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EVOLUTION OF MULTIHOST PARASITES

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Abstract.—Multihost parasites can infect different types of hosts or even different host species. Epidemiological models have shown the importance of the diversity of potential hosts for understanding the dynamics of infectious disease (e.g., the importance of reservoirs), but the consequences of this diversity for virulence and transmission evolution remain largely overlooked. Here, I present a general theoretical framework for the study of life-history evolution of multihost parasites. This analysis highlights the importance of epidemiology (the relative quality and quantity of different types of infected hosts) and between-trait constraints (both within and between different hosts) to parasite evolution. I illustrate these effects in different transmission scenarios under the simplifying assumption that parasites can infect only two types of hosts. These simple but contrasted evolutionary scenarios yield new insights into virulence evolution and the evolution of transmission routes among different hosts. Because many of the pathogens that have large public-health and agricultural impacts have complex life cycles, an understanding of their evolutionary dynamics could hold substantial benefits for management.

Key words.—Epidemiology, evolution, parasite, transmission, virulence.

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Multihost parasites can infect and exploit different types of host. These types refer to different variants (i.e., genotypes or phenotypes) within the same host species or to different host species (Taylor et al. 2001; Woolhouse et al. 2001; Haydon et al. 2002; Holt et al. 2003). In particular, most emerging human, domestic animal, and wildlife diseases are caused by parasites infecting multiple host species (Taylor et al. 2001). Several epidemiological studies have shown how the multiplicity of potential hosts can affect the dynamics of infectious disease (Anderson and May 1991; Dushoff 1996; Hess 1996; Woolhouse et al. 1997, 2001, 2002; Diekmann and Heesterbeek 2000; Haydon et al. 2002; Roberts and Heesterbeek 2003; Holt et al. 2003). This theoretical knowledge may help to design intervention measures. In particular, identifying and managing reservoirs of multihost parasites plays a crucial role in effective disease control (Haydon et al. 2002).

Despite the proliferation of epidemiological studies, the evolutionary consequences of multihost life cycles remain largely overlooked as classical models of virulence evolution focus on simpler, single-host systems (Frank 1996; Woolhouse et al. 2001). Because the machinery required for infection, exploitation, and transmission is likely to vary from one host to another, the selective pressures acting on parasites in different hosts may also vary. How should a parasite respond to this heterogeneity of their environment (i.e., host diversity)? First, the parasite may alter its exploitation strategies of the different habitats by, for example, evolving more intense exploitation (virulence evolution) of better-quality hosts. Second, the parasite may evolve habitat choice strategies (transmission evolution) to infect better-quality hosts. The evolution and the coevolution between virulence and transmission may yield very different parasite life cycles. For example, evolution in multihost environments may yield one (or several) specialist strategies able to exploit only a single host type, and/or a generalist parasite strategy able to exploit all these different hosts. Which factors govern the ultimate evolutionary and coevolutionary outcomes?

Here, I present a general theoretical framework for the study of parasite life-history evolution in a multihost context. This framework is derived from simple epidemiological models and can be used to derive evolutionary stable virulence and transmission strategies. This analysis demonstrates the importance of epidemiology (the relative quality and quantity of different types of infected hosts) and of the constraints among the different evolving traits (both within and between different hosts). I illustrate the potential use of this model through different examples under various ecological and evolutionary assumptions. I begin with an analysis of the evolution of parasite exploitation strategies and virulence under different transmission patterns. Next, I focus on the special case of the evolution of indirect (e.g., vector-borne) transmission and its coevolution with parasite virulence. These

different evolutionary scenarios illustrate the diversity of host-parasite life cycles. They show how epidemiology may act on life-history evolution and, reciprocally, how life histories may feed back on the epidemiological dynamics of the interaction. These complexities emerging from multihost models yield new and testable predictions on the evolution of parasites. In particular, these models yield new insights for the understanding of virulence evolution. The implications for public-health policies and virulence management are discussed.

Life Cycles and Epidemiological Dynamics

The parasite may infect n different types of host. Each host type may have different intrinsic mortality, δ_i, and, when infected, they may have different recovery rates, γ_i. The parasite life-history traits may also vary among different hosts. The transmission rate from one individual host to the next, β_{ji}, may depend on both the type of origin, j, and on the recipient type, i. The virulence of the parasite, α_i (the induced host mortality rate) may also vary across the different hosts. This yields the following system of n differential equations (where the dot refers to differentiation with respect to time):

$$\dot{y}_i = x_i \sum_j \beta_{ji} y_j - (\delta_i + \alpha_i + \gamma_i) y_i, \qquad (1)$$

where y_i and x_i refer to the density of infected and uninfected hosts of type i, respectively. In matrix form this yields $\dot{\mathbf{y}} = \mathbf{m}\cdot\mathbf{y}$, with $\mathbf{y} = (y_1, y_2, \ldots, y_n)$ and $\mathbf{m} = \mathbf{B} - \mathbf{D}$, where $\mathbf{B}$ is a matrix whose elements are $\beta_{ji}x_i$, the expected number of secondary infections of host type i per infected host of type j, and $\mathbf{D}$ is a diagonal matrix whose elements are $\delta_i + \alpha_i + \gamma_i$, the sum of mortality and recovery rates for each type of infected host. The matrix $\mathbf{m}$ can be used to derive the instantaneous growth rate of the parasite population (Appendix 1). Alternatively, the matrix $\mathbf{M} = \mathbf{BD}^{-1}$ can be used for the derivation of a per generation growth rate of the parasite population (Appendix 1). In particular, the basic reproductive ratio of the parasite (the per generation growth rate of the parasite introduced in a naive host population) is given by the dominant eigenvalue of $\mathbf{M}$.

For the sake of simplicity, in the remainder of this paper, I will only consider the simpler case with two hosts. Figure 1 gives a schematic representation of this life cycle. In this case the basic reproductive ratio is:

$$R_0 = \frac{\beta_{11}}{2(\delta_1 + \alpha_1 + \gamma_1)}\hat{x}_1 + \frac{\beta_{22}}{2(\delta_2 + \alpha_2 + \gamma_2)}\hat{x}_2 + \left\{\frac{(\beta_{12}\beta_{21} - \beta_{11}\beta_{22})}{(\delta_1 + \alpha_1 + \gamma_1)(\delta_2 + \alpha_2 + \gamma_2)}\hat{x}_1\hat{x}_2 + \left[\frac{\beta_{11}}{2(\delta_1 + \alpha_1 + \gamma_1)}\hat{x}_1 + \frac{\beta_{22}}{2(\delta_2 + \alpha_2 + \gamma_2)}\hat{x}_2\right]^2\right\}^{1/2} \qquad (2)$$

where the $\hat{x}_i$ values are the equilibrium densities of the different types of hosts in the absence of the parasite. The above quantity can then be used to determine if the parasite can maintain itself in the host population. If $R_0 > 1$, the parasite will be able to create an epidemic in a previously virgin population, and when $R_0 < 1$, it will always go extinct before producing any epidemic. More complex situations with higher number of hosts can be analyzed using similar methods (Diekmann et al. 1990; Diekmann and Heesterbeek 2000).

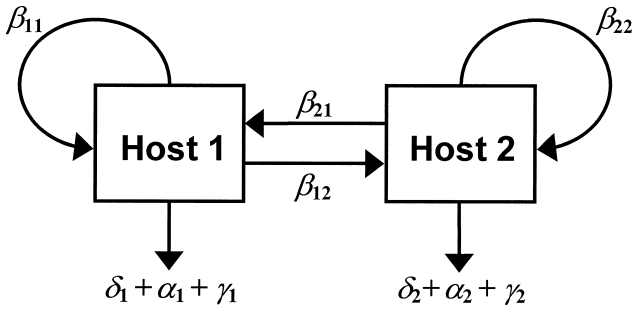

FIG. 1. Schematic representation of parasite life cycle with two different types of hosts. These two types of hosts may have different intrinsic mortality rates (δ_1 and δ_2). They may also suffer differentially from being infected, yielding different parasite-induced mortality rates (i.e., virulences α_1 and α_2) and different recovery rates (γ_1 and γ_2). The parasite transmission pattern is described by the four transmission rates that refer to within-type (β_{11} and β_{22}) and between-type (β_{12} and β_{21}) transmission.

Some simplification may occur depending on the pattern of transmission. Suppose, for example, that transmission is the product of two functions: $\beta_{ji} = \pi_j\phi_i$, where π_j measures the production of propagule of the parasite infecting a host type j, and ϕ_i is the susceptibility of the host type i (see scenario 1, below). In this situation $\beta_{12}\beta_{21} - \beta_{11}\beta_{22} = 0$, which yields:

$$R_0 = \frac{\beta_{11}}{\delta_1 + \alpha_1 + \gamma_1}\hat{x}_1 + \frac{\beta_{22}}{\delta_2 + \alpha_2 + \gamma_2}\hat{x}_2, \qquad (3)$$

which is the sum of reproductive ratios on each host (Anderson and May 1991; Dushoff 1996; Gandon et al. 2001a, 2003). Note that this sum involves only within-type transmission despite the fact that between-type transmission occurs.

Imagine another situation where the parasite sequentially exploits the two different types of hosts. This may occur when the parasite is sexually transmitted through heterosexual contacts (from one sex to another) or with vector-borne parasites (e.g., from vertebrate to invertebrates, see scenario 2 below). In these situations $\beta_{ii} = 0$ (for all i), which yields:

$$R_0 = \sqrt{\frac{\beta_{12}\beta_{21}}{(\delta_1 + \alpha_1 + \gamma_1)(\delta_2 + \alpha_2 + \gamma_2)}\hat{x}_1\hat{x}_2}. \qquad (4)$$

In contrast with equation (3), the basic reproductive ratio is a product (instead of a sum) of two quantities which describe between-type transmission. This product reflects the obligation for the parasite to exploit these two hosts sequentially. Note that the square root comes from the fact that the completion of the whole life cycle requires two generations: one generation from one host to the next and another generation to go back to the original host (Roberts and Heesterbeek 2003). It is also interesting to note that the situation in which all $\beta_{ii} = 0$ is analogous to the case in which the parasite infects a single host but produces free-living stages. Here, the parasite appears sequentially in two states: (1) within infected hosts; and (2) in the environment (as a free-living

propagule). If no direct transmission occurs (i.e., $\beta_{11} = 0$) and if propagules cannot reproduce in the environment (i.e., $\beta_{22} = 0$), this yields an expression of the basic reproduction ratio very similar to equation (4) (e.g., Bonhoeffer et al. 1996).

The importance of life-cycle architecture to the basic reproductive ratio has long been recognized (Anderson and May 1991; Dushoff 1996; Woolhouse et al. 2001, 2002; Haydon et al. 2002). Next, I emphasize the importance of such life-cycle geometry for parasite evolution.

Evolutionary Dynamics

In the above analysis, the parasite life-history parameters (α_i, β_{ji}, and γ_i) are fixed quantities. However, virulence, transmission and recovery will evolve if there is genetic variation in the parasite population. Consider a mutant parasite with life-history traits that differ from the resident parasite population, where $\mathbf{z}^* = (z_1^*, z_2^*, \ldots)$ is the vector of mutant traits and $\mathbf{z} = (z_1, z_2, \ldots)$ is the vector of resident traits. As an example, these vectors may be of size $n(n + 2)$ (i.e., n transmission rates, plus one virulence, plus one recovery rate, in each of the n hosts). The initial dynamics of a mutant introduced in a monomorphic resident population can be described by $\dot{\mathbf{y}}^* = \mathbf{m}^* \cdot \mathbf{y}^*$, with $\mathbf{y}^* = (y_1^*, y_2^*, \ldots)$ and where $\mathbf{m}^*$ is analogous to $\mathbf{m}$ but refers to the mutant parasite (Appendix 2). The fate of the mutant strategy (extinction or invasion) can be derived from its initial growth rate, which is given by the dominant eigenvalue, r^*, of $\mathbf{m}^*$ (Appendix 2). The recurrent invasion and fixation of mutants may ultimately lead to an evolutionarily stable strategy (ESS). The following condition must be satisfied for $\mathbf{z}$ to be at an evolutionary equilibrium:

$$\left.\frac{dr^*}{dz_i^*}\right|_{z=z^*} = 0, \quad \text{for all } i \in [1, n(n+2)]. \tag{5}$$

Note however, that equation (5) is the condition for an internal evolutionary equilibrium only. Additionally, higher order conditions must be used to check if this equilibrium is locally and globally stable (Taylor 1989; Geritz et al. 1998; Kisdi and Geritz 1999; Gandon et al. 2003; Leimar, in press). Global and/or local instability may lead to more complex situations (e.g., evolutionary bistability, evolutionary branching). Some of these complexities will be encountered and discussed in the analysis of the different examples presented below.

In the absence of any constraints (e.g., if each trait can evolve independently of the other traits), parasite evolution would lead to a minimization of virulences (α_i) and recovery rates (γ_i) and to a maximization of transmission rates (β_{ij}). Indeed, the parasite always benefits from longer duration of the infection and higher transmission. However, I assume some trade-off will constrain the range of possible phenotypes. Formally, this means that parasite traits will be correlated (e.g., transmission and virulence: $d\beta_{11}/d\alpha_1 \neq 0$) and, consequently, selection on a given trait (e.g., virulence) will be governed both directly by the effect of this trait on parasite's fitness and indirectly through the effect of correlated traits (e.g., transmission). The strength of such indirect effects will depend on statistical regression coefficients $C_{ij} = dz_j/dz_i$ between traits. The use of the chain rule on equation (5) yields:

$$\mathbf{C}\nabla r^* = \mathbf{0}, \tag{6}$$

where $\mathbf{0}$ is the vector of $n(n + 2)$ zero elements, $\mathbf{C}$ is the $n(n + 2) \times n(n + 2)$ matrix of regression coefficients C_{ij}, and ∇ is the gradient operator $(\partial/\partial z_1^*, (\partial/\partial z_2^*, \ldots)$, where everything is evaluated at the point where $\alpha_i^*, = \alpha_i$, $\beta_{ij}^* = \beta_{ij}$, and $\gamma_{ij}^* = \gamma_{ij}$. The matrix $\mathbf{C}$ is thus a function of the state $\mathbf{z}$ of the resident population. The constraints between the different parasite traits may change as the population evolves (i.e., $\mathbf{C}$ may change as the population proceeds toward the ESS equilibrium). However, note again that equation (6) provides only the condition for an evolutionary internal equilibrium. A fully dynamical theory of evolutionary change (allowing to track the speed of evolution of the different traits) requires further information regarding the additive genetic variance of each trait (Lande 1982; Charlesworth 1993; Abrams 2001; Day and Proulx 2004). In particular, note that $\mathbf{G} = \mathbf{CV}$, where $\mathbf{G}$ is the matrix of additive genetic covariances among the different traits and $\mathbf{V}$ is the vector of additive genetic variance of each trait. In the present paper, however, I assume there is sufficient genetic variance (sufficient to reach the equilibrium obtained with eq. 6) and will focus only on the analysis of factors that may modify this ultimate evolutionary outcome. At this ultimate equilibrium different modeling approachs all yield conditions very similar to equation (6). Quantitative genetics yield the classical result of selection on multivariate traits: $\mathbf{G}\nabla r^* = \mathbf{0}$ (Lande 1982; Charnov 1989; Iwasa et al. 1991; Charlesworth 1993). The canonical equation of adaptive dynamics (Dieckmann and Law 1996) yields $\mu y \boldsymbol{\sigma} \nabla r^* = \mathbf{0}$, where μ is half the mutation rate, y is the prevalence of the parasite, and $\boldsymbol{\sigma}$ is the variance-covariance matrix of the multivariate distribution of mutation (within this framework, the constraints between traits are assumed to emerge from the mutation process).

To facilitate the interpretation of equation (6), I replace r^* by an alternative fitness function (e.g., Taylor and Frank 1996; Frank 1998):

$$w^* = \sum_{i,j} v_j m_{ij}^* u_i = \sum_i c_i m_i^*, \tag{7}$$

where v_j is the individual reproductive value of parasites infecting an individual host of type j, m_{ij}^* is the element at the ith column and jth line of $\mathbf{m}^*$, and u_i is the density of infected hosts of type i (when the parasite has reached a stable distribution between the different types of hosts). The vectors $\mathbf{u}$ and $\mathbf{v}$ are dominant right and left eigenvectors of $\mathbf{m}$, respectively (see Appendix 1). Note that $\mathbf{m}^*$ is a function of both mutant and resident strategies ($\mathbf{z}^*$ and $\mathbf{z}$, respectively), whereas $\mathbf{u}$ and $\mathbf{v}$ depend only on the resident strategy. The final equality in (7) derives from the definition of the *class* reproductive value of parasites infecting host population of type i, $c_i = v_i u_i$, and the weighted sum of transitions between i and j, $m_i^* = \Sigma_j (v_j/v_i) m_{ij}^*$ (Taylor and Frank 1996). This yields the following condition for evolutionary equilibrium:

$$\sum_i c_i [\mathbf{C}\nabla(m_i^*)] = \mathbf{0}. \tag{8}$$

The use of equation (8) is particularly insightful because it

shows that the direction of evolution is given by the sum of the selective pressures acting within the different types of hosts, weighted by the reproductive values, c_i, of parasites infecting these different host populations (for other illustrations of the use of reproductive values to understand selection in heterogeneous environments, see also Holt 1996; Frank 1998; Rousset 1999). In other words, evolution may be altered by three factors: (1) $\mathbf{C}\nabla(m_i^*)$, the selection occurring in the different hosts (this includes both direct and indirect selection); (2) v_i, the quality of these hosts for the parasite (i.e., the individual reproductive values of parasites); and (3) u_i, the prevalence of the parasite among these different hosts. This last point indicates how epidemiology could feed back on parasite evolution.

As pointed out above, the relative intensity of direct and indirect selection is governed by **C.** Figure 2A gives a schematic representation of **C** when the parasites infect two types of hosts. It shows that constraints may occur within each type of host (between virulence, recovery, and transmission, as indicated by the gray cells in Fig. 2A) and/or between different types of hosts.

Within-Type Constraints

If parasite phenotypes in one host do not covary with phenotypes in the other, evolution proceeds independently in the two hosts. Here, as in classical models of virulence evolution (with only one host), parasite evolution is only constrained by within-host trade-offs.

It is often assumed that transmission and virulence are two phenotypic expressions of an underlying pleiotropic trait (e.g., host exploitation, parasite growth rate). This yields a positive relationship between the benefit of exploitation (transmission) and its cost (virulence): $d\beta_{11}^*/d\alpha_1^* > 0$. There is some empirical data on several very different host-parasite systems (Fenner and Fantini 1999; MacKinnon and Read 2003) supporting this hypothesis. This relationship yields intermediate values of evolutionarily stable virulence and transmission if it has the additional property transmission saturates with high virulence ($d^2\beta_{11}^*/d\alpha_1^{*2} < 0$). The empirical data supporting this hypothesis remains weak (probably because statistical tests of such saturating relationships are very demanding).

Similarly, recovery rates could also be linked to virulence and transmission because the ability to clear a parasite will also depend on its within-host growth rate (which also impacts on virulence and transmission). In particular, it is often assumed that faster reproducing parasites are more difficult to clear (Anderson and May 1982; Frank 1996). There is good empirical evidence supporting this hypothesis (Anderson and May 1982; Fenner and Fantini 1999; MacKinnon and Read 2003). A single trade-off between virulence and recovery may also yield intermediate levels of evolutionarily stable virulence (Anderson and May 1982; Frank 1996). However, in many situations, it would be more relevant to envision a trade-off in virulence with both transmission and recovery.

Between-Type Constraints

When some correlation exist between different hosts, the evolution of a trait expressed in one host depends also on the selection acting on traits expressed in different hosts. The direction of evolution will thus depend on the pattern of correlation between traits, which could potentially take any form (correlations could be all negative, all positive, or a mixture of positive, negative, and/or zero). However, in principle, it is possible to provide a mechanistic explanation for the emergence of a given pattern of correlation. I will focus here on two contrasting situations that illustrate cases with positive or negative between-host types correlations.

First, imagine that the same parasite machinery is required for the exploitation of both hosts but that some hosts are more resistant than others (e.g., if the immune system is more efficient in reducing within-host growth rate). Infection by the same parasite would thus result in different levels of exploitation in the two hosts, yielding also different levels of virulence, recovery, and transmission. A mutant parasite that adopts a more intense exploitation strategy would increase its exploitation on both hosts, and this would lead to a positive covariance between traits expressed in different hosts. For example, MacKinnon and Read (1999, 2003) found that more virulent strains of *Plasmodium chabaudi* produce more transmission stages (within-host trade-off between virulence and transmission) and that they are more difficult to clear (within-host trade-off between virulence and recovery). They also found that the most virulent strains in immunologically naive mice are also more virulent, transmissible, and difficult to clear in semi-immune mice (Mackinnon and Read 2003). This generates positive (virulence, transmission) and negative (recovery) genetic covariances between parasite traits expressed in naive and semi-immune mice (Fig. 2B). Best and Kerr (2000) obtained similar results using different strains of myxoma virus to infect laboratory rabbits (naive host) and naturally resistant rabbits.

Second, imagine a situation in which different machineries are required for the exploitation of the two hosts. This may well be the case if the two types of hosts are different species representing different resources for the parasite (e.g., malaria parasites where asexual growth occurs in the vertebrate host and sexual reproduction in the vector). Under such a scenario, one may expect no genetic covariation between traits expressed in different hosts. However, if the optimal exploitation of one type of host (adaptation to this host) is associated with a reduced ability to exploit another host (i.e., trade-off between the exploitation of the two hosts), this could result in negative genetic covariances. For example, Davies et al. (2001) observed a trade-off in the reproductive success of schistosomes in their mammalian and molluscan hosts (Fig. 2C). Further evidence of negative between-hosts correlations in parasite fitness come from serial-transfer experiments. When parasites are serially transmitted from one host to another host of the same type, the virulence in this host type increases but often with an accompanying decrease of virulence (i.e., attenuation) in other types of host (Ebert 1998).

The two contrasting situations presented above illustrate how mechanistic differences in the exploitation of the different hosts (i.e., whether the parasite uses the same machinery to exploit different hosts) influence the pattern of genetic covariances between traits. This point has previously been raised at the within-host level where a better under-

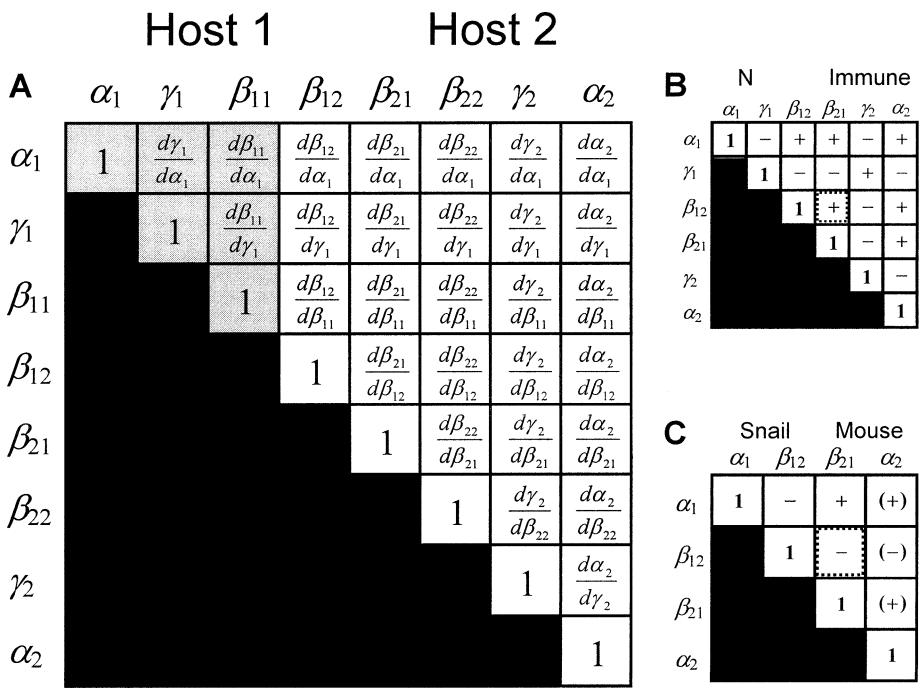

FIG. 2. Schematic representation of the regression matrix **C** between parasite life-history traits. (A) The full matrix for the general two-host model as it is presented in Figure 1. I do not give the values below the diagonal because they can be derived from values above the diagonal. I highlight in gray the regression coefficients required for the classical analysis of parasite evolution on a single host. The white cells show that adding another host in the system substantially increases the number of constraints that may act on parasite evolution. Covariances between traits expressed in different hosts have actually been measured in different host-parasite systems. (B) and (C) present qualitative summaries (only the sign of the regression) of results obtained for the rodent malaria (MacKinnon and Read 2003) and for schistosomes (Davies et al. 2001), respectively. In (B) the two types of hosts are naive and semi-immune mice (MacKinnon and Read, 2003). In (C) the two types of hosts are the snail (intermediate host) and the mouse (definitive host). The signs in parentheses indicate nonsignificant regression coefficients. Note that it is classically assumed that within a single host the regression between virulence and transmission is positive, the regression between recovery and virulence is negative, and the regression between recovery and transmission is also negative. Rodent malaria follows these assumption (see B), but not schistosome in the snails because transmission is negatively correlated with virulence (see C). The between-host constraints also differ in these two examples: the correlations of between-type transmission rates is positive in malaria and negative in schistosome. This qualitative difference is highlighted with a dotted square in B and C.

standing of the interaction between parasites and the immune system, for example, could help predict the relationship between virulence, recovery, and transmission (Antia et al. 1994; Ganusov et al. 2002; Gilchrist and Sasaki 2002; André et al. 2003; Ganusov and Antia 2003). The generalization of such mechanistic approach to multihost parasites may help us understand the emerging pattern of genetic covariances at both the within- and between-host levels (J. B. André and S. Gandon, unpubl. ms.).

In the following, I illustrate the use of the above evolutionary model (eq. 8) through different examples. For the sake of simplicity, I assume no recovery from infection and focus on virulence and transmission evolution. Moreover, the functions relating these two traits in the two different hosts will not emerge from an explicit description of within-host dynamics. Instead, I will use general functions derived from a mix between some available empirical knowledge and implicit arguments regarding within-host dynamics.

In the first evolutionary scenario, I focus on the evolution of the virulence of a parasite exploiting two hosts with different levels of resistance. This scenario is inspired from situations in which a fraction of the host population is naturally or artificially (e.g., vaccination) immunized. The main point here is to show how transmission routes (the relative amount of within-host-type and between-host-type transmission) and epidemiology (the relative abundance of the two hosts) may affect the evolutionary outcome.

The second evolutionary scenario focuses on the evolution of alternative transmission routes via a new host. This scenario is inspired from a situation in which a parasite may infect two different host species (the focal host and a vector). First, I study which factors may govern the evolution of vector-borne transmission and, second, I show how the emergence of a new transmission route may feed back on the evolution of virulence.

SCENARIO 1: VIRULENCE EVOLUTION UNDER DIFFERENT TRANSMISSION PATTERNS

Here I address the evolution of virulence when parasite phenotypes in both host types are under the control of a single pleiotropic trait, the host exploitation strategy, ε. The heterogeneity of the host population will affect the evolution of this trait when the selective pressures acting on it vary among different hosts. The weights associated with these different selective pressures are strongly dependent on the relative

amount of within- and between-type transmission. These different transmission routes will necessarily fall between two extreme cases of: (1) no between-type transmission ($\beta_{ij} = 0$ for $i \neq j$, and parasite life cycle consists of two direct cycles on two different hosts); and (2) no within-type transmission ($\beta_{ii} = 0$ for all i, and parasite life cycle consists of a single indirect cycle).

To illustrate these different situations, it is convenient to assume the following relationships:

$$\beta_{ij}[\varepsilon] = \pi_i[\varepsilon]\phi_{ij}. \tag{9}$$

The parameter $\pi_i[\varepsilon]$ refers to the production of propagules in the host of type i. Note that this production is assumed to depend on the host exploitation strategy, ε, which also affects parasite virulence (see below). The parameter ϕ_{ij} specifies the amount of transmission between propagules produced in an individual host of type i to other individuals of type j. In other words, the parameter ϕ_{ij} governs the shape of the transmission pattern. In the present example I assume that this transmission pattern is not affected by the host exploitation strategy of the parasite (i.e., ϕ_{ij} does not depend on ε), but this assumption will be relaxed below (scenario 2).

The characterization of the selective pressures acting in the two different hosts requires further assumptions regarding the within-host constraints and the relationship between virulence and transmission. Regoes et al. (2000) devised a two-host model where virulence in one host is traded off against virulence in the second host. They showed that such a negative relationship between virulence levels yields intermediate values of the evolutionarily stable virulence even in the absence of any link between transmission and virulence. Here I will analyze a different situation where traits expressed in the two hosts (virulence and transmission) are positively correlated, as in MacKinnon and Read (2003; see the above discussion of this work). Following Gandon et al. (2001a, 2003), I assume the following relations:

$$\pi_1[\varepsilon] = \frac{\varepsilon}{1 + \varepsilon}, \qquad \pi_2[\varepsilon] = \pi_1[(1 - \rho)\varepsilon] \quad \text{and} \tag{10a}$$

$$\alpha_1[\varepsilon] = \varepsilon, \qquad \alpha_2[\varepsilon] = (1 - \rho)\varepsilon. \tag{10b}$$

The logic behind these assumptions is as follows. Host exploitation allows the parasite to produce propagules (π is an increasing function of exploitation ε), but such exploitation has a deleterious effect on the host (virulence, α, increases with exploitation ε). These relationships vary among different hosts, and the parameter ρ governs these differences. This parameter could be viewed as a resistance mechanisms against the parasite (the parameter r_2 in Gandon et al. 2001a, 2003). Higher resistance decreases parasite within-host growth rate and, consequently, its transmission, π, and its virulence, α. Note that the above assumptions yield positive covariances between all the parasite life-history traits (as in Fig. 2B, with the exception of recovery rates).

The above assumptions also yield different optimal virulence strategies, α_i, in the two hosts: $\alpha_1 = \sqrt{\delta_1}$ on host type 1 and $\alpha_2 = \sqrt{\delta_2}/(1 - \rho)$ on host type 2 (Gandon et al. 2001a). One would expect that, when both hosts coexist, the selection acting on the evolution of the parasite would push the trait somewhere between these two optimal values. Will the evolutionary outcome be closer to the optimum for one host over the other? Will evolution in such a heterogeneous host environment always lead to a single generalist strategy, or could it lead to a polymorphic situation with two (or more) strategies specialized on the different types of hosts? The answers to these questions are obtained through the analysis of parasite fitness, which itself depends on the densities of each type of host (see eq. 8). Thus, a full evolutionary analysis requires first a complete description of the epidemiological model and, in particular, the dynamics of uninfected hosts. For the sake of simplicity, I assume as in Gandon et al. (2003) that:

$$\dot{x}_1 = \lambda(1 - p) - \left(\delta_1 + \sum_i \beta_{i1}y_i\right)x_1 \quad \text{and} \tag{11a}$$

$$\dot{x}_2 = \lambda p - \left(\delta_2 + \sum_i \beta_{i2}y_i\right)x_2, \tag{11b}$$

where λ is the rate of host immigration (this parameter refers to both immigration and fecundity) and p measures the proportion of the second type of hosts (the resistant ones) among immigrants.

Figure 3 illustrates the effect of different transmission patterns on the evolution of parasite virulence. I present a simple case where $\phi_{11} = \phi_{22} = 1$ and vary only the value of $\phi_{12} = \phi_{21}$ between 0.2 and 5.0. This allows me to contrast situations where the ratio of between- and within-type transmission varies.

Figure 3A shows the effect of the frequency of the second type of host among immigrants, p, on evolutionarily stable virulence. Not surprisingly an increase in p yields higher virulence (because the optimal virulence on the second type is higher, $\alpha_2 > \alpha_1$), but the effect of p depends strongly on the transmission patterns. When there is more within-type transmission ($\phi_{ii} > \phi_{ij}$), the evolutionarily stable virulence is always very close to the optimal virulence on the more abundant host. This yields a sharp increase of evolutionarily stable virulence for small variations in p when both hosts are abundant ($p \sim 0.5$). In other words, this pattern of transmission favors specialization to the most abundant host. This contrasts with the situation in which there is more between-type transmission ($\phi_{ii} < \phi_{ij}$), where intermediate values of virulence and more generalist strategies are favored.

Figure 3B shows the effect of another demographic parameter on virulence evolution, the intrinsic host death rate of the second type of host, δ_2. Again, the transmission pattern strongly affects the evolutionary outcome. When there is more between-type transmission ($\phi_{ii} < \phi_{ij}$), an increase in the intrinsic mortality of the resistant host (δ_2) favors higher evolutionarily stable virulence as one would expect from the analysis of classical single-host models of parasite virulence (Anderson and May 1982; Frank 1996; Dieckmann et al. 1999). However, when there is more within-type transmission the evolutionarily stable virulence may first increase but then decreases with larger values of intrinsic mortality, δ_2. Again, more within-type transmission favors specialization to the most abundant host, and an increase in the mortality of the second host type favors lower virulence when $\delta_2 > \delta_1$, be-

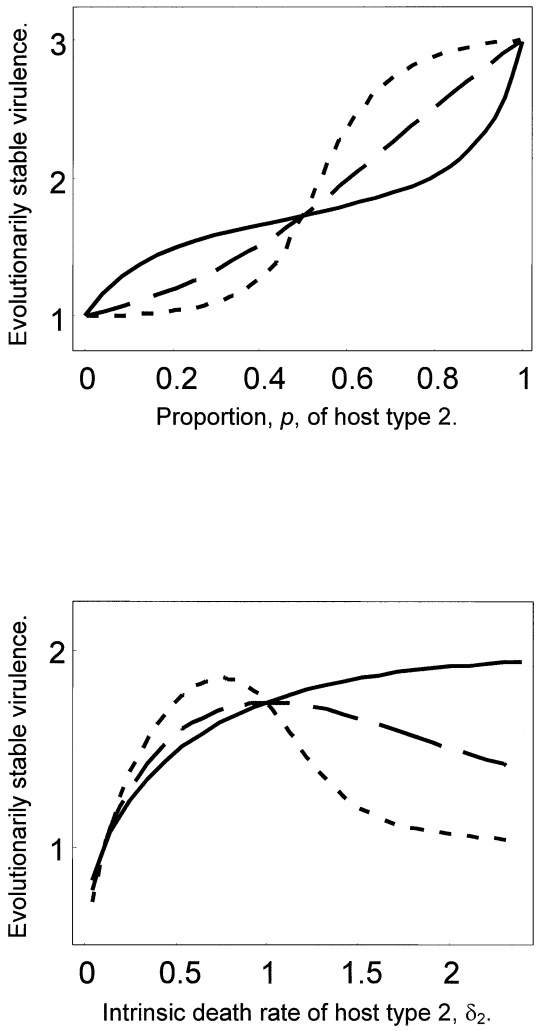

FIG. 3. Evolutionarily stable virulence (when measured on host 1) against (A) the proportion, p, of host 2 among immigrants and (B) the intrinsic death rate, δ_2, of host 2. Three different transmission patterns are considered. The dotted line shows a situation in which there is more within-type transmission than between-type transmission ($\phi_{11} = \phi_{22} = 1$ and $\phi_{12} = \phi_{21} = 0.2$). The dashed line shows a situation in which within-type transmission is equal to between-type transmission ($\phi_{11} = \phi_{22} = \phi_{12} = \phi_{21} = 1$). The full line shows a situation in which there is less within-type transmission than between-type transmission ($\phi_{11} = \phi_{22} = 0.2$ and $\phi_{12} = \phi_{21} = 1$). In all these situations the equilibrium value is always evolutionarily stable (i.e., no evolutionary branching). Other parameter values: $\lambda = 20$, $\delta_1 = 1$, $\delta_2 = 1$, $r = 2/3$.

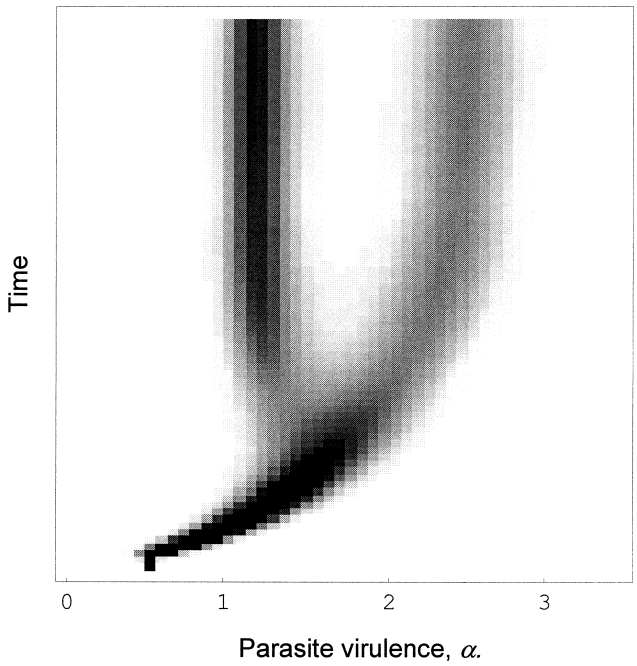

FIG. 4. Deterministic simulations showing the evolution of parasite virulence. At the beginning of the simulation the parasite population is monomorphic with virulence $\alpha = 0.5$. Mutation occurs at a rate $\mu = 0.01$ and allows this trait to evolve. This simulation illustrates a situation in which there is 10 times more transmission within the same host types than between different host types ($\phi_{11} = \phi_{22} = 1$ and $\phi_{12} = \phi_{21} = 0.1$). This transmission pattern leads to an evolutionary branching, yielding the coexistence of two different virulent strategies. The ratio of individual reproductive values on the two different types of hosts ($\bar{v}_1/\bar{v}_2$, see Appendix 1) can be used to measure the level of specialization of the two strains (Gandon et al. 2003). The low virulence strain is better adapted to the first host ($\bar{v}_1/\bar{v}_2 \approx 2.78 > 1$), and the high virulence strain is better adapted to the second host ($\bar{v}_1/\bar{v}_2 \approx 0.37 < 1$). Other parameter values are as in Figure 3.

cause the first host (in which optimal virulence is lower) becomes more frequent.

More generally, all these results can be explained by the differences in class reproductive values of parasites infecting different types of hosts. Reproductive values are the proper weights associated with the selective pressures acting in these different habitats. For example, with only between-type transmission ($\phi_{ii} = 0$), the ratio of class reproductive values is $(\delta_2 + \alpha_2)/(\delta_1 + \alpha_1)$ (Appendix 1). This ratio is independent of p, which explains why this parameter has no effect on evolution. With a larger fraction of within-type transmission, the ratio of class reproductive values depends more on the availability of the different hosts. In particular, Gandon et al. (2001a, 2003) studied a model with $\phi_{ii} = \phi_{ij}$ and showed how p (which could be viewed as a parameter measuring vaccination coverage) affects the evolution of parasite virulence. At the other extreme, when $\phi_{ij} = 0$ with $i \neq j$, the parasite population consists of two subpopulations evolving in different directions. This favors the emergence and coexistence of different virulence strategies, α_1 and α_2, adapted to each host. But evolution toward polymorphism may also occur with low values of between-type transmission. For example, Figure 4 shows a situation in which evolutionary branching may occur and lead to a polymorphic parasite population in which two virulence strategies coexist and each strain is specialized to a different host (reproductive values can be used to measure the level of specialization; see caption of Fig. 4).

SCENARIO 2: COEVOLUTION OF INDIRECT TRANSMISSION WITH VIRULENCE

The previous examples illustrate the importance of the pattern of transmission on virulence evolution. Here, I allow different transmission patterns to evolve and coevolve with virulence. As above, I assume the epidemiological dynamics

described by equations (1) and (11). I will also follow the assumption that transmission rates are the product of two components, the production of propagule and the transmission route ($\beta_{ji} = \pi_j\phi_{ji}$). The parasite can be transmitted directly from one individual to the next (where both individuals are of type 1) or it can be transmitted indirectly via another host species (host 2), which can be used as a vector toward the infection of the first host (the focal host). To keep things simple, this second host species is assumed not to suffer from the parasite (i.e., $\alpha_2 = 0$, because the parasite exploits only the focal host), but this assumption will be discussed later.

First, I analyze the evolution of the transmission pattern and explore what factors may favor indirect (e.g., vector-borne) transmission. Second, because vector-borne transmission is likely to affect the evolution of parasite virulence on the exploited host (Day 2001, 2003), I analyze the coevolution between the pattern of transmission and virulence.

Evolution of Indirect Transmission

Under what conditions will the parasite evolve strategies allowing transmission via a new host (e.g., a vector) when direct transmission may represent a seemingly simpler alternative? Of course, in the absence of any constraint on transmission, evolution would favor the strategy maximizing both direct and indirect transmission routes. But, as discussed above, it is very likely that different transmission routes will require specific adaptations. For example, a specialization toward more efficient between-type (indirect) transmission may yield less efficient within-type (direct) transmission. In the following, I thus assume a trade-off between these different transmission strategies:

$$\phi_{11}[\tau] = \tau^{q1} \quad \text{and} \tag{12a}$$

$$\phi_{12}[\tau] = (1 - \tau)^{q2}, \tag{12b}$$

where the parameters $q1$ and $q2$ allow consideration of different forms of trade-offs. For the sake of simplicity, I assume that no transmission occurs between vectors ($\phi_{22} = 0$) and that transmission from the vector to the exploited host is constant ($\phi_{21} = 1$). I also assume that the production of transmissible stages are constant in the two hosts ($\pi_1 = \pi_2 = 1$, but this assumption will be relaxed below). This yields the following transmission rates: $\beta_{11}[\tau] = \tau^{q1}$, $\beta_{12}[\tau] = (1 - \tau)^{q2}$, $\beta_{21} = 1$, and $\beta_{22} = 0$.

Figure 5 shows the effect of the abundance of the vector (where the ratio $p/[1 - p]$ measures the immigration rate of vectors relative to the immigration rate of exploited hosts) on the evolution of between-type transmission. Higher immigration and lower mortality of this second type of host (the vector) yields higher level of evolutionarily stable between-type transmission. Indeed, both larger densities and lower mortality makes it a better vector. Higher mortality of the first type of host (i.e., $\delta_1 + \alpha_1$) also yields higher evolutionarily stable between-type transmission (not shown) because this mortality lowers the efficacy of transmission by direct contact.

In Figure 5, I present a case with a convex trade-off (i.e., $q1 = q2 = 0.5$). This favors intermediate levels of between-host transmission. However, other types of constraints (e.g., linear or concave) can yield complex evolutionary outcomes.

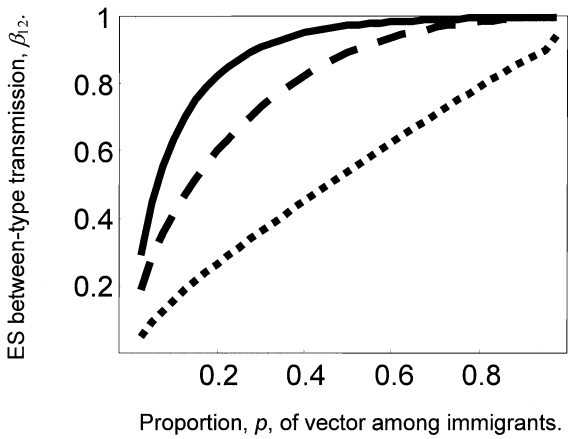

FIG. 5. Evolution of new transmission routes in response to a change in the abundance of the different types of host. The evolutionarily stable (ES) between-type level of transmission is plotted against the proportion, p, of the vector among immigrants. Note that the ratio $p/(1 - p)$ gives the rate of immigration of the vector relative to the exploited host. The upper line presents a case in which the virulence on the first type of host is $\alpha_1 = 5$ (full line). Lower virulence ($\alpha_1 = 1$, dashed line) and higher intrinsic host mortality of the vector ($\delta_2 = 3$, dotted line) favor lower ES between-type transmission. Default parameter values: $\lambda = 20$, $\alpha_1 = 1$, $\delta_1 = \delta_2 = 1$, $q_1 = q_2 = 0.5$.

Evolutionary bistability may occur where the two alternative equilibria are two extreme cases: (1) no indirect transmission (i.e., the parasite adopts a direct life cycle and exploits a single host); and (2) no direct transmission (i.e., the parasite adopts an indirect life cycle and exploits the two hosts sequentially). Under some situations evolutionary branching may also occur, leading to the coexistence of different transmission strategies (not shown).

Virulence Coevolution

Next, I explore how different transmission routes can coevolve with parasite virulence. I assume again that parasite transmission depends on both the production of propagules (π) and the transmission route (ϕ):

$$\beta_{ij}[\varepsilon, \tau] = \pi_i[\varepsilon]\phi_{ij}[\varepsilon, \tau]. \tag{13}$$

In contrast to the previous model, parasite transmission depends on two traits that may evolve independently.

First, the exploitation of host type 1, ε, affects the production of propagules and the virulence in the first type of host ($\pi_1[\varepsilon] = \varepsilon/(1 + \varepsilon)$ and $\alpha_1[\varepsilon] = \varepsilon$). However, it neither affects the transmission from the vector nor the virulence on this second host ($\pi_2 = 1$ and $\alpha_2 = 0$). Second, as in equation (12), the transmission strategy, τ, measures the allocation toward within-type transmission:

$$\phi_{11}[\varepsilon, \tau] = \tau^{q1}e^{-m\varepsilon} \quad \text{and} \tag{14a}$$

$$\phi_{12}[\tau] = (1 - \tau)^{q2}. \tag{14b}$$

As above, I assume that no transmission occurs between vectors ($\phi_{22} = 0$) and that transmission from the vector to the exploited host is constant ($\phi_{21} = 1$). Note the important difference that ϕ_{11} is now assumed to be a decreasing function of ε, while ϕ_{12} does not depend on ε. This is to express the

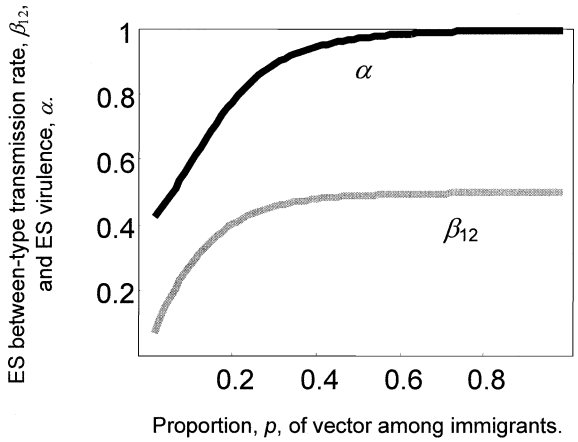

FIG. 6. Coevolution of the transmission pattern with virulence in response to a change in the abundance of the different types of host. The evolutionarily stable (ES) between-type level of transmission (in gray) and virulence on the first type of host (in black) are plotted against the proportion, p,, of the vector among immigrants. Parameter values: $\lambda = 20$, $\delta_1 = \delta_2 = 1$, $q_1 = q_2 = 0.5$, $m = 1$.

fact that morbidity may impose some cost on direct transmission but not on vector-borne transmission (Ewald 1983, 1994; Day 2001, 2003; Ewald and De Leo 2002). Indeed, the altered behavior of infected host may limit the contact with some hosts (host 1) but not with others (host 2). In the present model the parameter m refers to such morbidity cost.

Figure 6 presents the effect of the abundance of the vector on the evolution of both transmission and virulence. Higher vector densities yield more between-type transmission (as in Fig. 5) but also higher virulence. The increase in evolutionarily stable parasite virulence is due to an increase in the fraction of vector-borne transmission. Such transmission route releases the morbidity cost of virulence expressed only via direct transmission. Note the synergistic effects emerging through the coevolution between transmission and virulence. The evolution of larger between-type transmission increases the selection for higher virulence (because this reduces the morbidity cost of virulence) and, reciprocally, larger virulence tends to select for larger between-type transmission (because, as explained above, higher virulence lowers the efficacy of direct transmission). The above results suggests that the relative abundance of the different types of host (controlled by the parameter p in Figs. 5, 6) may be one of the key factors explaining the evolution of very different parasite life cycles.

DISCUSSION

Single-host models of parasite evolution have been very useful for understanding some of the selective pressures acting on parasite life histories (Frank 1996; Stearns 1999; Diekmann et al. 2002). However, many parasites live in different environments and exploit different types of host. The multihost framework presented here is an attempt to provide more general tools to understand the evolution of parasite life histories. The general condition (8) for evolutinary equilibrium identifies two main factors acting on this evolution. First, evolution depends on direct and indirect selection occurring in the different hosts (where indirect selection depends on correlations among parasite life-history traits) and, as discussed above, this is mainly governed by within-host dynamics. Second, evolution depends also on the relative quality of the different hosts (i.e., the class reproductive values), via the relative abundance of the different types of infected hosts and the transmission patterns among these hosts. In other words, evolutionary predictions strongly depend on both microscopic (within-host dynamics) and macroscopic (epidemiological dynamics) details of the host-parasite interaction.

The complexity emerging from the effects of both microscopic and macroscopic processes has practical implications for virulence management of multihost parasites. These two processes are likely to vary from one parasite species to another (e.g., cf. Figs. 2B and 2C) or even from one location to another if the abundances of the potential host species vary in these different locations. General recommendations to limit virulence evolution should thus be very cautious and virulence management, like more classical tools against infectious diseases, should focus on the development of specific strategies against specific pathogens.

General models, however, may help to provide a broader understanding of what shapes parasite life history. In particular, the generalization of simple single-host models generates new insights into the evolution of both virulence and transmission strategies.

Virulence Evolution

The different evolutionary scenarios presented here illustrate how transmission pattern among different hosts may affect virulence evolution. This pattern will affect virulence evolution as long as different costs of virulence are associated with the different transmission routes. Before analyzing the evolutionary consequences of various transmission patterns (i.e., the relative proportion of within- and between-type transmission), it might be useful to contrast different types of virulence costs. First, there might be fixed costs associated with some transmission routes. For example, virulence may carry a morbidity cost when transmission is direct (Ewald 1994; Day 2001). One may thus expect evolution to yield a positive correlation between virulence on the focal host and the amount of indirect transmission (Day 2001; Ewald and De Leo 2002; see also Fig. 6, where transmission and virulence are coevolving). There is some empirical evidence suggesting that, indeed, the case mortality is higher for vector-borne and water-borne diseases where morbidity has only little effect on transmission efficiency (Ewald 1983, 1994; Ewald and De Leo 2002). But these results are based on correlations that could also emerge because of confounding factors associated with these different transmission modes (e.g., vector-borne and water-borne diseases are more prevalent in developing countries). More controlled comparative studies and experiments artificially manipulating the mode of transmission are required to demonstrate the importance of different transmission patterns for virulence evolution. For example, Bull et al. (1991) showed experimentally that vertical transmission selects for decreased virulence. This evolution results from the fixed cost of virulence associated with

vertical transmission. Indeed, under this route of transmission, the parasite fails to infect new hosts when the parasite kills its host before reproduction.

Second, there might also be dynamical costs associated with transmission routes via some habitats (e.g., hosts), which emerge from maladaptations to these habitats. This is a dynamical cost because the level of maladaptation results from several factors including underlying constraints among the different parasite traits, the transmission pattern itself, and the relative abundance of the different hosts. Parasite adaptation to the most abundant host (Fig. 3A) may lead to maladaptive exploitation strategies in other, less frequent, hosts. In these situations the parasite individual reproductive values, v_i, provide a relevant measure of the level of adaptation to different types of hosts (Frank 1996, 1998; Gandon et al. 2001a, 2003). The maladaptation may either result from suboptimal exploitation of the host (avirulence) or, on the contrary, from overexploitation of the host (hypervirulence). Ganusov et al. (2002) illustrated this point with a model of parasite evolution that examined the effect of host population heterogeneity induced by variations in the efficacy of immunity on optimal virulence. In this model the proportion of different hosts is fixed (contrasting with the present framework, where heterogeneity depends on host demography and parasite transmission strategy). In the absence of host heterogeneity, parasites evolve toward a host exploitation strategy that maximizes transmission without incurring mortality. However, some heterogeneity yields an optimal strategy in which some case mortality occurs because parasite occasionally infect hosts with inefficient immune systems. This optimal strategy could appear maladaptive in both the most sensitive hosts (where infection is lethal) and the most resistant ones (where this strategy does not maximize the duration of the infection). Understanding virulence evolution thus requires a characterization of the selective pressures acting outside the focal host.

Biological examples of apparently maladaptive virulence of parasites living in different environments are increasingly coming to the forefront. For example, it has been suggested that avirulence genes may be retained in *Salmonella enterica* because they facilitate survival in nonhost environments. In comparison with the wild-type parent, mutation of the *pcgL* gene increased virulence and growth in vivo but strongly reduced survival in vitro under nutrient-limiting conditions (Mouslim et al. 2002; Foreman-Wykert and Miller 2003). Also, the virulence of *Cryptococcus neoformans*, a soil fungus that can infect mammalian hosts, may be the byproduct of an adaptation for protection against soil predators such as amoebae (Steenbergen et al. 2001).

There is also empirical evidence that different hosts may constrain virulence evolution in the focal host. In humans, the high virulence evolution of many zoonotic pathogens such as *Echinococcus multilocularis* is probably driven by selection occurring in the main animal hosts (Woolhouse et al. 2001). A human host infection may thus appear as an accidental event for both the host and the parasite.

A reduction of the relative amount of between-type transmission decreases the cost of specialization (i.e., maladaption in less frequent host) because these less frequent hosts are rarely infected. More within-type transmission thus favors specialization to the most frequent host (Fig. 3A). When the different hosts are equally frequent, small variation in the abundance of the different host may result in dramatic changes of the evolutionarily stable virulence. This variation of host frequency may be due to differences in host immigration rates (Fig. 3A) or to host mortality rates (Fig. 3B). This latter result contrasts with the classical prediction derived from the simplest host-parasite models that higher mortality should select for higher virulence (Anderson and May 1982; Frank 1996; Dieckmann et al. 1999). Recent theoretical studies have shown that other factors (superinfections, predation) may also alter this prediction (Gandon et al. 2001a,b; Williams and Day 2001; Choo et al. 2003). This demonstrates the potential impact of the ecological setting on parasite evolution.

Extreme bias toward within-type transmission may result in evolutionary branching and coexistence of different virulence strategies. Each of these strategies are specialized to the different types of hosts (Fig. 4). Note that evolutionary branching is favored in situations where the two hosts are equally frequent (not shown) because the density of the less frequent host may reach a threshold below which the parasite density cannot be maintained. Evolutionary branching may also emerge from other processes. For example, Regoes et al. (2000) showed that concave trade-offs between virulence in the two hosts favors coexistence of different virulence strategies. Similarly, in the second evolutionary scenario (i.e., evolution of indirect transmission), concave trade-offs may also favor the coexistence of different transmission strategies. The occurrence of multiple or superinfections (Nowak and May 1994; Gandon et al. 2001b; Pugliese 2002) and variable recovery rates among different hosts (J. B. André and S. Gandon, unpubl. ms.) may also yield evolutionary branching and virulence polymorphism.

In contrast, an increase in the relative amount of between-type transmission favors more generalist strategies. In these situations virulence evolution is relatively independent of the abundance of the two hosts (Fig. 3a) and is mainly governed by within- and between-hosts constraints on parasite life-history traits. Such between-host constraints may select for increased virulence in a given host if it is beneficial in another host. For example Davies et al. (2001) pointed out that the schistosome virulence on snails (the vector) may be a pleiotropic consequence of an increased reproductive output in the mice (i.e., $d\beta_{21}/d\alpha_1 > 0$, Fig. 2C). Between-host trade-offs may also select for lower virulence in some focal host. For example, the high parasite burdens associated with malaria virulence in rodents generate reduced survival in mosquito vectors (Ferguson et al. 2002). Such correlation may impose an extra cost on virulence and thus select for lower virulence strategies in the human host. A laboratory experiment of Ferguson et al. (2003), however, failed to find an overall relation between virulence levels in the different hosts. Nevertheless this interesting hypothesis deserves to be tested in natural populations of human malaria and with other vector-borne diseases. The examples discussed above show that the vector-borne scenario that I considered in the second evolutionary scenario (i.e., no virulence on the vector) is clearly an oversimplification. Even if vectors are classically assumed to suffer weakly from infection, there are multiple examples in which parasites have been shown to reduce vector survival

(Buxton 1935; Turell 1992; Anderson et al. 2000; Davies et al. 2001; Ferguson and Read 2002) or fecundity (Hacker 1971; Elsawaf et al. 1994; Hogg and Hurd 1995, 1997; Ferguson et al. 2003). The analysis of these more complex situations deserves further theoretical investigation.

Transmission Pattern Evolution

Transmission patterns may evolve in response to variation in host heterogeneity. Under the mass action law, when a host is more abundant it becomes more likely to be infected. It may thus be adaptive to evolve higher transmission to host types that are more frequent (Fig. 5). For example, it has been suggested that the evolution of a new route of transmission (direct oral transmissibility between intermediate hosts) in *Toxoplasma gondii* may be due to the human agricultural expansion (Su et al. 2003). The analysis of genetic polymorphism of *T. gondii* revealed that oral transmission ability emerged within the last 10,000 years. Su et al. (2003) thus suggested that this new transmission strategy may have been adaptive in the new environment resulting from the emergence of agriculture and, consequently, the high concentration of cats (definitive host) and other mammals (intermediate hosts). More generally, the dramatic diversity of parasite life-cycles ranging from the exploitation of a single to many different host species could have evolved from very different ecological and epidemiological settings. The extinction of previously exploited host species or the immigration a new host species may drive the evolution of new transmission strategies. Figure 5 illustrates the impact of host demography (i.e., the relative immigration rate of the two hosts) for the evolution of between-host transmission. But other transmission strategies could also evolve. The multihost framework could be used to study the evolution of free-living transmission (e.g. air-borne, water-borne) or trophic transmission (Lafferty 1999; Brown et al. 2001; Choisy et al. 2003; Parker et al. 2003). In particular, this formalism may provide some insights into the evolution of host behavior manipulation to facilitate transmission (Moore 2002).

Another potential use of this framework would be to study the evolution of vertical versus horizontal transmission. It is classically assumed that horizontally and vertically infected hosts are identical (Nowak 1991; Lipsitch et al. 1996) and that transmission evolution is constrained by a trade-off between vertical and horizontal transmission (for empirical evidence of such a trade-off see Turner et al. 1998; Vizoso and Ebert 2004). However, vertically infected hosts, because they are infected earlier in their development, may have much higher parasite density than horizontally infected ones. This may alter both the level of parasite virulence and the transmission efficiency. Vertically and horizontally infected hosts may thus appear to be very different habitats for the parasite. For example, Vizoso and Ebert (2004) studied the interaction between *Daphnia magna* and the microsporidian *Octosporea bayeri*. This parasite can be transmitted both vertically and horizontally, but vertically infected hosts have higher longevity and larger spore load than horizontally infected ones. This demonstrates the need for models that incorporate such between-host heterogeneity to understand the selective pressures acting on the evolution of vertical transmission.

Another interesting example is provided by other microsporidian species in which the level of virulence (and other traits) may be altered not only by the route of transmission, but also by the sex of the infected host. Indeed, male-killing microsporidia such as *Amblyospora* sp. benefit from killing the males through horizontal transmission to the intermediary hosts (various copepode species). When they infect female mosquitoes, however, the same parasite are often avirulent and achieve transmission via the infection of the offspring mosquitoes (Hurst 1991). It would be interesting to analyze models with the two routes of transmission and two host sexes (i.e., with four different types of hosts) to study the emergence of these fascinating conditional virulence behaviors.

Further Theoretical Developments

Transient dynamics

The above framework focused on evolutionary endpoints and therefore assume both epidemiological and evolutionary equilibrium. Ronce and Kirkpatrick (2001) showed how a transient perturbation of the demographic equilibrium may alter the evolutionary outcome (i.e., the level of adaptation to different habitats) in a general quantitative genetics model. With infectious diseases, this equilibrium assumption is likely to be violated in many important situations. For example, emerging infectious diseases which, by definition, acquired recently the ability to infect new host species are likely to be far from their optimal life-history strategy (Woolhouse et al. 2001). In addition, any therapeutic intervention (e.g., vaccination) will affect the prevalence of the disease and the heterogeneity of the host population. These modifications will only reach a new epidemiological equilibrium after several parasite generations. In all these situations, it would thus be more satisfying to develop a dynamical framework allowing follow-up of changes in both prevalence (epidemiology) and various parasite life-history traits (evolution). Day and Proulx (2004) developed a quantitative genetics model for a single-host model and showed how this formalism could be used to predict the instantaneous direction of evolution under different epidemiological situations. This quantitative genetics approach is particularly interesting because it allows us to make evolutionary predictions even if the host-parasite system is far from its epidemiological equilibrium. It would be interesting to extend this framework to multiple host parasites. The power of this approach comes from the possibility of measuring the variance-covariance matrix **G** of parasite populations (Davies et al. 2001; Mackinnon and Read 2003; see also Fig. 2B, C) and thus derive short-term predictions on their life-history evolution (Day 2003; Gandon and Day 2003). Note that this could only yield short-term predictions because **G** is likely to change through time because both the matrix of regression coefficients, **C**, and the additive genetic variance of parasite traits, **V**, may evolve. It would thus be particularly interesting to follow **G** across time and, in particular, after some medical interventions (e.g., vaccination). One potential limit to the quantitative genetics formalism comes from the difficulty arising as soon as the evolutionary equilibrium is not locally and/or globally stable (Abrams 2001).

Host heterogeneities

I focused on the analysis of simple scenarios with only two types of hosts. These black-and-white scenarios are inspired by realistic situations (e.g., vaccinated vs. unvaccinated hosts, human host vs. insect host for vector-borne diseases), but it is important to explore the evolutionary consequences of other sources of host heterogeneity. For example, I discussed above the situation in which vertically and horizontally infected hosts should be considered as two different types of hosts. It is interesting to note that in this situation susceptible hosts are assumed to be identical and host heterogeneity only emerge from the transmission pattern itself. Another example of this type of infection-driven heterogeneity occurs with multiple infections because hosts infected with different numbers of strains could be viewed as different types of hosts (van Baalen and Sabelis 1995).

It would also be interesting to study models with a higher number of different hosts. For example, natural immunity against malaria is slowly acquired in humans. Different age classes are thus associated with different levels of resistance. It may be interesting to explore how a perturbation in the age structure of the host population may affect parasite evolution.

The heterogeneity may also emerge from genetic differences among the host. This would allow host population to coevolve with the parasite. Classical host-parasite coevolutionary models fall between two extreme situations. On the one hand, some models focus on life-history coevolution between a single host and a single parasite (e.g., van Baalen 1998; Gandon et al. 2002a). On the other hand, other models focus on gene-for-gene coevolution between multiple hosts and multiple parasites (Hamilton 1980; Frank 1992). The generalization of the above framework to the coevolution between multihost parasite and multiparasite hosts may allow us to fill the gap between these two extreme cases (for an attempt to mix gene-for-gene coevolution with virulence evolution see Gandon et al. 2002b). Note also that the present framework could be easily modified to study the evolution of a single host infected by several parasites. For example, this extension could be used to study the evolution of various resistance mechanisms. Host evolution depends not only on the direct costs of resistance (e.g., fecundity, survival) but also on the correlated effect of resistance against the different parasites (Fellowes and Kraaijeveld 1998). Like multihost parasites, the evolution of multiparasite hosts will be governed by the matrix of constraints among the different evolving traits involved in the interspecific interaction.

The present framework is based on the assumption that the parasite evolves in a single well-mixed population where heterogeneity occurs between host individuals. It would be interesting to explore the effects of heterogeneities produced at both lower and larger spatial scales (i.e., within host individuals and between host populations). First, the ability to invade new host tissues is analogous to the ability to invade new host types and is often associated with important virulence consequences (Frank and Jeffrey 2001; Meyers et al. 2003). For example, several species of bacteria belonging to the genus *Borrelia* produce antigenic variants that accumulate in the brain, where they can avoid the host immune response and may cause later relapses after the host has cleared the parasite from the blood (Frank 2002). These different tissue tropisms may thus prolong the infection period, increase the total parasitemia, and thus the virulence of the parasite. Second, at a larger spatial scale, host metapopulation structure may also strongly impact on parasite evolution. For example, if the different types of hosts tend to be clustered together (e.g., because of local host dispersal) and if the parasite is transmitted by direct contact, transmission will be more likely to occur between the same types of hosts. This biased transmission pattern will promote the evolution of specialized parasite strategies (Figs. 3, 4). But it is difficult to extrapolate from the simple effect of biased transmission patterns because the emergence of competition among related parasites may strongly affect evolution (e.g., for the analysis of single host models of parasite virulence in space see van Baalen 2002). Spatial structure may also introduce an additional layer of heterogeneity in the host population if the abiotic environment of the host varies in the different populations. Heterogeneity may be produced by phenotypic variations (e.g., increased fecundity and survival in better-quality habitats) but also by genotypic variations if the host is allowed to evolve in the different habitats. The study of host-parasite interactions in metapopulations have shown that both local (e.g., selection within populations) and global processes (e.g., host and parasite migration among populations) govern the ultimate coevolutionary outcome (Thompson 1994, 1999; Gandon et al. 1996; Hochberg and van Baalen 1998; Dybdahl and Storfer 2003; Nuismer and Kirckpatrick 2003). More generally, the integration of the diversity of selection pressures acting at different spatial scales (host tissues, individual host, host type, host population, host habitat, host metapopulation) is a necessary step toward a general theory of the coevolution among multiple parasites and their multiple hosts.

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Appendix 1: Epidemiological Dynamics

The dominant eigenvalue, r, of $\mathbf{m}$ gives the instantaneous growth rate of the parasite population after reaching its stable distribution among the different hosts. In other words, $r > 0$ when the parasite is in an epidemic regime and $r = 0$ refers to an endemic situation where parasite prevalence is stable. However, it is often more convenient to manipulate a per generation growth rate because it gives the number of secondary cases produced by a typical infected host during its entire period of infectiousness. The per generation growth rate, R, is the dominent eigenvalue of the matrix $\mathbf{M} = \mathbf{BD}^{-1}$ that projects the population from one generation to the next (Caswell 2001).

Let us now consider a virgin host population (i.e., with no parasite) at a demographic equilibrium $\hat{\mathbf{x}} = (\hat{x}_1, \hat{x}_2 \ldots, \hat{x}_n)$, where the hat denotes the fact that there are no parasite. In this situation, the dominant eigenvalues r_0 and R_0 of $\mathbf{m}$ and $\mathbf{M}$, respectively, give the ability of the parasite to invade such a virgin host population (i.e., the parasite can invade if $r_0 > 0$ or if $R_0 > 1$).

For example, when there are only two types of hosts (as in the main text):

$$\mathbf{B} = \begin{pmatrix} \beta_{11}x_1 & \beta_{21}x_1 \\ \beta_{12}x_2 & \beta_{22}x_2 \end{pmatrix} \quad \text{and} \tag{A1}$$

$$\mathbf{D} = \begin{pmatrix} \delta_1 + \alpha_1 + \gamma_1 & 0 \\ 0 & \delta_2 + \alpha_2 + \gamma_2 \end{pmatrix}, \tag{A2}$$

and the dominant eigenvalue of $\mathbf{M}$ at $\hat{\mathbf{x}}$ yields equation (2). This method can be generalized to a situation with a higher number of potential hosts for the parasite (Diekmann et al. 1990; Diekmann and Heesterbeek 2000).

The utility of the instantaneous rate of increase comes from the fact that the notion of generation may depend on the type of host. In particular, generations will necessarily overlap when the expected duration of an infection varies among hosts. The stable distribution of the different types of infected hosts can be derived from the dominant right eigenvector $\mathbf{u}$ of $\mathbf{m}$, which yields:

$$\frac{u_1}{u_2} = \frac{y_1}{y_2} = \frac{r + \delta_2 + \alpha_2 + \gamma_2 - \beta_{22}x_2}{\beta_{12}x_2}. \tag{A3}$$

The individual reproductive values of parasites infecting individual hosts of different types can be derived from the dominant left eigenvector $\mathbf{v}$ of $\mathbf{m}$ (or $\mathbf{M}$), which yields:

$$\frac{v_1}{v_2} = \frac{r + \delta_2 + \alpha_2 + \gamma_2 - \beta_{22}x_2}{\beta_{21}x_1} = \frac{R(\delta_2 + \alpha_2 + \gamma_2) - \beta_{22}x_2}{\beta_{21}x_1}. \tag{A4}$$

Note that when the parasite can invade a virgin host population (i.e., $r_0 > 0$ and $R_0 > 1$) the system will ultimately reach an endemic equilibrium where $r = 0$, $R = 1$,

$$\frac{\bar{u}_1}{\bar{u}_2} = \frac{\bar{y}_1}{\bar{y}_2} = \frac{\delta_2 + \alpha_2 + \gamma_2 - \beta_{22}\bar{x}_2}{\beta_{12}\bar{x}_2}, \quad \text{and} \tag{A5a}$$

$$\frac{\bar{v}_1}{\bar{v}_2} = \frac{\delta_2 + \alpha_2 + \gamma_2 - \beta_{22}\bar{x}_2}{\beta_{21}\bar{x}_1}, \tag{A5b}$$

with $\bar{x}_i$ and $\bar{y}_i$ being the equilibrium densities of uninfected and infected hosts of type i, respectively.

Appendix 2: Evolutionary Dynamics

I will focus here on the ability of mutant parasite (with strategies α_i^*, β_{ij}^*, and γ_i^*) to invade a resident parasite population (with strategies α_i, β_{ij}, and γ_i). In principle, it is possible to track the evolution of the parasite population whatever the epidemiological state of the resident population (for nonequilibrium situations see the analyses of Frank 1996; Day and Proulx, in press). However, I focus here on situations where the mutant parasite is introduced in a resident population at its epidemiological equilibrium ($\bar{\mathbf{x}}$ and $\bar{\mathbf{y}}$, see Appendix 1). The logic behind this assumption is that epidemiological dynamics is assumed to be much faster than evolutionary dynamics.

As for the epidemiological analysis, the invasion of a mutant parasite in a resident parasite population may be measured with instantaneous or per generation growth rates. The initial instantaneous rate of increase of the mutant is given by the dominant eigenvalue, r^*, of

$$\mathbf{m}^* = \mathbf{B}^* - \mathbf{D}^* = \begin{bmatrix} \beta_{11}^*\bar{x}_1 - (\delta_1 + \alpha_1^* + \gamma_1^*) & \beta_{21}^*\bar{x}_1 \\ \beta_{12}^*\bar{x}_2 & \beta_{22}^*\bar{x}_2 - (\delta_2 + \alpha_2^* + \gamma_1^*) \end{bmatrix}, \tag{A6}$$

where $\mathbf{B}^*$ and $\mathbf{D}^*$ are analogous to $\mathbf{B}$ and $\mathbf{D}$ but refer to the mutant parasite.

The initial per generation growth rate of a small population of mutant parasite introduced in a resident parasite population (at its endemic equilibrium) is given by the dominant eigenvalue, R^*, of $\mathbf{M}^* = \mathbf{B}^*\mathbf{D}^{*-1}$. For a parasite infecting two types of hosts this yields:

$$R^* = \frac{\beta_{11}^*}{2(\delta_1 + \alpha_1^* + \gamma_1^*)}\bar{x}_1 + \frac{\beta_{22}^*}{2(\delta_2 + \alpha_2^* + \gamma_2^*)}\bar{x}_2 + \left\{ \frac{(\beta_{12}^*\beta_{21}^* - \beta_{11}^*\beta_{22}^*)}{(\delta_1 + \alpha_1^* + \gamma_1^*)(\delta_2 + \alpha_2^* + \gamma_2^*)}\bar{x}_1\bar{x}_2 + \left[\frac{\beta_{11}^*}{2(\delta_1 + \alpha_1^* + \gamma_1^*)}\bar{x}_1 + \frac{\beta_{22}^*}{2(\delta_2 + \alpha_2^* + \gamma_2^*)}\bar{x}_2 \right]^2 \right\}^{1/2} \tag{A7}$$

Both r^* and R^* can be used to study the evolution of any parasite's trait (here I only give R^* to facilitate comparison with eq. 2). However, a convenient alternative to the derivation of r^* and R^* is provided by the use of w^*, which is defined in equation (7). Note that there is another fitness function, W^*, which can be derived from $\mathbf{M}^*$, as w^* is derived from $\mathbf{m}^*$. The fitness function w^* presents the advantage that it decouples selection and parasite class reproductive values in the different hosts (see Discussion in the main text).