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Multiple infections, kin selection and the evolutionary epidemiology of parasite traits

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Abstract

The coinfection of a host by several parasite strains is known to affect selective pressures on parasite strategies of host exploitation. I present a general model of coinfections that ties together kin selection models of virulence evolution and epidemiological models of multiple infections. I derive an analytical expression for the invasion fitness of a rare mutant in a population with an arbitrary distribution of the multiplicity of infection (MOI) across hosts. When a single mutation affects parasite strategies in all MOI classes, I show that the evolutionarily stable level of virulence depends on a demographic average of within-host relatedness across all host classes. This generalization of previous kin selection results requires that within-host parasite densities do not vary between hosts. When host exploitation strategies are allowed to vary across classes, I show that the strategy of host exploitation in a focal MOI class depends on the relative magnitudes of parasite reproductive values in the focal class and in the next. Thus, in contrast to previous findings, lower within-host relatedness in competitive parasite interactions can potentially correspond to either higher or lower levels of virulence.

Introduction

Epidemiological models classically assume that infected hosts are infected by only one parasite strain, but there is overwhelming empirical evidence that most natural infections consist of multiple parasite strains or species (Petney & Andrews *et al.*, 1998; Balmer & Tanner, 2011; Schmid-Hempel, 2011). Because parasite strategies of host exploitation are shaped by selective pressures at the within-host and between-host levels (Mideo *et al.*, 2008), a major challenge of evolutionary epidemiology is to understand how the dynamics of within-host parasite diversity interplay with epidemiological processes to determine the outcome of parasite evolution.

This question has been addressed using two main classes of models. First, kin selection models of parasite virulence have been formulated to study how within-host relatedness between parasites (a measure of the diversity of infection) affects the evolution of virulence (Bremermann & Pickering, 1983; Frank, 1992, 1994, 1996). These models predict that lower within-host relatedness should select for higher virulence when parasites compete for host resources (Frank, 1992) and for lower virulence when parasite interactions are cooperative [Brown (2001), Brown *et al.* (2002), West & Buckling (2003), Buckling & Brockhurst (2008)]. However, these predictions rest upon the assumption that all hosts are infected by the same number of parasite strains. Furthermore, these models generally do not take into account the feedback between parasite life history and disease dynamics because they do not track the density of susceptible hosts and the distribution of parasite genotypes among infected hosts.

Some models have addressed these limitations by explicitly deriving parasite fitness from an epidemiological model of multiple infections. In the superinfection framework, within-host competition is assumed to lead to the exclusion of the less virulent strain on a fast timescale (Nowak & May, 1994; Gandon *et al.*, 2001). In the coinfection framework, one typically assumes that up to two parasite strains can coexist within the host (May & Nowak, 1995; van Baalen & Sabelis, 1995; Mosquera & Adler, 1998; Alizon & van Baalen, 2008; Alizon & Lion, 2011). Those models have confirmed that multiple infections by competing parasite strains

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generally select for higher virulence, but they have also provided additional insights on the interplay between host demography, epidemiological dynamics and parasite strategies of host exploitation. In particular, van Baalen & Sabelis (1995) have shown that epidemiological parameters have both a direct effect on optimal virulence and an indirect effect through the force of infection [the per capita rate at which individuals acquire an infection, Anderson & May (1991)].

Although kin selection and epidemiological models of mixed infections broadly lead to similar conclusions, they emphasize different aspects of the selection process. In particular, kin selection models focus on within-host relatedness, but provide a limited understanding of how the distribution of parasite strains across hosts is generated by epidemiological processes. On the other hand, epidemiological models tend to be more complex, and their conclusions do not have the appeal of the simple relationship between parasite virulence and relatedness. Thus, a cursory reading of existing theory may lead one to think either that kin selection models are too simple to reflect what happens in real infectious diseases or that the complexity of epidemiological models obfuscate the general pattern that within-host relatedness ultimately governs parasite evolution. Most importantly, kin selection and epidemiological models make different predictions on the relationship between virulence and demographic parameters. Specifically, van Baalen & Sabelis (1995), Gandon *et al.* (2001) have shown that, if the susceptibility of infected hosts to subsequent infections is high enough, increasing host background mortality need not select for higher virulence, in contrast to the result of Frank (1992)'s kin selection model.

My goal in this study is to bridge the gap between these formalisms by providing a kin selection interpretation of epidemiological models of multiple infections. I introduce a general model of coinfection that effectively extends van Baalen & Sabelis (1995)'s framework to an arbitrary number of coinfections. First, at a technical level, I derive a general expression for the invasion fitness of a rare mutant in an SIR epidemiological model of coinfections. Second, I show that tying together the kin selection and epidemiological frameworks sheds light on how selection pressures at the within- and between-host levels interplay. In particular, I show that whether multiple infections lead to higher or lower virulence is determined by the distribution of parasite reproductive values across host classes.

From within-host interactions to epidemiological parameters

Within-host interactions

Within-host parasite diversity can arise through rapid evolution within the host [which is typically the case with HIV, Shankarappa *et al.* (1999)], through simultaneous infection by different parasite strains or through independent infection events by different parasite strains (see Alizon *et al.* 2013 for a review). In this article, I focus on the evolutionary consequences of the latter cause of within-host parasite diversity. I consider that hosts can harbour a variable number of infections, which are acquired sequentially over time. I define the number of such coinfections as the 'multiplicity of infections' (MOI) of the host. (Note that this usage differs from the classical use of the term in virology, where MOI is defined as the number of viral particles per host cell, but is standard in other experimental fields) [e.g. Huijben *et al.* (2011)].

For the sake of simplicity, I assume that each infection is generated by a single parasite clone, which is characterized by a strategy of exploitation of the host resources, x. Within-host competition and regulation (e.g. through interaction with the immune system) will affect the dynamics of the densities of each clone. In the following, I will use a standard assumption of models of virulence evolution and assume that within-host dynamics reach an equilibrium on a fast timescale relative to epidemiological dynamics [but see Alizon & van Baalen (2008), Mideo *et al.* (2008)]. Hence, each infection can be characterized by its equilibrium density and the exploitation strategy of the parasite clone.

Note that, to be as general as possible, we need to allow the total parasite density to depend both on the composition of the mixed infection (i.e. the exploitation strategies of each clone) and on the number of coinfections. Indeed, even if all parasite clones have the same strategy of exploitation, the number of coinfections can still have an impact on the disease, for instance, if subsequent infections progress to different organs, if the disease proceeds through the formation of different lesions (a frequent characteristic of plant diseases) or if conspecific strains face a different immune response upon reinfection (e.g. because of immunoactivation or immunodepression).

Epidemiological parameters

Epidemiological parameters (such as transmission and virulence) are determined by within-host interactions between the parasites and the host's defence mechanisms. In general, transmission and virulence will depend on within-host parasite densities and on the distribution of host exploitation among infections.

In theoretical studies, virulence is typically assumed to depend on total parasite density, N, and/or on the average level of host exploitation, $\bar{x}$ (see Table 1 for a description of the main notations). For instance, virulence can be assumed to depend on the aggregate level of host exploitation, $N\bar{x}$ (e.g. the number of toxins, or infectious particles, produced by the mixed infection). This bears a close resemblance with the conceptual

Table 1 List of main variables and parameters.

Level	Notation	Description
Within-host	N	total parasite density
	x	parasite strategy of host exploitation
	p	frequency of focal (mutant) parasite clone
Between-host	β	total transmission of a host
	f	fraction of mutant propagules
	α	virulence
	μ	background mortality rate
	γ	recovery rate
	λ	force of infection in a monomorphic population
	σ_k	susceptibility of hosts with k infections
	σ_S	susceptibility of uninfected hosts
	δ_k	removal rate of hosts with k infections ($\delta_k = \mu + \alpha_k + \gamma_k + \sigma_k\lambda$)
Population	I_k	density of hosts with k infections
	S	density of uninfected hosts
	R	density of recovered hosts

framework used by Little *et al.* (2010), where virulence is expressed as the product of within-host parasite density and the degree of damage caused by each parasite. As Little *et al.* (2010) note, both N and $\bar{x}$ are potentially under the control of both the host and the parasites. Some models assume that virulence is solely determined by the total parasite load, N [e.g. Alizon & van Baalen (2008)], which may be relevant for pathogens that do not produce virulence factors.

For transmission, one must distinguish between total transmission (the per capita rate of production of parasite propagules, β) and the net transmission of a focal parasite clone. Here, I assume that a focal strain occupying a fraction p of the total parasite density N in a host contributes a fraction f to the total pool of propagules produced by the host. Potentially, p and f both depend on x, which allows for substantial flexibility in the model. In particular, plastic responses of the parasite can be modelled in this framework (Reece *et al.*, 2009).

Similar considerations apply for recovery, susceptibility and other epidemiological parameters. At this stage, I will leave the relationship between within-host and between-host parameters unspecified and assume that all epidemiological parameters potentially depend on N and $\bar{x}$.

Monomorphic population

If the host population is infected by parasites with the same level of host exploitation, x, it is possible to lump all hosts with k infections into a single epidemiological class I_k, with epidemiological parameters determined by the exploitation strategy x and the total within-host density N_k (which is itself a function of x). I define the transmission rate β_k as the per capita rate of production of propagules by a I_k host. Similarly, I define α_k as the virulence (e.g. disease-induced mortality) of I_k hosts, γ_k as their recovery rate and σ_k as their susceptibility to infection. In the next section, I describe the epidemiological dynamics of such a monomorphic host population.

Epidemiological dynamics

Consider a well-mixed population of hosts infected by parasites with exploitation strategy x_w. The state of the population is given by the vector $(S, I_1, \ldots, I_n, R)$, where S is the density of uninfected hosts, I_i is the density of hosts harbouring i infections, and R is the density of recovered individuals. For simplicity, I assume that recovery is total. I further assume that a host with n infections can no longer be infected, but in general it will be convenient to take $n \to \infty$ and to consider that the distribution of the MOI is generated by the susceptibilities of the different classes of hosts. The dynamics of the resident population is given by the following system of equations (Appendix A)

$$\begin{aligned}
\frac{dS}{dt} &= B(S, I_1, I_2, \ldots, I_n) - \mu S - \sigma_S \lambda S \\
\frac{dI_1}{dt} &= \sigma_S \lambda S - \delta_1 I_1 \\
\frac{dI_k}{dt} &= \sigma_{k-1} \lambda I_{k-1} - \delta_k I_k, \quad k > 1 \\
\frac{dR}{dt} &= \sum_k \gamma_k I_k - \mu R
\end{aligned} \tag{1}$$

where $\delta_k = \mu + \alpha_k + \gamma_k + \sigma_k\lambda$ are the rates at which hosts are removed from the I_k class, through background mortality (at rate μ), disease-induced mortality (virulence), recovery or further infection by another strain. Such reinfection events occur at rate $\sigma_k\lambda$, where σ_k is the susceptibility of hosts with k infections (note that $\sigma_n = 0$), and λ is the force of infection defined as

$$\lambda = \sum_{k=1}^{n} \beta_k I_k. \tag{2}$$

Furthermore, B is, very generally, a function that gives the rate at which uninfected hosts are created (note that there is no vertical transmission in this model).

The dynamics (1) can be written more compactly as a function of the density of uninfected individuals S and of the total density of infected individuals $I = \sum_{k=1}^{n} I_k$

$$\begin{aligned}
\frac{dS}{dt} &= B - \mu S - \sigma_S \bar{\beta} I S \\
\frac{dI}{dt} &= \sigma_S \bar{\beta} I S - (\mu + \bar{\alpha} + \bar{\gamma}) I \\
\frac{dR}{dt} &= \bar{\gamma} I - \mu R
\end{aligned}$$

where $\bar{\beta}$, $\bar{\alpha}$ and $\bar{\gamma}$ are the average transmission, virulence and recovery across all MOI classes (i.e. $\bar{z} = \sum_k z_k I_k / I$). This yields the following expression for the equilibrium density of uninfected hosts:

$$\hat{S} = \frac{\mu + \bar{\alpha} + \bar{\gamma}}{\sigma_S \bar{\beta}},$$

that is $\hat{S} = 1/R_0$, where R_0 is the basic reproductive number of the parasite. Throughout the study, I focus on ecological scenarios where the endemic equilibrium is stable.

Evolutionary analysis

Invasion fitness

My aim is to analyse the invasion dynamics of a rare mutant with trait x_m in the resident population at equilibrium. Because I assume the mutant is rare, I will neglect hosts coinfected by more than by one mutant strain. As the order of arrival of the mutant in the host may have an effect on within- and between-host dynamics (Read & Taylor, 2001; de Roode *et al.*, 2005a; Alizon & van Baalen, 2008; Ben-Ami *et al.*, 2008), I will consider the dynamics of the class (k,j) of hosts infected by 1 mutant strain, $k-1$ resident strains, and in which the mutant is the j^{th} infection (i.e. $1 \leq j \leq k$). Let $\beta_{k,j}$ and $\delta_{k,j}$ be the transmission and removal rate of the (k, j) class. Then, the expected number of infectious units produced by a (k,j) host is $\beta_{k,j}/\delta_{k,j}$, of which mutant propagules represent a fraction $f_{k,j}$. Hence, $f_{k,j}$ measures the intensity of within-host competition for transmission between the mutant and the resident strain. In general, this will depend on the strategies of host exploitation of each strain, on the total number of infections in the host and on the order of arrival of each strain.

For a structured host population like the one I consider here, the invasion fitness (Metz *et al.*, 1992; Geritz *et al.*, 1998) will generically take the form of the sum of the reproductive values of the mutant parasite after infection of a given host class, weighted by the density of that class (Taylor & Frank, 1996; Frank, 1998; Gandon, 2004). The invasion fitness can also be expressed in terms of the epidemiological parameters as follows (Appendix B):

$$\mathcal{R} = \frac{1}{\lambda} \sum_{k=1}^{n} I_k \sum_{j=1}^{k} f_{k,j} \beta_{k,j} \prod_{i=j}^{k} \frac{\delta_i}{\delta_{i,j}}, \tag{3}$$

where λ is the force of infection of the resident parasite. Thus, invasion fitness takes the form of a ratio between the forces of infection of the mutant vs. resident parasites. The invasion of the mutant parasite is successful if $\mathcal{R} > 1$.

For a neutral mutant, the order of arrival does not affect the mean exploitation strategy, nor the total parasite density N_k. Thus, $\delta_{i,j} = \delta_i$ and $\beta_{k,j} = \beta_k$. However, the contribution of each clone to the total pool of propagules potentially depends on the order of arrival. This is clearly seen if, for instance, each infection occupies a distinct organ with a different productivity for the parasite. Then, the number of propagules produced by a focal lineage will depend on which organ it infects.

Noting $\tilde{f}_{k,j}$ the fraction of neutral mutant infectious units produced by a (k,j) host, the condition for neutrality ($\mathcal{R} = 1$) simplifies to

$$\sum_{j=1}^{k} \tilde{f}_{k,j} = 1, \tag{4}$$

which means that the fractions of infectious units produced by each infection sum to 1, as expected when all parasites have the same exploitation strategy. Condition (4) holds true in particular if $\tilde{f}_{k,j} = 1/k$, that is, the order of arrival does not affect within-host competition between strains with the same exploitation strategy, in which case each infection reaps an equal share of the infectious units produced by the host.

Selection gradient

For small mutational steps, the direction of selection is given by the selection gradient [the derivative of the invasion fitness with respect to x_m, evaluated at neutrality; Eshel (1983), Geritz *et al.* (1998)]. Let us assume, for simplicity, that mutation can affect the transmission rates $\beta_{k,j}$, the competition between parasites within the host through the factor $f_{k,j}$ or the amount of time a parasite spends in an MOI class, through the rates $\delta_{k,j}$. I show in Appendix C that the selection gradient takes the form

$$\frac{\partial R}{\partial x_m} = \frac{1}{\lambda} \sum_{k=1}^{n} I_k \sum_{j=1}^{k} \left[\frac{\partial (f_{k,j} \beta_{k,j})}{\partial x_m} - v_{k,j} \frac{\partial \delta_{k,j}}{\partial x_m} \right], \tag{5}$$

everything being evaluated at neutrality ($x_m = x_w = x$). Equation (5) depends on the marginal effect of mutation on parasite transmission and competition and on the marginal effect on host survival. The effect on survival is weighted by the factor

$$v_{k,j} = \frac{1}{L_k} \sum_{i=k}^{n} \tilde{f}_{i,j} \frac{\beta_i}{\delta_i} L_i,$$

where L_i is the probability of surviving from class 1 to class i for a neutral mutant parasite, $L_1 = 1$, and $\tilde{f}_{i,j}$ is the fraction of the host resource reaped by a neutral mutant pathogen in a (i,j) host. Hence, $v_{k,j}$ measures the expected reproductive output of a neutral mutant parasite in a (k,j) host from that stage onward, which is Fisher (1930)'s definition of reproductive value (Appendix D).

In the limit where only single infections are possible, $v_1 = \beta_1/(\mu + \alpha_1 + \gamma)$, which is the parasite's basic reproductive number (Anderson & May, 1991). Hence, noting β_1^m and δ_1^m the transmission and removal rates of hosts infected by the mutant parasite, singular strategies

can be found from a form of the marginal value theorem

$$\frac{\partial \beta_1^m}{\partial \delta_1^m} = \frac{\beta_1}{\mu + \alpha_1 + \gamma}.$$

With multiple infections, however, equation (5) shows that the marginal selective effects need to be averaged over all classes of hosts, taking into account the multiplicity of infections k (through the sum over k) and the order of infections (through the sum over j).

Evolutionary singularities [i.e. candidate evolutionarily stable strategies (ESS)] can be found by calculating the zeros of equation (5), and their evolutionary stability can be analysed through the computation of the second-order derivative of the invasion fitness (Eshel, 1983; Geritz *et al.*, 1998), for which I give a general expression in Appendix S1 in the Supporting Information.

Transmission-virulence trade-off with within-host competition

Equation (5) can be used to analyse specific models if the link between epidemiological parameters and within-host interactions is made explicit. In Appendix E, I investigate what happens when transmission and virulence depend on both parasite density and host exploitation through the aggregate level of host exploitation $N\bar{x}$. For clarity, however, I shall focus in this section on a simpler model and assume that virulence $\alpha_{k,j}$ and total transmission $\beta_{k,j}$ depend on the average level of host exploitation $\bar{x}_{k,j} = p_{k,j}x_m + (1 - p_{k,j})x_w$, where the frequency of mutant parasites within the host, $p_{k,j}$, potentially depends on x_w and x_m. Then

$$\alpha_{k,j} = \alpha_0(\bar{x}_{k,j})^{\xi} \tag{6}$$

$$\beta_{k,j} = \beta_0\bar{x}_{k,j}, \tag{7}$$

where the parameter ξ controls the shape of the trade-off between transmission and virulence. I also assume that the share of total propagule production reaped by the mutant parasite depends on the fraction of host exploitation realized by the mutant strain as follows:

$$f_{k,j} = \frac{p_{k,j}x_m}{\bar{x}_{k,j}}. \tag{8}$$

For a neutral mutant ($x_m = x_w = x$), we have $\tilde{\alpha}_{k,j} = \alpha_0 x^{\xi} \equiv \alpha$, $\tilde{\beta}_{k,j} = \beta_0 x \equiv \beta$, and $\tilde{f}_{k,j} = \tilde{p}_{k,j}$. A direct consequence of this assumption is that virulence and total transmission do not depend on the MOI in a monomorphic population. This is obviously a strong assumption, but it will be helpful when trying to clarify the connections with previous models of multiple infections [e.g. Frank (1992, 1996)]. The analysis of Appendix E relaxes this assumption and shows that, in general, the selection gradient will have an additional component collecting the indirect selective effects through parasite densities in all host classes.

Evolutionarily stable virulence

Plugging expressions (6)–(8) into equation (5), I show in Appendix E that virulence at an ESS must satisfy the following equation

$$\alpha = \frac{\mu + \gamma}{\xi\rho - 1}. \tag{9}$$

Apart from notational variations, equation (9) is essentially identical to Frank (1992)'s equation (5), with one key difference: the relatedness parameter in Frank (1992)'s expression is replaced with a demographic average ρ, where

$$\rho = \sum_{k=1}^{n} \frac{I_k}{I} \sum_{j=1}^{k} \frac{v_{k,j}}{R_0} r_{k,j}, \tag{10}$$

is the average of the product of within-host relatedness ($r_{k,j} = \partial\bar{x}_{k,j}/\partial x_m$), times the reproductive value of the parasite, $v_{k,j}$, relative to the parasite's R_0, which is simply $\beta/(\mu+\alpha+\gamma)$ for this particular example. The product of relatedness and reproductive value has been called the life-for-life relatedness (Hamilton, 1972) and measures the overall transmission success of a parasite's gene to future generations. A higher average transmission success of the parasite's genes (as measured from the average life-for-life relatedness of the parasite ρ) will lead to lower virulence. This formalizes Frank (1992)'s verbal prediction that, when the relatedness of coinfecting parasites varies between hosts, the Evolutionarily stable (ES) virulence should depend on some averaging of relatedness among hosts. I also recover the result that, if the trade-off is not sufficiently concave (i.e. if $\rho < 1/\xi$), there is no intermediate ESS and maximal virulence is selected for. Note also that when all hosts are infected by the same number k of strains, $s_j = 1$ for all $j < k$ and $s_k = 0$, which leads $\rho = 1/k$, that is, the average life-for-life relatedness is equal to the reciprocal of the MOI.

Although equation (9) is formally similar to Frank (1992)'s result, it is important to realize that, in general, virulence will also depend on the feedback between host exploitation and parasite densities. The resulting expression for the selection gradient is given in Appendix E. In the general case, the relationship between virulence and within-host relatedness may not be as simple as predicted by equation (9).

Geometric distribution of MOI

I will now analyse in more detail a special case by making the additional assumptions that the susceptibilities of infected hosts are the same for all MOI classes ($\sigma_k = \sigma_I$ for all k) and that the order of infection does not matter. Then, the transition probabilities from MOI class k to MOI class k+1 become independent of k, that is, $s_k \equiv s = \sigma_I\lambda/(\mu + \alpha + \gamma + \sigma_I\lambda)$ for all k. As a

consequence, the MOI is geometrically distributed with parameter $1-s$, and it follows from equation (10) that $\rho = 1-s = 1/M$, where $M = 1/(1-s)$ is the average MOI in the population. Hence, equation (9) can be rewritten as

$$\alpha^* = \frac{\mu+\gamma}{\xi\frac{1}{M}-1}, \tag{11}$$

provided $M < \xi$. Furthermore, α^* is evolutionarily stable (Appendix S1).

From equation (11), it is easy to see that one expects a positive correlation between average MOI and ES virulence. However, the impact of specific life-history traits, such as background mortality μ or recovery rate γ, is less straightforward because they have an indirect effect on virulence through the average MOI M. For single infections ($M = 1$), the picture is clear, and the ES virulence, when it exists, increases linearly with both mortality and recovery. However, Gandon *et al.* (2001) have shown that, in a superinfection model, increased mortality and recovery rates can lead to lower levels of optimal virulence. In Fig. 1a, I show that similar results are obtained in a coinfection model with a geometric distribution of the MOI. For low values of the ratio σ_I/σ_S, the ES virulence increases with the background mortality rate, but the opposite pattern is observed for high values of σ_I/σ_S. For a population with constant size ($S+I = 1$), I further show in Appendix S2 that the turning point occurs when $\sigma_I = \sigma_S$. The relationship between virulence and recovery is more complex and not necessarily monotonous (Fig. 1b).

For single infections ($M = 1$), the ES virulence only depends on the trade-off parameter ξ and on the life-history traits of the host that affect parasite survival (μ and γ). In contrast, for multiple infections ($M > 1$), the strength of transmission β_0 and host fecundity b alter the ES virulence through their effect on the average MOI in the population. In Fig. 1c, I find that virulence increases with host fecundity and with the strength of transmission. This makes sense because higher transmission will shift average MOI towards higher values. Likewise, a higher fecundity rate increases the total number of infected individuals, which in turn increases the overall force of infection and leads to higher average MOI (van Baalen & Sabelis (1995); Fig. 1d).

Other models of within-host interactions can be investigated in this framework. In Online Appendices S.3 and S.4, I provide a proof-of-concept analysis for two previously analysed models: a model of pure resource competition (Frank, 1994) and a model of public goods production (Alizon & Lion, 2011). In particular, I show that, in the resource competition model, increasing background mortality always leads to lower

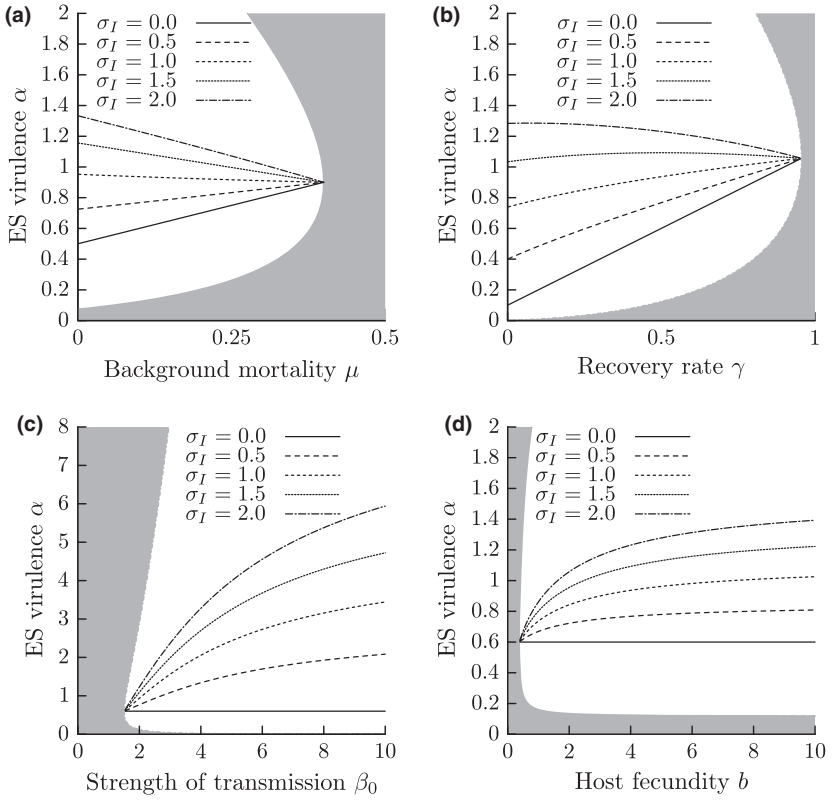

Fig. 1 ES level of virulence as a function of (a) background host mortality μ, (b) recovery rate γ, (c) strength of transmission β_0 and (d) host fecundity b for a geometrically distributed MOI. In each graph, the singular virulence α^* is shown for different values of the susceptibility of infected hosts $\sigma_I = 0$, 0.5, 1, 1.5 and 2. Host demography is chosen to be $B(S, I_1,) = bS(1-S-I)$ (i.e. infected hosts do not reproduce). When they are fixed, parameters are $\mu = 0.1$, $\gamma = 0.5$, $\beta_0 = 2$ and $b = 4$. Other parameters are $\alpha_0 = 0.9$, $\xi = 2$ and $\sigma_S = 1$. The gray areas represent the combination of parameter values for which the parasite population goes extinct.

ES virulence, which is markedly different from the results of Fig.1a.

Class-specific strategies of host exploitation

Until now, I have looked at selective pressures on mutations with a pleiotropic effect on all MOI classes. I now consider that parasites may have different strategies in the different classes of hosts and focus on the strategy $x^{k,j}$ of a parasite that constitutes the j^{th} infection of a host with MOI k. From the selection gradient (5), an ES strategy of exploitation (if there is one) must satisfy the following equation

$$\frac{\partial(f_{k,j}\beta_{k,j})/\partial x_m^{k,j}}{\partial \delta_{k,j}/\partial x_m^{k,j}} = v_{k,j}. \tag{12}$$

Equation (12) generalizes equations (15) and (17) in van Baalen & Sabelis (1995) and indicates that the evolution of host exploitation has a resting point where the marginal change in transmission relative to the change in survival scales as the reproductive value of the parasite.

For a parasite, the likelihood of future infections may affect the optimal strategy of exploitation. If there is a direct link between the strategy of host exploitation and parasite virulence, we can write $\alpha_{k,j} = p_{k,j}\alpha_m + (1 - p_{k,j})\alpha_w$. Let us assume that the net transmission of the focal parasite strain is a saturating function of its virulence ($f_{k,j}\beta_{k,j} \equiv \hat{\beta}_{k,j}(\alpha_m)$) and that transmission and virulence are the only evolving traits. With these assumptions, equation (12) can be rewritten as follows

$$\frac{\partial \hat{\beta}_{k,j}}{\partial \alpha_m} = r_{k,j} v_{k,j}. \tag{13}$$

Assuming, for simplicity, that there is a unique evolutionary attractor, equation (13) lends itself to a simple graphical description of the ESS. Indeed, the slope of the tangent at the ESS is simply the life-for-life relatedness of the parasite. I further show in Appendix F that the y-intercept has the following expression

$$\phi = (1 - r_{k,j}^*)\hat{\beta}_{k,j}^* + r_{k,j}^* \sigma_k \lambda^* (v_{k,j}^* - v_{k+1,j}^*), \tag{20}$$

where the stars indicate that all variables depend on the ESS α^*. It is easy to see that, for a saturating transmission-virulence trade-off, higher values of ϕ correspond to higher values of optimal virulence (Fig. 3b; Appendix F).

The expression of ϕ shows that the magnitude of virulence is determined by a balance between within-host and between-host selection, which is quantified by the amount of within-host relatedness. The first term of ϕ represents the net output of within-host selection, $\hat{\beta}_{k,j}^*$, times the fraction of selection that occurs within hosts, $1 - r_{k,j}^*$ (Frank, 2012). The second term gives the difference between current and future reproductive values $v_{k,j}^* - v_{k+1,j}^*$, weighted by the force of infection, $\sigma_k \lambda^*$, and by the fraction of selection that occurs at the between-host level, $r_{k,j}^*$.

Equation (14) clearly shows that selection will mainly operate at the within-host level if within-host relatedness is low or if the probability of infection is low, either because the host's susceptibility σ_k is low or because the overall force of infection λ is weak. In that case, ϕ reduces to the within-host component $(1 - r_{k,j}^*)\hat{\beta}_{k,j}^*$ (Fig. 2a), and we recover the canonical result that an increase in within-host relatedness will lead to lower values of virulence (Bremermann & Pickering, 1983; Nowak & May, 1994; Frank, 1996).

When within-host relatedness and the chance of further infection are high, however, the between-host component becomes important. In contrast to the within-host component, equation (14) indicates that it can have either a positive or a negative effect on ES virulence, depending on the relative magnitude of the reproductive values in the focal class ($v_{k,j}^*$) and in the next ($v_{k+1,j}^*$). In particular, if the focal infection occupies a large share of the host ($r_{k,j}^* \to 1$), or if the force of infection is large, an increase in virulence (compared to the $\sigma_k = 0$ case) will be selected for if

$$v_{k+1,j}^* < v_{k,j}^*, \tag{15}$$

or equivalently, in terms of the class basic reproductive number, if

$$v_{k,j}^* < \frac{\hat{\beta}_{k,j}^*}{\mu + \alpha^* + \gamma_k}. \tag{16}$$

Parasites should thus exploit their hosts less prudently if there is a high risk that they move to an MOI class in which their reproductive value would be lower.

As an illustration, I plot in Fig. 3 the ES virulence in singly and doubly infected hosts in a simple example where hosts can harbour at most 3 infections. When the virulence in triply infected hosts varies, the optimal level of virulence in singly infected hosts can be either higher or lower than predicted in a single-infection model. The two models only coincide when the reproductive values in singly and doubly infected hosts are equal. For doubly infected hosts, the same pattern approximately holds, because the within-host component is negligible in this example.

In general, equation (14) shows that what ultimately matters is the (potentially intricate) interplay between the within-host and between-host levels. This clearly depends on the biological details of the interaction between the parasite and its host. For instance, within-host relatedness not only affects the balance between the within-host and between-host components of ϕ, it has also a potential effect both on the net transmission of the parasite (the within-host effect) and on the

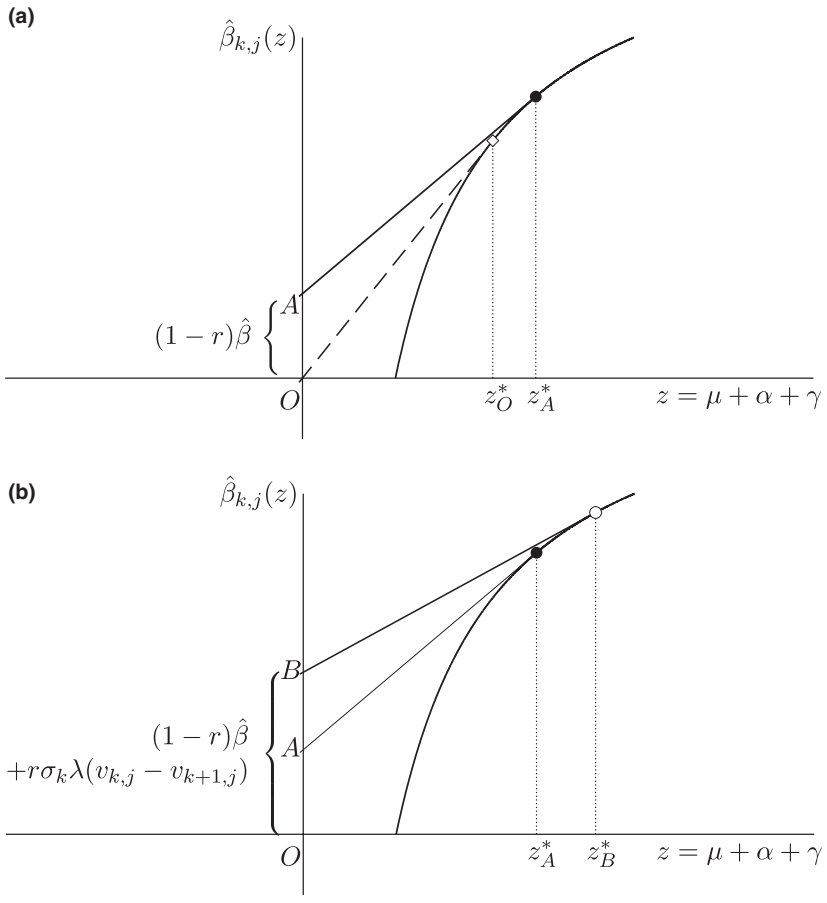

Fig. 2 Graphical interpretation of the ES strategy of exploitation of hosts with MOI k, for an hypothetical trade-off relationship between transmission and virulence. (a) If hosts in MOI class k are immune to subsequent infections ($\sigma_k = 0$), the ESS is the point at which the tangent to the transmission-virulence trade-off curve passes through the origin (dashed line). Lower within-host relatedness leads to higher virulence (solid line). — (b) If subsequent infections are possible ($\sigma_k > 0$), an ESS is a point at which the tangent has y-intercept $\phi = (1 - r^*_{k,j})\hat{\beta}^*_{k,j} + r^*_{k,j}\sigma_k\lambda^*(v^*_{k,j} - v^*_{k+1,j})$. Higher values of ϕ correspond to higher levels of virulence (compare A and B).

difference in reproductive values (the epidemiological effect). Further insights into the evolutionary dynamics of class-specific exploitation strategies would require an explicit model of within-host dynamics.

Discussion

This article presents a general theoretical framework to study the effect of multiple infections on the evolution of parasite strategies of host exploitation. This approach clarifies the connection between kin selection and epidemiological models of multiple infections and allows for a variety of within-host interactions. Specifically, I investigate the evolutionarily stable level of host exploitation (1) when a single mutation affects parasite strategies in all host classes and (2) when host exploitation is allowed to vary across classes.

Kin selection and epidemiology

The reproductive value of a parasite infecting a host with MOI k plays a key role in the outcome of the model. This is a general insight of models of multi-host parasites. Gandon (2004) showed that selection can be affected by three factors: the direct and indirect effects of selection in each host type, the individual reproductive value of parasites in the different hosts and the distribution of the parasites across the different host classes. As Gandon (2004) emphasized, hosts with a different MOI can be seen as different types of hosts, and therefore, this general insight applies. More fundamentally, inclusive fitness theory predicts that, in class-structured populations, the fitness effects on each class are weighted by reproductive value (Taylor & Frank, 1996).

Although derived from a more traditional invasion analysis, the expression of parasite fitness I obtain allows for a similar kin selection interpretation in terms of the within-host relatedness and reproductive value of the parasite in each class of hosts. This provides some tools to better understand the results of earlier theory and generalizes previous kin selection models that were based on the assumption that all hosts harbour the same number of infections and that there are no epidemiological feedbacks (Frank, 1992, 1996). In contrast, I explicitly take into account the feedback between epidemiological dynamics and the distribution of multiplicity of infections (MOI) across hosts.

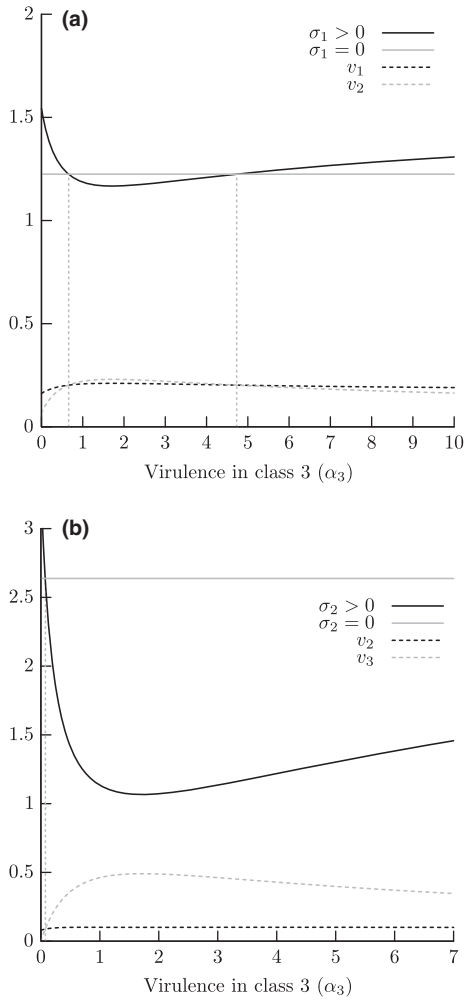

Fig. 3 ES virulence in singly (a) and doubly (b) infected hosts when hosts can harbour up to 3 infections. In both panels, the ES virulence is plotted as a function of the virulence in triply infected hosts, α_3. The ES virulence (black line) is compared with the optimal virulence when subsequent infections are impossible ($\sigma_k = 0$, gray line). The reproductive values in the focal class and the next are also given. For this figure, I assume that infected hosts cannot reproduce nor recover, and that the order of infection does not matter. Parameters are (a) $\alpha_2 = 1$; (b) $\alpha_1 = 1$. Other parameters are $B(S, I_1, I_2, I_3) = bS, b = 2, \mu = 1, \gamma_i = 0$, $\sigma_S = 1, \sigma_i = 1, r_i = 1/i, \beta_1(\alpha_1) = f(\alpha_1), \beta_2(\alpha_2) = f(\alpha_2), f(x) = x/(x+1.5)$, $\beta_3(\alpha_3) = 4\ln(1+\alpha_3)$. Note that, with these assumptions, the force of infection is constant, $\lambda = (b-\mu)/\sigma_S$.

First, when parasites are not able to vary their strategy of host exploitation across host classes, I show that the relationship between virulence and life-history traits is driven by a weighted average relatedness, the weights being the reproductive values of parasites in the different classes of hosts. This result provides a simple generalization of Frank (1992)'s expression for ES virulence as a function of life-history traits and within-host relatedness. The ES virulence in my model is obtained simply by replacing the constant relatedness in Frank (1992)'s expression by a demographic average of within-host relatedness across all MOI classes. Nevertheless, it is important to note that this simple result hinges upon the assumption that within-host parasite densities are not affected by the parasite's exploitation strategy. For many infectious diseases, parasite densities are a good proxy for the intensity of host exploitation, and this simplifying assumption is unlikely to hold. As shown in Appendix E, additional demographic feedbacks would then need to be taken into account.

Second, when parasites can adapt their strategy of host exploitation to the host class they infect, I show that, for a given trade-off between virulence and transmission, the evolutionarily stable virulence depends on a balance between within-host and between-host selection. Higher values of within-host relatedness shifts selection towards the between-host level. Interestingly, a higher amount of between-host selection can correspond to either higher or lower levels of ES virulence, depending on the distribution of reproductive values between the focal host class and the next. Thus, if the probability that the host acquires another infection is not negligible, a conflict between within-host and between-host selection can arise, with higher amount of within-host relatedness corresponding to lower virulence at the within-host level, and higher virulence at the between-host level. This conflict occurs when the parasite has a higher reproductive value in the focal class that in the next.

The consequence is that parasites should exploit less prudently the hosts in which they have a higher reproductive value. Although this may look counter-intuitive at first sight, this makes sense because increasing the mortality of hosts in the focal class leads to both a higher transmission and a lower rate of transition to the next MOI class. Hence, such a strategy allows parasites to produce more propagules, while preventing resources from being wasted in hosts with a lower reproductive value. This is what van Baalen & Sabelis (1995) depicted as the need for the parasite to 'anticipate' later infections: even if a parasite is alone in its host, the feedback effect of double infections can cause selection to favour increased levels of virulence. In this paper, this indirect effect of multiple infections is shown to operate for any multiplicity of infections. However, the feedback between the distribution of MOI and the optimal exploitation of hosts with MOI k is potentially more complex when hosts with MOI k+1 are not immune to infection. In van Baalen & Sabelis (1995)'s model, only double infections are possible so that the reproductive value of parasite in doubly infected hosts is merely $\beta_2/(\mu + \alpha_2 + \gamma)$, the class basic reproductive number. Hence, it is only affected by the exploitation strategy of co-infected hosts and parasites in singly infected hosts face a simple optimization

problem. By contrast, if $\sigma_k > 0$, the reproductive value v_{k+1} depends in general on the force of infection, and therefore on the strategies of host exploitation in all classes. Hence, some patterns of host exploitation across MOI classes can potentially cause hosts with MOI k+1 to be more valuable to the parasites than hosts with MOI k, in which case selection will favour a more prudent exploitation of the latter hosts than when $\sigma_k = 0$.

The key role played by reproductive value in this story suggests some analogies with age-structured population models. The general expression for the selection gradient I derive shows that, within a given MOI class, the effect of the trait on transmission is given weight unity and the effect on host survival is weighted by the reproductive value v_k of parasites in the focal host class. In a recent paper, Day *et al.* (2011) similarly showed in an age-structured model that the effect on host mortality, but not that on transmission, is weighted by the reproductive value of an infection at a given age. My model is stage-structured rather than age-structured, but the same logic applies. As Day *et al.* (2011) note, this stems from the fact that changes in transmission only affect the reproductive output of the focal class, whereas mortality affects propagule production in future classes as well. This result is also reminiscent of the expressions of Hamilton (1966)'s forces of selection on fecundity and survival. However, despite this superficial analogy, the implications are very different. In particular, Hamilton (1966)'s forces of selection decline with age, whereas the forces of selection on transmission and survival in my model do not necessarily decline with increasing MOI. For instance, for a geometric distribution of MOI, it can be shown that the force of selection on transmission is stronger for an MOI close to the mean MOI in the population and decreases as one moves away from the mean MOI (S. Lion, unpublished).

Empirical implications

The prediction that within-host competition between different parasite strains should lead to more severe host exploitation has found equivocal experimental support. Some studies have found that multiple infections lead to increased virulence (Herre, 1995; Davies *et al.*, 2002; de Roode *et al.*, 2005b), whereas others have shown that less virulent strains were favoured (Taylor *et al.*, 1998; Turner & Chao, 1999; Harrison *et al.*, 2006) or that the outcome depends on the mode of transmission of the parasite (Vizoso & Ebert, 2005) or on the order of the arrival of the strains (Read & Taylor, 2001; de Roode *et al.*, 2005a; Ben-Ami *et al.*, 2008). Existing theory suggests that such conflicting observations can be explained by the type of within-host interaction (in particular, whether parasites compete for resources or cooperate), by epidemiological feedbacks (if the experimental set-up induces or mimics changes in host life-history traits, Ebert & Mangin (1997), Gandon *et al.* (2001)), and by specific characteristics in the host and parasite life cycles.

The general framework I present here sheds light on three experimental questions. First, it confirms that multiple infections can affect the relationship between host or parasite life-history traits and host exploitation. Hence, experimental tests of the effect of multiple infections must take care not to unintentionally alter other traits (such as host mortality or recovery; Ebert & Mangin (1997), Gandon *et al.* (2001)).

Second, many experimental studies of multiple infections focus on how within-host interactions determine overall virulence in coinfected hosts, but there are few experimental demonstrations of the effect of coinfections on the evolution of virulence *per se* (see Alizon *et al.* (2013) for a review). Among those, most compare the dynamics of virulence in mixed vs. single infections. This does not give a full picture of what would happen in nature, because mixed and single infections are considered in isolation. In contrast, equation (14) suggests that the allocation of host exploitation across MOI classes will in general be determined by the distribution of parasite reproductive values across MOI classes and by the pattern of cross-infection between host classes. Hence, experiments are needed that preserve the interplay between within-host and between-host selection.

In general, manipulating the frequency of mixed infections in competition experiments is likely to be difficult. Microbial host–parasite interactions (e.g. bacteriaphage) offer the best perspectives because genetical engineering allows in principle to create mutants with different susceptibilities to superinfection or with different productions of infectious particles. In principle, this provides a way to test the predictions of my model by manipulating the distribution of MOI in the population and the reproductive values of each MOI class, although one must be wary of potential trade-offs with other life-history traits. Spore-producing parasites are also good candidates for such experimental evolution studies, because they allow transmission success to be relatively easily assessed.

Third, my model stresses that the evolution of parasite traits is governed by different rules whether parasite strategies are plastic or not. Along with the well-recognized prediction that the type of parasite interactions may affect the evolutionary outcome, this calls for caution when interpreting data without a sufficient understanding of the biology of the interaction.

Epidemiological consequences of different forms of within-host interactions

The general selection gradient I present can be used to investigate a variety of models of within-host interactions.

In particular, I show that different assumptions about within-host competition lead to different predictions for the effect on virulence of life-history traits such as recovery and host mortality. Under the classical assumption of a trade-off between virulence and transmission, an increased host mortality is predicted to lead to higher levels of virulence if the MOI is below a threshold. On the other hand, virulence is predicted to decrease when host mortality increases if transmission is assumed to depend on the share of resources reaped by a parasite strain (Appendix S3). In this case, the distribution of MOI across hosts has only a quantitative effect on the relationship between virulence and host mortality. Note that these results were obtained under the assumption that the distribution of MOI is geometric: if the rates of transition between MOI classes are not the same across all MOI classes, different patterns could be observed.

General models of multiple infections have many degrees of freedom. Because epidemiological traits can depend on the composition of the mixed infection, they can be used to investigate the evolutionary ecology of plastic parasite strategies (Reece *et al.*, 2009; Mideo & Reece, 2012). In the last section, I consider that parasites can adjust their strategies to the MOI of the host and is therefore a first step in that direction. Choisy & de Roode (2010) also consider plastic traits in a different epidemiological setting. A broader analysis would consider how parasites should allocate their exploitation strategies to the different MOI classes by modelling the joint evolution of parasite strategies in each class. This can be achieved for instance using the canonical equation of adaptive dynamics for vector traits (Dieckmann & Law, 1996). Ultimately, it would be interesting to use this framework to model plastic strategies of experimental systems such as malaria, for which the multiplicity of infections is of clinical importance and can be manipulated in the laboratory.

Furthermore, a great variety of mechanistic links between within-host interactions and epidemiological traits can be envisioned. In this study, I have often made the assumption that epidemiological parameters can depend on the within-host parasite densities of each infection ($n_{k,j}$), on the exploitation strategy of the parasite (x) or on the aggregate level of host exploitation ($n_{k,j}x$, for example the total amount of toxins produced by the infection). Other relationships could be used, and other complexities could be introduced. For instance, a more precise model for the within-host structure of the parasite population could be needed to understand the dynamics of some infectious diseases. Evidence for meta-population structure at the organism and even tissue level in HIV (Frost *et al.*, 2001) points to the need to incorporate more biological realism in the way coinfections are modelled. As is often the case, however, greater biological realism may come at the expense of general insight.

Perspectives

The model analysed here makes some assumptions on the recovery and infection processes. First, I assume that all infections are cleared at the same time upon recovery. However, partial recovery is observed in many infections, for instance, due to a less efficient action of the immune system or to competitive exclusion of one parasite strain by the others. Such processes could be taken into account by assuming that hosts can clear only one strain at a time. Then, γ_k would measure the transition rate from MOI k to MOI $k-1$. Second, I do not take into account the possibility of alternative transmission strategies, such as vertical transmission. As vertical transmission has been predicted to select for lower virulence (Frank, 1996; Lipsitch *et al.*, 1996; van Baalen, 2000), the interplay between vertical transmission and within-host competition is likely to affect the evolution of host exploitation. For instance, Vizoso & Ebert (2005) showed experimentally that mixed infections of daphnia by microsporidia can increase spore production when transmission is horizontal, but not when it is vertical. Finally, different predictions could also be obtained when other parasite life cycles are considered, such as those of semelparous parasites (e.g. lytic phages), or vector-borne diseases.

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Appendix A: Epidemiological equilibrium

From the epidemiological dynamics, we have at endemic equilibrium

$$I_1 = \frac{\sigma s \lambda}{\delta_1} S \tag{A1}$$

$$I_i = \frac{\sigma_{i-1}\lambda}{\delta_i} I_{i-1} \tag{A2}$$

$$I_i = \prod_{j=2}^{i} \frac{\sigma_{j-1}\lambda}{\delta_j} I_1. \tag{A3}$$

With the notations $\sigma_0 = \sigma_S$, $I_0 = S$ and $\prod_{i=j}^{j-1} = 1$, this implies that, for $k \geq i \geq 1$

$$\frac{I_k}{I_i} = \prod_{j=i+1}^{k} \frac{\sigma_{j-1}\lambda}{\delta_j} = \prod_{j=i}^{k-1} \frac{\sigma_j \lambda}{\delta_{j+1}} = \frac{\delta_i}{\delta_k} \prod_{j=i}^{k-1} \frac{\sigma_j \lambda}{\delta_j}. \tag{A4}$$

Note that $s_j = \sigma_j \lambda / \delta_j$ is the probability that a host survives from MOI class j to MOI class $j + 1$. Hence, $L_k = \prod_{j=1}^{k-1} s_j$ is the probability that the host survives from MOI class 1 to MOI class k. Using this notation, we can rewrite equation (A.4) as

$$\frac{\delta_k I_k}{\delta_i I_i} = \frac{L_k}{L_i}. \tag{A5}$$

Furthermore, we have

$$\sum_i \frac{dI_i}{dt} = \lambda \sigma_S S - \sum_i (\mu + \alpha_i + \gamma_i) I_i = 0.$$

This allows us to express the density of uninfected hosts at equilibrium in terms of the average epidemiological parameters

$$S = \frac{\mu + \bar{\alpha} + \bar{\gamma}}{\sigma_S \bar{\beta}},$$

where $\bar{z} = \sum_{i=1}^{n} z_i I_i / I$ for the trait z.

Simpler expressions can be obtained in the limit where n is large and the parameters do not depend on the MOI, that is, $\beta_k = \beta$, $\delta_k = \delta$ and $\sigma_k = \sigma_I$. Then, noting $s = \sigma_I \lambda / \delta$ the survival probability from one MOI class to the next, we have

$$I_k = I_1 s^{k-1},$$

so that the total density of infected hosts is $I = I_1 \sum_{k=1}^{\infty} s^{k-1} = I_1/(1-s)$. This yields for the fraction of infected hosts with MOI k

$$\frac{I_k}{I} = (1-s)s^{k-1},$$

that is, the MOI follows a geometric distribution with parameter $1-s$. Hence, the average MOI in the population is

$$M = \frac{1}{1-s}.$$

Appendix B: Invasion fitness

A host in class (k,j) can stay in this class, die or move to the class $(k+1,j)$. The probability that the latter event occurs can be calculated from the rates of infection, recovery and death as

$$s_{k,j} = \frac{\sigma_k \lambda}{\delta_{k,j}} = \frac{\sigma_k \lambda}{\mu + \alpha_{k,j} + \gamma_{k,j} + \sigma_k \lambda}. \tag{B1}$$

In other words, $s_{k,j}$ is the probability that a host 'survives' from the class (k,j) to the class $(k+1,j)$

Now consider the fate of a focal mutant individual pathogen. Such a pathogen can infect a host in MOI class k with probability $\sigma_k I_k$ (with $0 \leq k \leq n$ and the convention $I_0 = S$). The host then immediately enters MOI class $k+1$. As long as it stays in this class, it will contribute β_{k+1}/δ_{k+1} infectious units to the force of infection, of which a fraction $f_{k+1,k+1}$ will be of the mutant type. The host then enters the MOI class $k+2$ with probability $s_{k+1,k+1}$. We can now repeat the argument to find that, for an initial infection in MOI class k, the total contribution is

$$\sigma_k I_k \sum_{j=k+1}^{n} f_{j,k+1} \frac{\beta_{j,k+1}}{\delta_{j,k+1}} \prod_{i=k+1}^{j-1} s_{i,k+1}. \tag{B2}$$

with the convention $\prod_{i=k+1}^{k} s_{i,j} = 1$. Expression (B.2) is the product of the number of uninfected hosts in class k ($\sigma_k I_k$) times the expected reproductive output of a mutant parasite after infecting such a host, which is exactly Fisher (1930)'s definition of reproductive value. Hence, the invasion fitness can be written as the sum of the numbers of secondary infections for each class of hosts, that is,

$$\mathcal{R} = \sum_{k=0}^{n} \sigma_k I_k v^m_{k+1,k+1},$$

where $v^m_{k+1,k+1}$ is the reproductive value of the mutant parasite in a $(k+1,k+1)$ host (Appendix D).

Using $s_{i,k+1} = \sigma_i \lambda / \delta_{i,k+1}$ in equation (B.2), we can use equation (A.4) twice and rewrite $\mathcal{R}$ as

$$\begin{aligned}\mathcal{R} &= \sum_{k=0}^{n}\sigma_k I_k \sum_{j=k+1}^{n} f_{j,k+1}\frac{\beta_{j,k+1}}{\delta_{j,k+1}}\left(\prod_{i=k+1}^{j-1}\frac{\delta_i}{\delta_{i,k+1}}\right)\frac{\delta_j I_j}{\delta_{k+1}I_{k+1}}\\ &= \sum_{k=0}^{n}\frac{\sigma_k I_k}{\delta_{k+1}I_{k+1}}\sum_{j=k+1}^{n} f_{j,k+1}\beta_{j,k+1}I_j\left(\prod_{i=k+1}^{j}\frac{\delta_i}{\delta_{i,k+1}}\right)\\ &= \frac{1}{\lambda}\sum_{k=0}^{n}\sum_{j=k+1}^{n} f_{j,k+1}\beta_{j,k+1}I_j\left(\prod_{i=k+1}^{j}\frac{\delta_i}{\delta_{i,k+1}}\right)\\ &= \frac{1}{\lambda}\sum_{j=1}^{n} I_j\sum_{k=1}^{j} f_{j,k}\beta_{j,k}\left(\prod_{i=k}^{j}\frac{\delta_i}{\delta_{i,k}}\right),\end{aligned}$$

which is equation (3) in the main text with the j and k subscripts exchanged.

Appendix C: Selection gradient

Differentiating equation (3) with respect to x_m and evaluating the selection gradient at neutrality ($x_m = x_w$), we obtain

$$\frac{\partial\mathcal{R}}{\partial x_m} = \mathcal{S}_T + \mathcal{S}_D$$

where

$$\mathcal{S}_T = \frac{1}{\lambda}\sum_{j=1}^{n} I_j\sum_{k=1}^{j}\frac{\partial(f_{j,k}\beta_{j,k})}{\partial x_m} \tag{C1}$$

collects the marginal effects on within-host competition and transmission, and

$$S_D = \frac{1}{\lambda}\sum_{j=1}^{n} I_j\sum_{k=1}^{j}\tilde{f}_{j,k}\tilde{\beta}_{j,k}\frac{\partial}{\partial x_m}\left(\prod_{i=k}^{j}\frac{\delta_i}{\delta_{i,k}}\right)$$

is the marginal effect on host survival. For a neutral mutant parasite, the order of arrival only affects within-host competition (the $f_{k,j}$'s), hence $\tilde{\beta}_{j,k} = \beta_j$ and $\tilde{\delta}_{k,j} = \delta_k$. Then the marginal effect on host survival can be rewritten as follows

$$\begin{aligned}\mathcal{S}_D &= -\frac{1}{\lambda}\sum_{j=1}^{n} I_j\sum_{k=1}^{j}\tilde{f}_{j,k}\beta_j\frac{\prod_{i=k}^{j}\delta_i}{\left(\prod_{i=k}^{j}\delta_i\right)^2}\frac{\partial}{\partial x_m}\left(\prod_{i=k}^{j}\delta_{i,k}\right)\\ &= -\frac{1}{\lambda}\sum_{j=1}^{n} I_j\sum_{k=1}^{j}\tilde{f}_{j,k}\beta_j\frac{1}{\prod_{i=k}^{j}\delta_i}\sum_{i=k}^{j}\left(\frac{\partial\delta_{i,k}}{\partial x_m}\prod_{\ell=k,\ell\neq i}^{j}\delta_\ell\right)\\ &= -\frac{1}{\lambda}\sum_{j=1}^{n} I_j\sum_{k=1}^{j}\tilde{f}_{j,k}\beta_j\sum_{i=k}^{j}\left(\frac{1}{\delta_i}\frac{\partial\delta_{i,k}}{\partial x_m}\right)\\ &= -\frac{1}{\lambda}\sum_{j=1}^{n}\sum_{i=1}^{j}\sum_{k=1}^{i}\tilde{f}_{j,k}\beta_j I_j\left(\frac{1}{\delta_i}\frac{\partial\delta_{i,k}}{\partial x_m}\right) \qquad \text{(C2)}\\ &= -\frac{1}{\lambda}\sum_{i=1}^{n}\sum_{k=1}^{i}\sum_{j=i}^{n}\tilde{f}_{j,k}\beta_j I_j\left(\frac{1}{\delta_i}\frac{\partial\delta_{i,k}}{\partial x_m}\right).\end{aligned}$$

Collecting equations (C.1) and (C.2), we obtain finally after a circular permutation of indices i, j and k

$$\frac{\partial\mathcal{R}}{\partial x_m} = \frac{1}{\lambda}\sum_{k=1}^{n}\sum_{j=1}^{k}\left[I_k\frac{\partial(f_{k,j}\beta_{k,j})}{\partial x_m} - \frac{1}{\delta_k}\frac{\partial\delta_{k,j}}{\partial x_m}\sum_{i=k}^{n}\tilde{f}_i\beta_i I_i\right]. \tag{C3}$$

This can be rewritten as a function of reproductive value using equation (D.1), which gives equation (5) in the main text.

Appendix D: Reproductive value

Invasion fitness can also be written as $\mathcal{R} = \sum_{k=0}^{n}\sigma_k I_k v^m_{k+1,k+1}$, where

$$v^m_{k,k} = \sum_{i=k}^{n} f_{i,k}\frac{\beta_{i,k}}{\delta_{i,k}}\prod_{\ell=k}^{i-1} s_{\ell,k}$$

and $s_{\ell,k}$ is the survival probability defined in equation (B.1). The quantity $v^m_{k,k}$ is the reproductive value of a mutant parasite in a host in class (k,k) (i.e. a host with k clones of which the mutant is the last infection). More generally, the reproductive value of a mutant parasite in a (k,j) host ($j \leq k$) is

$$v^m_{k,j} = \sum_{i=k}^{n} f_{i,j}\frac{\beta_{i,j}}{\delta_{i,j}}\prod_{\ell=k}^{i-1} s_{\ell,j}.$$

For a neutral mutant parasite, we assume that the order of arrival only affects the share of propagules reaped by the mutant, but not the overall epidemiological parameters. Hence, the reproductive value at neutrality is

$$v_{k,j} = \sum_{i=k}^{n}\tilde{f}_{i,j}\frac{\beta_i}{\delta_i}\prod_{\ell=k}^{i-1} s_\ell$$

Defining $L_i \equiv \prod_{\ell=1}^{i-1} s_\ell$ the probability to survive from MOI class 1 to MOI class k, we see that $v_{k,j}$ takes a form analogous to Fisher (1930)'s expression for reproductive value in age-structured population

$$v_{k,j} = \frac{1}{L_k}\sum_{i=k}^{n}\tilde{f}_{i,k}\frac{\beta_i}{\delta_i}L_i.$$

We can simplify things further using equation (A.5), which yields the following expression for the individual reproductive value of a neutral mutant parasite infecting a host in class k

$$v_{k,j} = \frac{1}{\delta_k I_k}\sum_{i=k}^{n}\tilde{f}_{i,j}\beta_i I_i. \tag{D1}$$

Note that reproductive value can be partitioned into current and future reproduction as follows

$$v_{k,j} = \tilde{f}_{k,j}\frac{\beta_k}{\delta_k} + \frac{1}{\delta_k I_k}\sum_{i=k+1}\tilde{f}_{i,j}\beta_i I_i = \tilde{f}_{k,j}\frac{\beta_k}{\delta_k} + s_k v_{k+1,j}. \tag{D2}$$

Appendix E: Selection gradient for the model of section 4

In order to link within-host interactions to epidemiological parameters, a possible choice is to assume that virulence $\alpha_{k,j}$ and total transmission $\beta_{k,j}$ depend on the aggregate level of host exploitation $N_{k,j}\bar{x}_{k,j}$, where $N_{k,j}$ is the total density of parasites within a (k,j) host, and $\bar{x}_{k,j} = p_{k,j}x_m + (1-p_{k,j})x_w$, the mean level of host exploitation. Note that the frequency of mutant parasites within the host, $p_{k,j}$, potentially depends on x_w and x_m. Then

$$\alpha_{k,j} = \alpha_0\left[N_{k,j}\bar{x}_{k,j}\right]^{\xi} \tag{E1}$$

$$\beta_{k,j} = \beta_0\left[N_{k,j}\bar{x}_{k,j}\right], \tag{E2}$$

where the parameter ξ controls the shape of the trade-off between transmission and virulence.

What share of the total production of propagules is reaped by the mutant parasites is determined by $f_{k,j}$. Let us assume that it depends on the fraction of host exploitation realized by the mutant strain

$$f_{k,j} = \frac{p_{k,j}N_{k,j}x_m}{N_{k,j}\bar{x}_{k,j}} = p_{k,j}\frac{x_m}{\bar{x}_{k,j}}. \tag{E3}$$

For a neutral mutant ($x_m = x_w = x$), we have $\tilde{\alpha}_{k,j} = \alpha_0(N_k x)^{\xi} = \alpha_k$, $\tilde{\beta}_{k,j} = \beta_0 N_k x = \beta_k$, and $\tilde{f}_{k,j} = \tilde{p}_{k,j}$.

We can rewrite equation (5) as

$$\mathcal{S} = \frac{1}{\lambda}\sum_{k=1}^{n} I_k \sum_{j=1}^{k}\left[\beta_0\frac{\partial(n_{k,j}x_m)}{\partial x_m} - v_{k,j}\xi\alpha_0(\tilde{N}_k x)^{\xi-1}\frac{\partial(N_{k,j}\bar{x}_{k,j})}{\partial x_m}\right].$$

With some rearrangements, the selection gradient can be partitioned into two components, $\mathcal{S} = \mathcal{S}_x + \mathcal{S}_N$, where

$$\mathcal{S}_x = \frac{1}{x} - \xi\frac{1}{x\lambda}\sum_{k=1}^{n} I_k \sum_{j=1}^{k} v_{k,j}\frac{\partial\bar{x}_{k,j}}{\partial x_m}\alpha_k$$

is obtained by taking the derivative of the x terms. The partial derivative of mean trait with respect to the mutant's trait is simply within-host relatedness (Frank, 1996)

$$r_{k,j} \equiv \frac{\partial\bar{x}_{k,j}}{\partial x_m} = \tilde{p}_{k,j}.$$

Using the fact that $\lambda = \bar{\beta}I$, we find

$$\mathcal{S}_x = \frac{1}{x}\left(1 - \frac{\langle\alpha\rangle}{\mu+\bar{\alpha}+\bar{\gamma}}\rho\right), \tag{E4}$$

where ρ is the average life-for-life relatedness defined in equation (10) in the main text, and $\langle\alpha\rangle$ is a weighted average measure of virulence, where the weights are the life-for-life relatedness coefficients for each class, relative to the parasite's basic reproductive number, $R_0 = \bar{\beta}/(\mu+\bar{\alpha}+\bar{\gamma})$:

$$\langle\alpha\rangle = \frac{\sum_{k=1}^{n}\alpha_k\left(\sum_{j=1}^{k}\frac{v_{k,j}}{R_0}r_{k,j}\right)\frac{I_k}{I}}{\sum_{k=1}^{n}\left(\sum_{j=1}^{k}\frac{v_{k,j}}{R_0}r_{k,j}\right)\frac{I_k}{I}}.$$

Note that the denominator of the previous expression is ρ, the average life-for-life relatedness.

A similar calculation yields the following expression for $\mathcal{S}_N$.

$$\mathcal{S}_N = \frac{1}{x}\frac{1}{\lambda}\sum_{k=1}^{n} I_k \sum_{j=1}^{k}\left(\beta_k\frac{\partial ln(n_{k,j})}{\partial x_m} - \xi\alpha_k v_{k,j}\frac{\partial ln(N_{k,j})}{\partial x_m}\right). \tag{E5}$$

This partitions the selective pressures into two main components: the direct selective effect of host exploitation $\mathcal{S}_x$ and the indirect selective effect via parasite densities $\mathcal{S}_N$. All these effects are averaged over all MOI classes and all infections. Such a partition is reminiscent of inclusive fitness analyses of demographic models (Rousset & Ronce, 2004), where the selection gradient is shown to depend on a demographic average of the marginal effects of the trait for a given demographic state (here $\mathcal{S}_x$) and on additional selective pressures stemming from changes in the demographic state of the population (here, the term $\mathcal{S}_N$). Although the biological question I consider is different, the same logic is at play. Note that, as expected from the details of the within-host interaction, demography affects virulence through the effect of host exploitation on total parasite density $N_{k,j}$, but transmission is only impacted through the within-host density of the focal parasite, $n_{k,j} = p_{k,j}N_{k,j}$ (equation (E.5)).

If parasite densities depend neither on host exploitation nor on host type (i.e. $N_{k,j} \equiv N \equiv$ cte), then all the results given in the main text follow and we obtain a simple expression for ES virulence which is formally similar to previous results (Frank, 1992, 1996).

Appendix F: Class-specific strategies of host exploitation

Assuming strategies of parasites can differ in each host class, we are interested in an optimal strategy of exploitation of a host with MOI k, given a background of fixed strategies for parasites in hosts with a different MOI. Noting $z = \mu + \alpha_{k,j} + \gamma_{k,j}$, all epidemiological parameters can be expressed as functions of z as follows: $f_{k,j}\beta_{k,j} = \hat{\beta}(z)$, $v_{k,j} = v(z)$, $\sigma_k\lambda = h(z)$ and $\delta_{k,j} = \delta(z) = z + h(z)$. From equation (12) in the main text, the following relationship holds at an ESS

$$\hat{\beta}'(z) = r(z)v(z) \tag{F1}$$

where $r(z) = r_{k,j}$. Noting $u(z) = v_{k+1}$, we have from equation (D.2) $v(z) = \hat{\beta}(z)/\delta(z) + h(z)/\delta(z)u(z)$. Hence, the ESS condition can be rewritten as

$$z\hat{\beta}'(z) - r(z)\hat{\beta}(z) = r(z)h(z)(u(z) - v(z)). \tag{F2}$$

We can find a useful graphical interpretation if we note that the equation of the tangent to the ESS $(z, \hat{\beta}(z))$ in the $\mu + \alpha_k + \gamma_k, f_k\beta_k$ plane is

$$y = \hat{\beta}'(z)x + \hat{\beta}(z) - z\hat{\beta}'(z),$$

which, using equation (F.2), can be rewritten as

$$y = r(z)v(z)x + (1 - r(z))\hat{\beta}(z) + r(z)h(z)(v(z) - u(z)),$$

which shows that the y-intercept of the tangent is

$$\phi = (1 - r^*_{k,j})\hat{\beta}^*_{k,j} + r^*_{k,j}\sigma_k\lambda^*(v^*_{k,j} - v^*_{k+1,j}).$$

For biologically meaningful trade-off functions, $\hat{\beta}(z)$ can be assumed to be defined on $\mathbb{R}_+$, positive, increasing, twice differentiable and concave (saturating trade-off). Let $g(z) = z\hat{\beta}'(z) - \hat{\beta}(z)$. Then, $g'(z) = z\hat{\beta}''(z) < 0$ because we assume a saturating trade-off. Hence, $g(z)$ is a monotonously decreasing function. Noting that equation (F.2) can be written as

$$g(z) = -(1 - r(z))\hat{\beta}(z) - r(z)h(z)(v(z) - u(z)) \equiv -\phi(z),$$

this means that ϕ is an increasing function of the ESS z. Hence, higher values of ϕ lead to higher values of virulence, as can be seen graphically in Fig. 2.

If $r((z)$ is close to 1, we can make some further progress. Indeed, the ESS condition takes the following simple form

$$g(z) = h(z)(u(z) - v(z)). \tag{F3}$$

Furthermore, g has a unique zero z_0 which is the ESS when $\sigma_k = 0$. Because $g(z)$ is a decreasing function, $z > z_0$ iff $u(z) < v(z)$, which can be written with the notations of the main text as

$$v_{k+1} < v_k,$$

or equivalently iff $v(z) < \hat{\beta}(z)/z$, which gives the following condition

$$v_k < \frac{\hat{\beta}_k}{\mu + \alpha_k + \gamma_k}.$$

The first inequality holds in particular if future reproduction (in hosts with MOI greater than k) contributes little to the reproductive value of parasites in hosts with MOI k.

For $n = 2$ and $k = 1$, $r_{1,1} = 1$ and the latter condition can be rewritten as

$$\frac{\hat{\beta}_2}{\mu + \alpha_2 + \gamma_2} < \frac{\hat{\beta}_1}{\mu + \alpha_1 + \gamma_1},$$

which holds in particular when $\beta_2/(\mu + \alpha_2 + \gamma_2)$ is low as discussed by van Baalen & Sabelis (1995).

Supporting information

Additional Supporting Information may be found in the online version of this article:

Appendix S1 Second-order derivative of invasion fitness.

Appendix S2 Complementary results for Transmission-virulence trade-off with within-host competition.

Appendix S3 A model of pure resource competition (Frank, 1994).

Appendix S4 A model of Public Goods production (Alizon & Lion, 2011).

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