text{eq}})}{(d + \beta(v_{\text{eq}}))v_{\text{eq}}} - \frac{(a + d)u}{c} = 0, \tag{A 1}$$

which—using the substitution $s = v_{\text{eq}}/\text{ID}_{50}$—can be rewritten as

$$h(s) = \rho. \tag{A 2}$$

Here, $h(s) = s^{\kappa - 1}/[d + (1 + d)s^{\kappa}]$ is a hump-shaped function of the normalized parasite concentration s, and $\rho = [(a + d)u\text{ID}_{50}]/(\lambda c)$. The positivity of the equilibria (3.5) is equivalent to the requirement that the maximum of the hump-shaped function h is larger than ρ. h attains its maximum at

$$s_{\max} = \left(\frac{(\kappa - 1)d}{(1 + d)}\right)^{1/\kappa}, \tag{A 3}$$

which immediately leads to equation (3.5).

This criterion is analogous to the condition '$R_0 > 1$' in the case of the standard model (2.1)–(2.3). In terms of the standard basic reproductive rate, $R_0^{\text{standard}} = \lambda \beta c/[d(a + d) u]$ (with $\beta = \kappa/(4\text{ID}_{50})$ as defined in § 3c) condition (3.5) can be written as

$$R_0^{\text{standard}} > R_{\text{thres}} := \frac{\kappa^2}{4}\left(\frac{1 + d}{(\kappa - 1) d}\right)^{(\kappa - 1)/\kappa}. \tag{A 4}$$

Thus, the positivity condition is equivalent to a minimum standard basic reproductive rate of the parasite which, in most cases, is larger than unity. (R_{thres} can be less than 1 if κ is slightly larger than 1, or the death rate of uninfected hosts, d, is very large.)

For the other sigmoidal infection models with dose-dependent virulence (equations (4.1)–(4.3)) and dose-dependent reproduction rate (equations (4.4)–(4.6)), positivity conditions cannot be derived analytically. However, having chosen ID_{50} to be the reference point at which the parameters of the models coincide, the positivity conditions of these two models are less restrictive than condition (3.5).

APPENDIX B: EQUILIBRIA

Here, (approximate) expressions are given for the three equilibrium solutions of the sigmoidal infection model (3.1)–(3.3). The uninfected equilibrium is given by

$x_0 = \lambda/d$, $y_0 = 0$ and $v_0 = 0$ as for the standard model (2.1)–(2.3).

For $R_0^{\text{standard}} \gg R_{\text{thres}}$ approximate expressions for the infected equilibria can be derived. Rearranging the terms gives the equilibrium condition (A 2) gives

$$\frac{d}{s^\kappa} = \frac{1}{\rho} - (d+1)s. \qquad (B\ 1)$$

From this expression, it is possible to calculate an approximation for the infected stable equilibrium by assuming that the left-hand side of equation (B 1) vanishes.

$$\hat{v} \approx \frac{\lambda c}{(a+d)(1+d)u}; \qquad (B\ 2)$$

$$\hat{y} = \frac{\hat{v}u}{c} \approx \frac{\lambda}{(a+d)(1+d)}; \qquad (B\ 3)$$

$$\hat{x} = \frac{\lambda}{d + \beta(\hat{v})}. \qquad (B\ 4)$$

By neglecting the second term on the right-hand side of equation (B 1) an approximation for the unstable equilibrium is obtained:

$$\check{v} \approx \left(\frac{d(a+d)u\text{ID}_{50}^\kappa}{\lambda c}\right)^{1/(\kappa-1)}; \qquad (B\ 5)$$

$$\check{y} = \frac{\check{v}u}{c}; \qquad (B\ 6)$$

$$\check{x} = \frac{\lambda}{d + \beta(\check{v})}. \qquad (B\ 7)$$

The unstable equilibrium lies 'between' the stable uninfected and infected equilibrium, $x_0 > \check{x} > \hat{x}$, $\hat{y} > \check{y} > 0$ and $\hat{v} > \check{v} > 0$. It is interesting to note that $\check{v}$ and $\hat{v}$ are inversely related: $\check{v} = \{(d\text{ID}_{50}^\kappa)/[(1+d)\hat{v}]\}^{1/(\kappa-1)}$.

Analogously, approximate expressions for the other sigmoidal infection models can be derived. For the model with dose-dependent virulence (4.1)–(4.3), we obtain the following infected equilibrium solution:

$$\hat{v} \approx \left(\frac{\lambda c\text{ID}_{50}^\kappa}{(1+d)\alpha u}\right)^{1/(\kappa-1)}; \qquad (B\ 8)$$

$$\hat{y} = \frac{\hat{v}u}{c} \approx \left(\frac{\lambda u^\kappa \text{ID}_{50}^\kappa}{(1+d)\alpha c^\kappa}\right)^{1/(\kappa-1)}; \qquad (B\ 9)$$

$$\hat{x} = \frac{\lambda}{d + \beta(\hat{v})}. \qquad (B\ 10)$$

Hereby, it is assumed that the dose-independent virulence, a, of the sigmoidal infection model (3.1)–(3.3), is related to the dose-dependent virulence, αv, of model (4.1)–(4.3) as $a = \alpha\text{ID}_{50}$, i.e. that these parameters coincide at the ID_{50}. The unstable equilibrium can be approximated by

$$\check{v} \approx \left(\frac{d^2 u\text{ID}_{50}^\kappa}{\lambda c}\right)^{1/(\kappa-1)}; \qquad (B\ 11)$$

$$\check{y} = \frac{\check{v}u}{c}; \qquad (B\ 12)$$

$$\check{x} = \frac{\lambda}{d + \beta(\check{v})}. \qquad (B\ 13)$$

Note that the unstable equilibrium concentration of the parasite, $\check{v}$, is smaller than that of the sigmoidal infection model (3.1)–(3.3): $[(d^2u\text{ID}_{50}^\kappa)/\lambda c]^{1/(\kappa-1)} < \{[d(a+d)u\text{ID}_{50}^\kappa]/(\lambda c)]\}^{1/(\kappa-1)}$, i.e. the invasion threshold for the parasite is reduced in the model with dose-dependent virulence (4.1)–(4.3).

For the model with dose-dependent reproduction rate (4.4)–(4.6), the infected equilibrium can be approximated by

$$\hat{v} \approx \frac{\lambda c\text{LD}}{\lambda c + (1+d)(a+d)u(1 - \text{ID}_{50}/\text{LD})}; \qquad (B\ 14)$$

$$\hat{y} \approx \frac{u\hat{v}}{c(1 + \hat{v}/\text{LD})}; \qquad (B\ 15)$$

$$\hat{x} = \frac{\lambda}{d + \beta(\hat{v})}. \qquad (B\ 16)$$

Hereby, we assumed that the dose-independent reproduction rate, c, of the sigmoidal infection model (3.1)–(3.3), is related to the dose-dependent reproduction rate, $c_{\max}(1 - \text{ID}_{50}/\text{LD})$, of model (4.4)–(4.6) as $c = c_{\max}(1 - \text{ID}_{50}/\text{LD})$, i.e. that these parameters coincide at the ID_{50}. The unstable equilibrium solution is approximately given by

$$\check{v} \approx \left[\frac{d(a+d)u\text{ID}_{50}^\kappa(1 - \text{ID}_{50}/\text{LD})}{\lambda c}\right]^{1/(\kappa-1)}; \qquad (B\ 17)$$

$$\check{y} \approx \frac{u\check{v}}{c(1 + \check{v}/\text{LD})}; \qquad (B\ 18)$$

$$\check{x} = \frac{\lambda}{d + \beta(\check{v})}. \qquad (B\ 19)$$

Note that again the unstable equilibrium concentration of the parasite, $\check{v}$, is smaller than that of the sigmoidal infection model (3.1)–(3.3): $\{[d(a+d)u\text{ID}_{50}^\kappa(1 - \text{ID}_{50}/\text{LD})]/(\lambda c)\}^{1/(\kappa-1)} < \{[d(a+d)u\text{ID}_{50}^\kappa]/(\lambda c)\}^{1/(\kappa-1)}$.

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