Evolution, 57(7), 2003, pp. 1489–1497

WITHIN-HOST PARASITE DYNAMICS, EMERGING TRADE-OFF, AND EVOLUTION OF VIRULENCE WITH IMMUNE SYSTEM

JEAN-BAPTISTE ANDRÉ,[1,2] JEAN-BAPTISTE FERDY,[1,3] AND BERNARD GODELLE[1,4]
[1]*Laboratoire Génome, Populations, Interactions, Adaptation, UM2-IFREMER-CNRS UMR 5000, Université Montpellier II-CC 063, Bâtiment 13, RdC, Place Eugène Bataillon, 34095 Montpellier Cedex 5, France*
[2]*E-mail: jbandre@crit.univ-montp2.fr*
[3]*E-mail: ferdy@crit.univ-montp2.fr*
[4]*E-mail: godelle@crit.univ-montp2.fr*

Abstract.—Virulence is an evolutionary paradox because parasites never benefit from their host's death. The adaptive explanation of virulence is classically based upon the existence of physiological constraints that create a trade-off between parasites' epidemiological traits (virulence, transmissibility, and clearance). Here we develop an epidemiological model where infections are dynamic processes and we demonstrate how these dynamics generate a trade-off between emerging epidemiological parameters. We then study how host's immune strength modifies this trade-off and hence influences virulence evolution. We found that in acute infections, where parasites are engaged in a race with immune cells, immunity restrains more the duration of the infection than its intensity. As a consequence parasites evolve to provoke more virulent but shorter infections in strongly immunized hosts.

Key words.—Acute infections, evolution of virulence, microparasites, specific immunity, trade-off, within-host models.

Received November 8, 2002. Accepted February 11, 2003.

Predicting the evolution of parasites' virulence is both a scientific challenge and a major public health concern. Virulence per se, here defined as the pathogen-induced host mortality, first appears as paradoxical for evolutionists, because killing the host decreases parasite transmission (Anderson and May 1979; May and Anderson 1979). The main interpretation of virulence is thus based on physiological constraints: virulence is selected as a side-effect of selection for other parasite traits, primarily high transmissibility and/or resistance to host's immunity (Anderson and May 1982; Antia et al. 1994; Antia and Lipsitch 1997; van Baalen 1998; Gandon and Michalakis 2000; Gandon et al. 2001a,b; Ganusov et al. 2002). As the base of these constraints, the physiology of host-parasite interaction is therefore a key feature shaping the parasite's evolutionary stable (ES) virulence.

The immune system is a central element in the physiology of host-parasite interaction; understanding its influence on virulence evolution is therefore crucial. A major prediction in this field is that ES virulence increases with host's recovery rate (Frank 1996; van Baalen 1998). This is because the benefit of low virulence—longer infectious period—is reduced by the risk of immune clearance. However, this occurs when clearance is assumed to be determined solely by the host, whereas the clearance rate of an infection depends on both host's and parasite's features (see Restif and Koella 2003). Empirical data on myxoma virus (Fenner and Ratcliffe 1965) as interpreted by Anderson and May (1982) are, on this point, very enlightening. Several field-collected viruses have been tested for virulence and clearance against a standard laboratory strain of rabbit. There is variability for clearance, and a significant negative correlation is found with virulence: the more virulent a virus is, the better it resists immunity.

In a recent paper Gandon et al. (2001b) built a model where both host's immunity and parasite's strategy control all infectious epidemiological traits: transmissibility, virulence, and clearance. This model is still phenomenological however, with physiology considered as a black-box. The trade-offs relating epidemiological traits to host's and parasite's characteristics are assumed a priori, which is always somehow arbitrary. For instance, studying the evolution of virulence when vaccines designed to reduce pathogen growth rate are used (so-called r_2 vaccines), Gandon et al. (2001b) assumed that all epidemiological traits are affected proportionally by the vaccine so that the trade-off between them is not changed, which might not be true.

However, making realistic assumptions regarding the effect of both parasite and immunity on infectious traits is impossible in a model giving general results such as that of Gandon et al. (2001b). This can only be done by building mechanistic models in precise infectious situations. In this context, the within-host parasite dynamics are a key feature of infections and must be considered. Antia et al. (1994) developed such an explicit model. They studied the case of microparasites interacting with a specific immune system. For simplicity and to keep the model tractable, Antia et al. (1994) assumed a lethality threshold: host mortality is infinite above a given parasite density and negligible below this threshold. These authors predict that optimal parasite should replicate as fast as possible but without ever attaining the lethal density (Antia et al. 1994). Because they assume a lethality threshold, the ES virulence (parasite induced host mortality) in their model is always zero whatever be the host's immune strength. This model can therefore predict the evolution of a major parasite life-history trait, such as replication rate, but not of virulence per se.

Antia and Lipsitch (1997) and Ganusov et al. (2002) prolonged this model by incorporating variation between hosts regarding vulnerability to the parasite. Because of their heterogeneity, the parasite cannot adjust its replication rate to every host; hence, at evolutionary equilibrium, it is still lethal to a fraction of the host population. Virulence is here maintained by maladaptation, increasing with the amount of host heterogeneity (Ganusov et al. 2002).

Still, maladaptation due to host heterogeneity cannot generally be the only reason for maintaining virulence. Hence one should relax the hypothesis of a lethality threshold and build models with continuous mortality. This would allow the study of the evolution of virulence per se when it is determined by within-host parasite dynamics. Gilchrist and Sasaki (2002) developed such a model of dynamic infections with host mortality increasing continuously with parasite density. However, they focus on the coevolution of parasite's traits and host's immunity and do not follow the evolution of virulence. In this purpose they assume that growth rate of immunity is strictly proportional to within-host parasite density, which is unlikely for acute infections in which parasites attain very high densities. They also assume that the duration of infections is a constant (assumed infinite in mathematical derivation), but infection's duration should depend largely on parasite and host traits, which makes immune clearance controlled by both partners. Finally the model of Gilchrist and Sasaki (2002) is not actually suitable for the study of virulence evolution.

We ultimately aim to deal with the question of how virulence evolves in response to host's immune system, by developing a model of microparasitic infections with explicit within-host dynamics. We will consider that host mortality and parasite transmissibility increases continuously with within-host parasite density. We will consider that infection is cleared when within-host parasite density falls below a threshold. Virulence, transmissibility, and clearance will hence be controlled by within-host dynamics and thus by both interacting partners. A precise model of parasite-immunity interaction will be introduced when needed, based upon previous work by Antia et al. (1994).

We will finally discuss how our model of continuous mortality relates to models with lethal threshold but host heterogeneity (Antia et al. 1994; Antia and Lipsitch 1997; Ganusov et al. 2002) and how, asking different questions as ours these authors bring up the same mechanisms.

Methodology: The Model

We assume that (1) within-host parasite density varies over time after infection's initiation; (2) if it does not die, the host ultimately eliminates the parasite a time T after infection's initiation (i.e., immune clearance is deterministic); and (3) infection's instantaneous virulence and transmissibility are both continuous functions of the within-host parasite density and therefore vary over time (see also Sasaki and Iwasa 1991; Day 2001; Gilchrist and Sasaki 2002).

The model has two nested integrated levels, as previous work by Gilchrist and Sasaki (2002). The first level is the host that contains a population of parasites. The dynamics of that population depends on parasite replication and on the strength of the immune system. The second level is the population of hosts, with epidemiological dynamics due to parasite transmission from infected to uninfected hosts, host death, and immune clearance.

We first build a general epidemiological model that can apply to any infection of which transmissibility and virulence vary over time after initiation and of which clearance is deterministic. We then define the relationship between within-host density and both transmissibility and virulence of the infection. Finally, when necessary we define the physiological determinism of within-host parasite dynamics.

Table 1. Parameters for the epidemiological model.

$Y(t)$	density of infected hosts in the population at time t
$X(t)$	density of uninfected hosts in the population at time t
$\beta(\tau)$	transmissibility of an infection at stage τ (i.e., a time τ after initiation of infection)
$m(\tau)$	mortality rate of an infection at stage τ
μ	mortality rate of an uninfected host
T	maximum duration of an infection (i.e., infection's duration if the host does not die)
$\bar{\beta}$	expected transmissibility of a random infection in the population
$\bar{m}$	expected mortality rate of a random infection in the population
$\bar{\alpha}$	expected virulence of a random infection in the population
$\bar{\gamma}$	expected clearance of a random infection in the population
$\bar{D}$	expected duration of an infection
$\sigma(\tau)$	probability that the host is still alive at time τ after initiation of infection
σ_T	stands for $\sigma(T)$
P_{kill}	stands for $1 - \sigma(T)$

The host population is supposed to be infinite, transmission purely horizontal and coinfections and superinfections are assumed to be rare and are therefore ignored. The model is valid under the condition that infections are short relative to the time scale of epidemiology (transmission). This restriction is also required in previous models (see Antia et al. 1994; Gilchrist and Sasaki 2002).

Epidemiological Model of Host Population

Epidemiological parameters

We derive three epidemiological parameters emerging from any dynamic infection with deterministic clearance (see Appendix, Table 1).

Average transmissibility is:

$$\bar{\beta} = \frac{\int_0^T \beta(\tau)\sigma(\tau)\, d\tau}{\bar{D}}, \tag{1}$$

average virulence is:

$$\bar{\alpha} = \frac{1 - \sigma_T}{\bar{D}} - \mu, \tag{2}$$

and average clearance rate is:

$$\bar{\gamma} = \frac{\sigma_T}{\bar{D}}, \tag{3}$$

where τ is the infectious stage (i.e., the time since infection's initiation), $\beta(\tau)$ is the parasite transmissibility at stage τ, μ is the natural host mortality, and T is the maximum duration of infection (i.e., the time at which immune clearance occurs). $\sigma(\tau)$ is the probability of a host surviving to stage τ and is derived in the Appendix (eq. A2). σ_T stands for $\sigma(T)$, the probability of a host surviving until clearance. $\bar{D} = \int_0^T \sigma(\tau)\, d\tau$

TABLE 2. Parameters for the instantaneous trade-offs models.

b	transmissibility of one parasite unity
ν	unitary virulence of parasite (linear model)
u	proportionality parameter relating parasite replication rate to unitary virulence (activity-based model)
φ	strength of the effect of replication rate on unitary virulence (activity-based model)

is the expected duration of an infection, the infection being stopped either because of host death or immune clearance.

The three parameters $\bar{\beta}$, $\bar{\alpha}$, and $\bar{\gamma}$ sum up the epidemiological properties of the dynamic infection at equilibrium stage structure. They are strictly equivalent to parameters used in constant models of infection. We will refer to them as the ''integrative epidemiological'' parameters or simply ''average'' parameters of the parasite strain.

Epidemiological model

The density variation of infected hosts $Y(t)$ can finally be derived by summing every cause of change:

$$\frac{dY}{dt} = \bar{\beta}XY - (\mu + \bar{\alpha})Y - \bar{\gamma}Y, \tag{4}$$

where X and Y are the density of susceptible and infected hosts in the population at time t, respectively.

Under the hypothesis that a mutant population of infections attains its stable stage structure before affecting the density of susceptible hosts (condition of fast within-host dynamics, relative to epidemiology), an invasion analysis is performed from equation (4) as in constant models of infection (see for example Anderson and May 1982). A parasite strain is evolutionary stable only if the parameter $B = \bar{\beta}/(\mu + \bar{\alpha} + \bar{\gamma})$ is maximized. B is the per-host transmission factor of the infection, that is, the expected number of new infections initiated by an infected host in a population where there would be constantly one susceptible host (van Baalen and Sabelis 1995). From equations (1), (2), and (3), B is simplified to:

$$B = \int_0^T \beta(\tau)\sigma(\tau)\, d\tau. \tag{5}$$

This expression of B in a dynamic infection has been directly derived by Sasaki and Iwasa (1991), Antia et al. (1994), Day (2001), and Gilchrist and Sasaki (2002).

Instantaneous Trade-offs

We now define how to compute transmissibility and host's mortality at any stage of infection as a function of parasite density at this stage. By this way, we explicitly show how any change in transmissibility is linked to a change in host mortality, therefore defining the instantaneous trade-off between these two epidemiological parameters. Our model applies to any kind of such trade-off, we actually studied two possibilities. Parameters are listed in Table 2.

Trade-off 1: Linear model

Virulence and transmissibility linearly increase with parasite density:

TABLE 3. Parameters for the within-host dynamics model.

r	within-host parasite replication rate
ρ	replication rate of immune cells
k	killing rate of parasite by immune cells
$P(\tau)$	within-host parasite density at stage τ
$I(\tau)$	density of active immune cells at stage τ
P_0	parasite density at initiation of infection
I_0	density of immune cells at initiation of infection
P_M	maximum parasite density ever attained in the host

$$\beta(\tau) = bP(\tau) \quad \text{and} \tag{6a}$$

$$m(\tau) = \mu + \nu P(\tau), \tag{6b}$$

where b is the transmissibility of one parasite unity and ν is the host mortality induced by such unity (ν is called the ''unitary'' virulence and is a fixed constant).

Trade-off 2: Activity-based model

This model is equivalent to the previous one, with the additional hypothesis that parasite unitary virulence, ν, is dependent on replication rate:

$$\beta(\tau) = bP(\tau) \quad \text{and} \tag{7a}$$

$$m(\tau) = \mu + ur^{\varphi}P(\tau), \tag{7b}$$

where u is a proportionality constant (see also Gilchrist and Sasaki 2002) and φ is positive and measures the strength of the effect of replication rate.

Infection Dynamics

The infection dynamics allow us to derive parasite and immune system density as a function of time since the beginning of infection (parameters listed in Table 3). Parasites and immune cells both replicate within the host. The parasites are killed at a constant rate by immune cells. In early stages of infection parasite density is low, the immune system not fully activated, and immune cells' replication rate depends on parasite density. However rapidly, for an acute infection parasite density reaches a threshold above which immune system is fully activated and immune cells replicate at maximum rate ρ. This full-activation threshold can reasonably be expected to be orders of magnitudes smaller than the maximum parasite density (Antia et al. 1994). Neglecting the short low-activation stages leads to the following pair of differential equations:

$$\frac{dI}{d\tau} = \rho I \quad \text{and} \tag{8a}$$

$$\frac{dP}{d\tau} = rP - kIP, \tag{8b}$$

where P and I are the densities of parasites and immune cells respectively, r and ρ their respective replication rates, and k the rate at which immune cells kill parasites.

Equations (8a,b) integrate into:

$$I(\tau) = I_0 e^{\rho\tau} \quad \text{and} \tag{9a}$$

$$P(\tau) = P_0 \exp\left[r\tau + \frac{kI_0}{\rho}(1 - e^{\rho\tau})\right]. \tag{9b}$$

The unity is defined so that $I_0 = 1$ and therefore k represents the killing efficiency of immune system at initiation. The end of the infection is defined as the time when parasite density decreases below its initial value, P_0.

Numerical Computations

Within-host parasite density is given by an explicit formula as a function of infectious stage τ (eq. 9b). From that value we calculate instantaneous virulence and transmissibility as a function of time using a given instantaneous trade-off (trade-off 1 or 2). The maximum duration of infection (T) is derived by solving numerically the equation $P(\tau) = P_0$. Survival probability $\sigma(\tau)$ for all infectious stages $\tau \in [0, T]$ is evaluated numerically with equation (A2) of the Appendix. Parameters $\bar{\beta}$, $\bar{\alpha}$, $\bar{\gamma}$, and B are then computed according to corresponding equations (respectively, eqs. 1, 2, 3, 5). All integrations and maximizations are performed numerically.

RESULTS

Linear Trade-Off

This case is analyzed with no reference to any particular infectious dynamics. Recalling that $\beta = bP$ and $m = \mu + \nu P$ and using $d\sigma = -m\sigma d\tau$, we have $bP\sigma d\tau = (b/\nu)(d\sigma + \mu\sigma d\tau$ and equation (5) therefore simplifies to:

$$B = \frac{b}{\nu}\left[\int_{\sigma_T}^{1} d\sigma - \mu \int_0^T \sigma \, d\tau\right]$$

$$= \frac{b}{\nu}(1 - \sigma_T - \mu\bar{D}) = \frac{b}{\nu}P_{kill}, \qquad (10)$$

where σ_T is the probability that the host is still alive at the end of the infection, $\mu\bar{D}$ is the probability that the host dies from natural causes during the infection, and $P_{kill} = 1 - \sigma_T - \mu\bar{D}$ is the probability that the host dies because of the parasite. B is the per-host transmission factor, a trait that is maximized by selection.

If host's natural mortality is negligible, equation (10) becomes $B = (b/\nu)(1 - \sigma_T)$. A greater parasite replication rate (r) decreases σ_T in all realistic cases, because it increases both infection duration (T) and parasite density at any stage. Therefore B always increases with r and the optimal replication rate is the maximum possible. This is not true when infection duration becomes very large ($T \to +\infty$), because then σ_T approaches zero and therefore $B \to b/\nu$ and does not depend anymore on the infection dynamics.

If host's natural mortality is not negligible, the effect of r cannot be found analytically. Equation (5) is numerically evaluated, in the case of acute infection (with eqs. 9a,b). Under these conditions, we found that B always increases with r (results not shown).

Activity-Based Trade-Off

Here we consider that $\beta = bP$ as previously and $m = \mu + ur^{\varphi}P$ (parasite unitary virulence depends on replication rate). Neglecting host's natural mortality and using equation (10) with $\nu = ur^{\varphi}$ gives:

$$B = \frac{b}{ur^{\varphi}}(1 - \sigma_T). \qquad (11)$$

As in the linear model, a greater r decreases the probability of host survival at the end of infection (σ_T), which increases B. But the ratio of transmission over virulence of each parasite unity is a decreasing function of r. Therefore, increasing r lessens the efficiency of host exploitation. In the acute infection model, $(1 - \sigma_T)$ can be evaluated numerically and plotted as a function of r. B, which is proportional to the ratio $(1 - \sigma_T)/r$, is maximized, and hence parasite replication rate optimal, when the tangent to the curve passes through the origin (see Fig. 1a).

As shown in Figure 1b, the host survival when the parasite is at ESS (σ_T^*) increases with the cost of high replication rate (φ). A qualitatively identical result is obtained when the proportionality constant u increases (not shown). When the cost of intense host exploitation is strong, the advantage of exploiting more completely the host is rapidly counterbalanced. Hosts are therefore incompletely exploited and their survival is higher at an optimum.

We can also show the effect of parasite replication rate in a more classical way. The infection average transmissibility ($\bar{\beta}$) and overall rate of stop (virulence plus clearance $\bar{\alpha} + \bar{\gamma}$) are evaluated numerically in the acute infection model for various parasite replication rate (see Fig. 1c). Parasite strategy is optimal when $B = \bar{\beta}/(\bar{\alpha} + \bar{\gamma})$ is maximum, that is, when the tangent to the curve passes through the origin (van Baalen and Sabelis 1995). $\bar{\beta}$ always increases with r, which benefits the parasite. However, because $\bar{\gamma}$ always decreases and $\bar{\alpha}$ always increases with r, the effect of r on the denominator $\bar{\alpha} + \bar{\gamma}$ is not monotone. $\bar{\alpha} + \bar{\gamma}$ decreases for low values of r, because the effect on clearance is the strongest and increases for high values of r, because then the effect on virulence is the most important.

In Figure 1d, B is represented as a function of r. A maximum is attained for an intermediate value of r. Classically, such an optimal strategy is possible only if some saturating relationships are supposed. Here no saturating relationship has been a priori supposed and the result is a natural consequence of within-host dynamics and of activity-based trade-off.

We are now able to compare various situations differing by the host properties. For a given set of parameters, the optimal parasite replication rate can be found numerically by maximizing B (eq. 11) and the optimal virulence (the average virulence when replication rate is optimal) can be derived. Optimal virulence is plotted in Figure 2a as a function of host's immune cells replication rate (ρ). Optimal virulence is increasing with ρ. The effect of immune killing efficiency (k) is shown in Figure 2b: the optimal virulence is also higher when k increases. The effect of initial immune cells density (I_0) is not distinct from the effect of k, because both parameters only intervene as a product of each other. The initial killing efficiency of immune system (kI_0) is the single relevant parameter.

The effect of immune system is also shown on Figure 2c. For various replication rate of immune cells we plotted the expected duration of infections ($\bar{D}$) as a function of the average virulence ($\bar{\alpha}$), along with the hyperbola representing $\bar{D}$

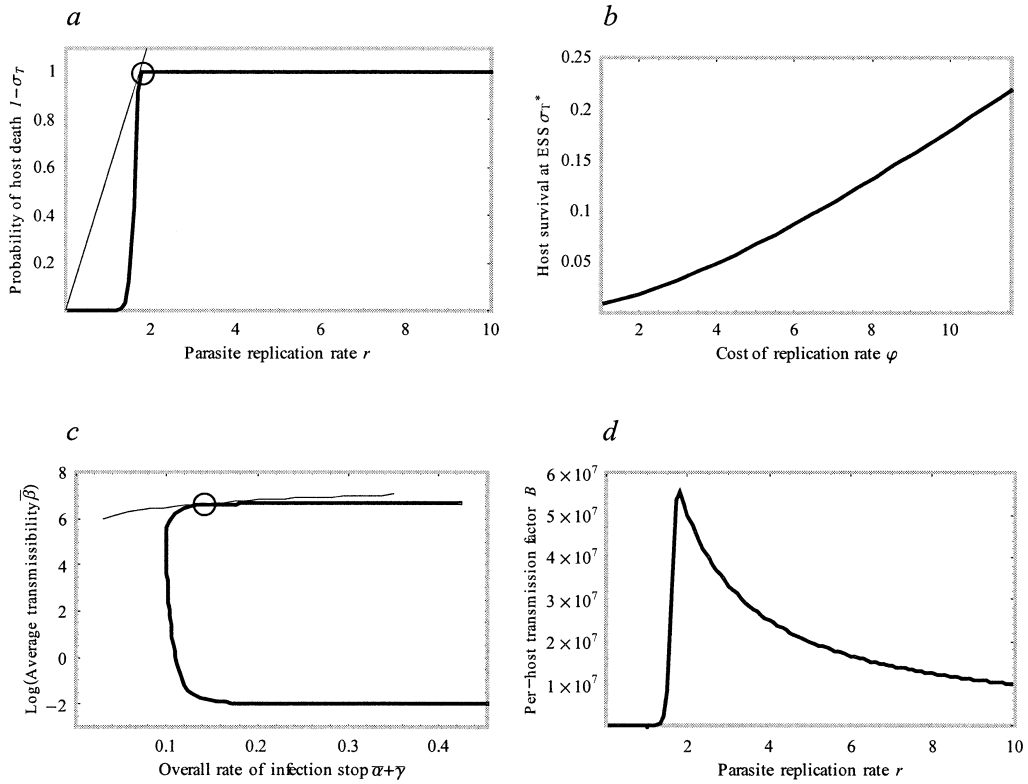

FIG. 1. (a) Probability of host death because of infection ($1 - \sigma_T$), evaluated numerically as a function of parasite replication rate in the activity based model with acute infection dynamics. The optimal replication rate is where the tangent passes through the origin. Replication rate of immune cells $\rho = 1$; initial killing efficiency of immunity $k = 10^{-3}$; transmissibility of one parasite unity $b = 10^{-2}$; constant relating replication rate to unitary virulence $u = 10^{-10}$ and $\varphi = 1$; natural host mortality $\mu = 0$. (b) Optimal probability of final host survival (i.e., host survival in infections with optimal replication rate), plotted as a function of the virulence cost of replication rate. All parameters are as in Figure 1a, except φ varies from 1 to 11.5. (c) Average transmissibility of parasite ($\bar{\beta}$), plotted on a log scale as a function of the overall rate of infection stop (clearance $\bar{\gamma}$ plus virulence $\bar{\alpha}$). The optimal strategy is reached where the tangent passes through the origin. All parameters are as in Figure 1a. (d) Per-host transmission factor of parasite, plotted as a function of replication rate. The optimal replication rate is for the maximum of B. All parameters are as in Figure 1a.

$= 1/\bar{\alpha}$. If virulence is high, the host always dies before clearance ($\sigma_T = 0$) and the infection duration is only controlled by virulence ($\bar{D} = 1/\bar{\alpha}$, see eq. 2): the host exploitation is complete. If virulence is low, the infections may stop also by clearance and are therefore shortened ($\bar{D} < 1/\bar{\alpha}$): the host exploitation is incomplete. The difference between $\bar{D}$ and $1/\bar{\alpha}$ is therefore due to clearance and represents unexploited host resources. As shown by Figure 2c, when immune cells replicate faster, virulence has to be higher for the same quantity of unexploited resources.

A more classical way to understand this same effect is shown in Figure 2d. Using the acute infection model, we plotted the average virulence of infection ($\bar{\alpha}$) as a function of their average clearance ($\bar{\gamma}$) for various immune strength. When immune strength is higher, the infection is more virulent for the same clearance. Higher immune strength modifies the emergent trade-off in the direction of a larger virulence.

This effect can be explained on the basis of infection physiology. In Figure 2e we show infection dynamics for various host and parasite parameters. When replication rate of immune cells increases, by replicating faster parasites can compensate for the height of the infectious peak (P_M), while the duration of infection (T) keeps strongly limited.

In Figure 2f we plot the parasite sojourn time (T) as a function of the maximum density attained in the host (P_M) for various ρ. Immune strength affects the trade-off between T and P_M: when ρ is higher, the sojourn time is lower for the same maximum parasite density. As a consequence, the expected infection duration ($\bar{D}$) is lower for the same average virulence ($\bar{\alpha}$; see Fig. 2c, d), which finally leads to the effect shown in Figures 2a, b.

DISCUSSION

This paper dealt with the evolution of infectious properties, when parasite within-host dynamics based on physiology are taken into account. We built a two-level model, where within-host parasite dynamics are integrated into an epidemiological framework.

We first showed that host survival at the end of infection represents a lost resource for the parasite, a life-point of the

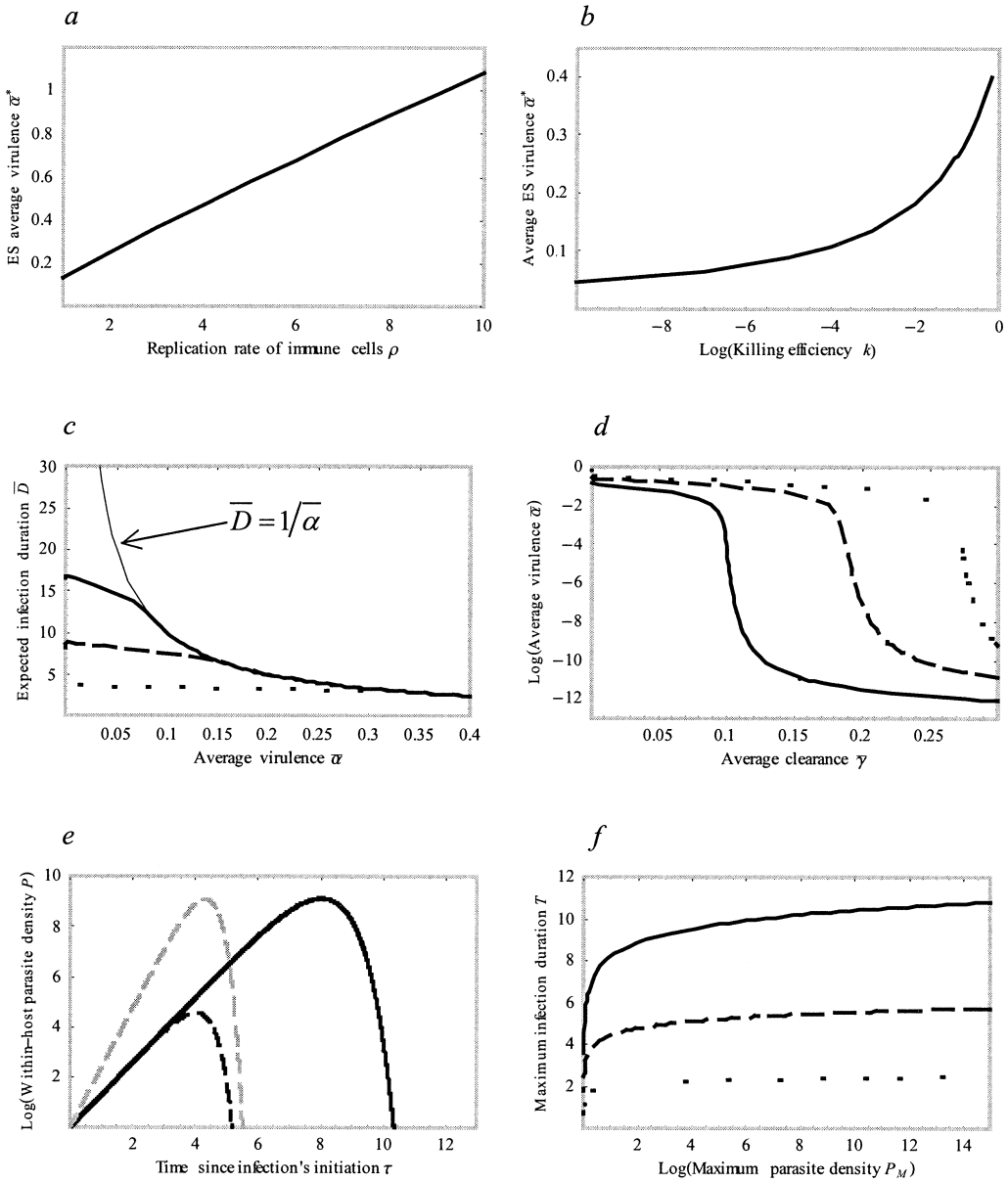

FIG. 2. (a) Optimal average virulence (i.e., average virulence of infections with optimal replication rate), plotted as a function of immune cells' replication rate, ρ. All parameters are as in Figure 1a, except ρ varies from 1 to 10. (b) Optimal average virulence, plotted as a function of the logarithm of immune cells' killing rate, k. All parameters are as in Figure 1a, except k varies from 10^{-10} to 0.7. (c) Expected duration of infection, $\bar{D}$, plotted as a function of average virulence, $\bar{\alpha}$. All parameters are as in Figure 1a, except ρ is equal to 1 (solid line), 2 (dashed line), or 5 (dotted line). The thin line is the ensemble of points where $\bar{D} = 1/\bar{\alpha}$. (d) Logarithm of average infection virulence plotted as a function of average clearance. All parameters are as in Figure 2c. (e) Logarithm of within-host parasite density (P) as a function of infectious stage (τ). Initial killing efficiency of immunity $k = 10^{-3}$. Immune cells replication rate $\rho = 1$ and parasite replication rate $r = 3$ (solid black line); or immune cells replication rate $\rho = 2$ (dashed lines) and parasite replication rate $r = 3$ (black) or 5.5 (gray). (f) Maximum sojourn time of parasite in the host plotted as a function of the logarithm of maximum parasite density. All parameters are as in Figure 2c.

host that has not been converted into transmission. If the two relationships linking parasite density to transmission and virulence are both linear and not depending upon parasite replication rate, then the parasite will evolve to minimize host survival, that is, maximize host exploitation, regardless of the form of infection dynamics. In this case physiology of infection may limit host exploitation to an upper attainable bound. For instance, parasite replication rate itself could be limited to a maximum; or high parasite density could activate replication of immune cells, making it impossible for the

parasite to increase density above a maximum (see Gilchrist and Sasaki 2002).

In more realistic analyses, we introduce a cost of infection's intensity: the unitary virulence of parasite is supposed to increase with replication rate, which makes the host exploitation efficiency (the ratio transmission/virulence) decrease with parasite replication rate. We also tested the effect of different kinds of costs of intense exploitation, mediated by parasite density and not replication rate (the ratio transmission/virulence decreases with parasite density). All the results of the paper are valid in both cases (not shown).

A numerical treatment of the model—in the case of acute infections—shows that optimal parasites have intermediate replication rate with resultant intermediate virulence and that they do not necessarily kill their host. The host exploitation is therefore incomplete at ESS (host may not be killed) because of the cost of intense infection. The stronger is the cost of intensity, the larger will be the probability of host survival at ESS (see Fig. 1b).

We also show that, in any case of dynamic infection, some average epidemiological parameters reflecting global infectious properties can be derived, they are strictly equivalent to those used in constant models of infections. We show that the trade-off between these parameters is emerging from physiology and that it determines the ES parasite strategy. Therefore, paradoxically, simple models involving three constant epidemiological parameters can be seen as taking into account the dynamics and physiological aspects of infections, providing the true relationships between the parameters are mimicked through adequate artificial trade-off.

The next step was to compare the optimal infectious properties obtained with different host immune strength. Numerical evaluation shows that, in acute infections, parasite will evolve to provoke more virulent and shorter infections when host's immune system is stronger, that is, immune cells replicate faster or kill the parasite more efficiently.

This classical effect of immune strength is usually understood as a response of parasite to a precarious environment due to imminent clearance. However, this effect is not so trivial here and requires a more extensive analysis. When confronting stronger immunity, the parasite actually has two co-occurring responses: (1) developing resistance to immunity by undertaking a race with immune cells; and (2) becoming more virulent by replicating faster (to compensate for the risk of clearance). These two responses are, at the same time, conflicting and interrelated—conflicting because if the parasite really resists immunity and recovers a low clearance rate, then it does not need to be more virulent any more, but interrelated because resistance to immunity is mediated by faster replication, which implies higher virulence.

Conclusively if ES virulence increases with immune strength in acute infections, it is merely because immunity affects the trade-off faced by the parasite. As shown by Figure 2d, when immunity is stronger the virulence is higher for a given clearance. This particular effect of immunity is specific to acute infections. Due to its exponential growth with constant killing efficiency of each cell, the immune system's total killing rate gets very high along the infection, and at some point it is difficult for the parasite to ensure a positive net reproduction. Mathematically, the time of parasite decline (time of infectious peak) can be shown to increase only with the logarithm of parasite replication rate. Therefore, the parasite can only improve relatively narrowly the infection's duration (see Fig. 2f). Conversely, in the first stages of the infection parasite density is almost solely controlled by parasite replication rate because immune response is virtually absent. Therefore, the parasite can increase strongly its density by replicating faster (see Fig. 2f). As a consequence, when immunity is stronger infectious peak must be higher for a given parasite sojourn time. Briefly, in acute infections immunity limits more the duration than the intensity of infection; as a consequence, ES virulence increases with immune strength.

However, this effect of immunity on the trade-off should not be universal and might actually be the reverse: infection less virulent for a given clearance, when immunity is stronger. This might happen if the immune system attenuates more than eradicates the infection, and this should lead to a reduction of ES virulence as an adaptation to stronger immunity. One could think of situations where the immune system specially limits parasite density in some particularly crucial niches, such as blood, but is unable to eradicate parasite from other niches where it is less harmful; or where a parasite responds to immunity more by hiding than by escalating conflict (for a review of parasite response to immunity, see Antia and Lipsitch 1997). For instance bacteria of the genus *Mycobacterium* respond to immunity by replicating very slowly and having a dormant hidden stage (Antia et al. 1996). Their infections are typically long lasting and moderately virulent. They constitute an adaptation to immunity in their particular physiological niche.

The two-directional effect of immunity discussed here must be compared with the results of Gandon et al. (2001b) that show that vaccination (host immune status) can also have both effects on parasite evolution. However, the effects studied by these authors are of totally different nature. The use of r_2 vaccines yields an increased ES virulence in Gandon et al. (2001b), but it is because virulence is measured in nonvaccinated hosts: when parasites become adapted to vaccinated they get more virulent in nonvaccinated hosts. However, if the host population was monomorphic, the optimal virulence would be unaffected by vaccination, because parasites can perfectly compensate for it. Host polymorphism maintains the increased virulence such as found by Ganusov et al. (2002). In contrast, in this paper we show that in acute infections parasites cannot compensate for increased immune strength because the trade-off is modified.

Gilchrist and Sasaki (2002) developed a model of dynamic infections with continuous mortality such as ours. However, they assume immune growth rate to be strictly proportional to parasite density. We make the opposite assumption of a constant growth rate, more relevant for acute infections. They also assume a complete linearity in parasite transmission. We consider no transmission (infection stops) when parasite density drops below a threshold, which occurs at a time depending on dynamics. As a consequence, in Gilchrist and Sasaki (2002) it may be adaptive for the parasite to have no replication rate when immune system is strong. This is not reasonable in acute infections, where a parasite keeping its

density below its initial value (no replication) would be eliminated very rapidly from the host.

In the domain of within-host models, our work is strongly connected to the work by Ganusov et al. (2002), who studied the evolution of acute infections in a heterogeneous host population, in the case where host death occurs deterministically with a lethality threshold. The constraints undergone by parasites are indeed the same in their work: parasites must replicate fast to transmit and guarantee a long infectious period, but not too fast to limit the risk of host death. However, in Ganusov et al. (2002), the risk of host death is due to host heterogeneity: a given parasite will definitely kill some hosts, while never killing more resistant ones. In our model, the risk to kill the host is a stochastic death of all hosts occurring along the infection. The hazard of death occurring for every host in our model is present in Ganusov et al. (2002) through the randomness of host-parasite association. Therefore, our results cannot strictly be compared to that of Ganusov et al. (2002), but they are analogous: the continuous mortality of our work can be seen as equivalent to the host heterogeneity of Ganusov et al. (2002). The two main results we obtained in this paper have analog in a heterogeneous host model with lethality threshold. First, the effect of immune strength on optimal virulence in acute infections might be the same in both models (even if it was not analyzed by Ganusov et al. 2002): if immune system is stronger, physiology is constrained so that parasites are forced to take more risk to kill their host, which is true whatever mediates this risk: stochastic host death or host heterogeneity. Second, host survival at the end of infection is a lost resource for the parasite and is possible at ESS only if infection's intensity is costly because of a nonlinear relationship between virulence and transmission. In the model of Ganusov et al. (2002), this nonlinear relationship (the cost of infection's intensity) lies in the nonuniform distribution of host parameters. At some point, when the parasite increases its replication rate, it increases suddenly the proportion of hosts it can kill, which is not adaptive. Ganusov et al. (2002) show that the probability of host survival at ESS increases with the aggregation of the distribution (analogue to Figure 1b of this work). The extreme case is when host parameters are totally aggregated (hosts are all identical) and host survival is therefore certain at ESS (Antia et al. 1994). Therefore, although asking different questions, the analysis of Ganusov et al. (2002) is profoundly related to ours.

An important assumption of our model is that immune cells' growth rate is constant, while, obviously, immunocytes' replication should be activated by parasite density. Our approximation is justified by the fact that immunocytes have a maximum replication rate, which is attained for parasite densities measuring orders of magnitude smaller that the maximum parasite density attained in most infections. Hence, the infectious stages where parasite density is low and immune cells replicate slower than maximum can be neglected. This assumption would be violated if parasites remained long at low densities, as a strategy to hide from immunity. However, we argue here that such a strategy is most probably impossible. First, the parasite cannot have a low and constant replication rate. Because, even if slowly, immune cells always increase in density and would rapidly eradicate the infection. Second, it is possible that the parasite might have a low replication rate at initiation to delay the activation of immunity and instigate the acute phase when appropriate. This does not seem realistic either, however, because of the asymmetry of parasite-immunity interaction, each moment the parasite waits before escalating the conflict is an occasion for immunity to enforce. Therefore, the best strategy for the parasite seems to be to escalate the race as soon as possible and provoke an immediate acute infection.

The assumption of exponential growth of immunity would hence fail only in very different within-host models, with an advantage for the parasite to remain at low densities. Two neglected mechanisms could intervene. Parasites could be able to destroy immune cells, which would break the asymmetry with immunity, rendering a delaying strategy plausible; or parasites could have a refuge niche, somehow protected from immunity, with a consequent eventual hiding strategy. Certainly our model does not apply if the parasite can escape immune suppression by the generation of antigenic variants. Conclusively, our model is relevant for acute infections in a rather general way. However, it should not be extended to all infections, especially if parasites can maintain for a long time at low density. Different models of within-host physiology are needed in these cases.

Acknowledgments

We specially thank D. Roze for interesting suggestion concerning the activity-based model. We thank M. van Baalen for always enriching discussions, and we are grateful to S. Gandon for a fertile discussion at the origin of this work. We thank J. Koella and two anonymous reviewers for very constructive remarks on a previous version of this manuscript.

Literature Cited

Anderson, R. M., and R. M. May. 1979. Population biology of infectious diseases. Part I. Nature 280:361–367.

———. 1982. Coevolution of hosts and parasites. Parasitology 85: 411–426.

Antia, R., and M. Lipsitch. 1997. Mathematical models of parasite responses to host immune defences. Parasitology 115: S155–S167.

Antia, R., B. R. Levin, and R. M. May. 1994. Within-host population dynamics and the evolution and maintenance of microparasite virulence. Am. Nat. 144:457–472.

Antia, R., J. Koella, and V. Perrot. 1996. Models of the within-host dynamics of persistent mycobacterial infections. Proc. R. Soc. Lond. B 263:257–263.

Day, T. 2001. Parasite transmission mode and the evolution of virulence. Evolution 55:2389–2400.

Fenner, F., and F. N. Ratcliffe. 1965. Myxomatosis. Cambridge Univ. Press, Cambridge, U.K.

Frank, S. A. 1996. Models of parasite virulence. Q. Rev. Biol. 71: 37–78.

Gandon, S., and Y. Michalakis. 2000. Evolution of parasite virulence against qualitative or quantitative host resistance. Proc. R. Soc. Lond. B 267:985–990.

Gandon, S., V. A. A. Jansen, and M. van Baalen. 2001a. Host life history and the evolution of parasite virulence. Evolution 55: 1056–1062.

Gandon, S., M. J. Mackinnon, S. Nee, and A. F. Read. 2001b. Imperfect vaccines and the evolution of pathogen virulence. Nature 414:751–756.

Ganusov, V. V., C. T. Bergstrom, and R. Antia. 2002. Within-host

population dynamics and the evolution of microparasites in a heterogeneous host population. Evolution 56:213–223.
Gilchrist, M., and A. Sasaki. 2002. Modeling host-parasite coevolution: a nested approach based on mechanistic models. J. Theor. Biol. 218:289–308.
May, R. M., and R. M. Anderson. 1979. Population biology of infectious diseases. Part II. Nature 280:455–461.
Restif, O., and J. C. Koella. 2003. Shared control of epidemiological traits in a coevolutionary model of host-parasite interactions. Am. Nat. 161:*in press*.
Sasaki, A., and Y. Iwasa. 1991. Optimal growth schedule of pathogens within a host: switching between lytic and latent cycles. Theor. Popul. Biol. 39:201–239.
van Baalen, M. 1998. Coevolution of recovery ability and virulence. Proc. R. Soc. Lond. B 265:317–325.
van Baalen, M., and M. W. Sabelis. 1995. The dynamics of multiple infection and the evolution of virulence. Am. Nat. 146:881–910.

Corresponding Editor: R. Poulin

Appendix

We first derive the equilibrium stage structure of the population of infected hosts. $\sigma(\tau)$ is the probability of a host surviving to stage τ, of which the derivative is (see also Gilchrist and Sasaki 2002):

$$\frac{d\sigma}{d\tau} = -m(\tau)\sigma(\tau)\, d\tau, \tag{A1}$$

where $m(\tau) = \mu + \alpha(\tau)$ is the host mortality rate at stage τ, with $\alpha(\tau)$ the parasite virulence. Equation (A1) is integrated to yield:

$$\sigma(\tau) = \exp\left[-\int_0^\tau m(s)\, ds\right]. \tag{A2}$$

At equilibrium stage structure (when the times of infections' initiation follow a uniform distribution), the population stage structure is described by $Q(\tau)$, the density probability that an infection taken at random is exactly at stage (τ), with

$$Q(\tau) = \frac{\sigma(\tau)}{\int_0^T \sigma(s)\, ds} = \frac{\sigma(\tau)}{\bar{D}}. \tag{A3}$$

The expected transmissibility of an infection taken at random in the population is therefore $\bar{\beta} = \int_0^T Q(\tau)\beta(\tau)\, d\tau$, which gives equation (1).

The expected mortality rate of an infected host taken at random is $\bar{m} = \int_0^T Q(\tau)m(\tau)\, d\tau$. Subtracting natural mortality and remarking that the derivative of $\sigma(\tau)$ relative to τ is $-m(\tau)\sigma(\tau)$ gives equation (2).

The elimination of parasite from the host is a deterministic process occurring only at stage T. During a small period δt the cleared infections are those of which stage lies in the range $[T - \delta t, T]$. In the limit where δt becomes an infinitesimal period dt, the proportions of hosts that clear their infection during dt is $\sigma_T dt/\bar{D}$, and $\bar{\gamma}$, the average clearance rate in the population, is therefore given by equation (3).