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Evolution of Acute Infections and the Invasion-Persistence Trade-Off

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Abstract

We seek to understand the conditions favoring the evolution of acute, highly transmissible infections. Most work on the life-history evolution of pathogens has focused on the transmission-virulence trade-off. Here we focus on a distinct trade-off that operates, even among avirulent pathogens, between a pathogen's speed of invasion and its ability to persist in a finite host population. Other authors have shown how this invasion-persistence trade-off can lead to intermediate pathogen attack rates but have done so only by imposing trade-offs between the pathogen's transmissibility and the duration of the infectious period. Here we delve deeper, by linking a model of within-host pathogen dynamics—in which pathogen life-history parameters figure directly—to an epidemiological model at the population level. We find that a key determinant of the evolutionary trajectory is the shape of the dose-response curve that relates within-host pathogen load to between-host transmission. In particular, under the usual assumption of proportionality we find that pathogens tend to evolve to the edge of their own extinction. Under more realistic assumptions, a critical host population size exists, above which highly acute pathogens are buffered from extinction. Our study is motivated by the emergence of acuteness in two human pathogens, *Bordetella pertussis* and *Bordetella parapertussis*, which independently evolved from an ancestor, *Bordetella bronchiseptica*, characterized by chronic (nonacute) infection of wildlife. In contrast to the plethora of models that predict evolution of more aggressive pathogens in larger or denser populations, the invasion-persistence trade-off also operates for frequency-dependent pathogens.

Keywords

acute infection; trade-off; evolution of infectious disease; pathogen evolution; dose response; *Bordetella*

Introduction

Rapidly transmitting pathogens that cause acute disease are among the most important public health concerns worldwide because of their high burden of mortality and morbidity, their violent outbreaks, and their implication for biosecurity. Understanding the conditions that favor the evolution toward acute and highly contagious pathogens is therefore of obvious interest. A related question concerns the conditions that allow continued circulation and persistence of such strains. Understanding these issues is tantamount to understanding the evolutionary forces shaping the life histories of pathogens.

Life-history theory has proven to be of great value for explaining and predicting optimal patterns of virulence in pathogens (Antia et al. 1994; Lenski and May 1994; Frank 1996). For example, the classic trade-off theory predicts that a virulent pathogen may kill its host so fast, or stimulate such a strong immune response, that it may have little time to transmit to a secondary host (May and Anderson 1983). A more commensalistic pathogen, by contrast, may have so low a within-host multiplication rate that it fails to shed sufficiently many propagules to engender infection in recipient hosts. This trade-off can lead to an intermediate optimal host-exploitation rate with associated intermediate infectious period and degree of acuteness. In this model, evolution is assumed to favor life histories that maximize the basic reproductive ratio, R_0 , under the trade-off between the transmission rate and the infectious period. This theory has garnered important empirical support (Fenner 1983; Messenger et al. 1999). However, as pointed out by Antia et al. (1994), Frank (1996), and Gilchrist and Sasaki (2002), it is one thing to postulate a particular transmission-virulence trade-off and deduce the corresponding optimal life-history traits, but it is quite another to deduce the trade-off from its basis in within-host dynamics and the biology of transmission. Moreover, the transmission-virulence trade-off cannot explain differences in infectious period among equally virulent pathogens.

For pathogens that replicate within hosts, transmit between them, and spread among local host populations within metapopulations, selection may happen and tradeoffs may occur at several different levels (Keeling 2000; Gilchrist and Sasaki 2002; Boots et al. 2004; van Ballegooijen and Boerlijst 2004; Gilchrist and Coombs 2006). Arising at the level of the host population, the “invasion-persistence” trade-off, described by Grenfell (2001), mediates a balance between a strain’s infectious period and its instantaneous rate of transmission. Over the short term, an acute strain with short infectious period and high transmission rate has the evolutionary advantage in that it will spread more rapidly through a population than a strain with a longer infectious period and lower instantaneous transmission rate (Grenfell 2001). However, epidemics of the more transmissible strain will exhibit more violent fluctuations and suffer greater risk of extinction—reflected in a higher critical community size (Bartlett 1956; Keeling and Grenfell 1997)—than those of their less transmissible

equivalents. Thus, short-term invasion advantage comes at the cost of diminished intermediate-term persistence.

Grenfell (2001), using a simple susceptible-infectious-recovered (SIR) formalism and under the artificial restriction that competing strains shared an identical basic reproductive ratio (R_0), showed that evolution would favor an intermediate acuteness. Here, we remove the restriction of equal R_0 and replace the oversimple SIR framework with a more mechanistic model of within-host pathogen dynamics. In effect, we parameterize pathogen fitness in terms more directly related to pathogen life history. This allows us to predict the direction of pathogen life-history evolution as a function of host population structure and the coupling between pathogen load and transmission potential (the dose-response curve) without the need for artificial restrictions on parameters.

Keeling (2000) examined the mathematical underpinnings of the invasion-persistence trade-off in infinite meta-populations. He showed that, in competition between a highly transmissible but extinction-prone strain and a strain that is less prone to extinction but is also less transmissible, evolution may favor either strain, depending on within-patch relative competitive ability, patch-level relative extinction rate, and degree of stochasticity (itself related to patch size). Here, we examine the dependence of these parameters on more basic parameters that govern pathogen life history and the coupling of within-host pathogen dynamics to between-host transmission. With respect to the latter, the almost invariable practice in the literature has been to assume that instantaneous transmission rate is simply proportional to within-host pathogen load. Here we show that even small deviations from this assumption can have profound consequences on the ability of the optimal life-history strategy to persist. In particular, when transmission depends nonlinearly on pathogen load, we find that robust persistence of acute pathogens is facilitated in host populations above a size threshold.

Our study is loosely motivated by the different life-history strategies observed in the bacterial genus *Bordetella*. The species *Bordetella bronchiseptica* is a common pathogen/commensal in a very diverse range of mammals both wild and domesticated (reviewed in Bjørnstad and Harvill 2005). Symptoms of *B. bronchiseptica* infection are usually very mild to asymptomatic in most hosts; over the typical course of infection, early inflammation is followed by rapid clearance of the bacteria from the lower respiratory tract and a chronic avirulent infection of the upper respiratory tract and nasal cavity (Kirimanjeswara et al. 2003). Although chronic avirulence appears to be the norm, certain more virulent strains can cause atrophic rhinitis in pigs and kennel cough in dogs. *Bordetella bronchiseptica* has only rarely been documented in humans, and then usually as an opportunistic infection in immunocompromised patients. In contrast, humans are the almost exclusive host of two other species within the complex, *Bordetella pertussis* and *Bordetella parapertussis*. Genomic and phylogenetic analyses reveal that these two species represent evolutionarily independent lineages emerging in relatively recent times, with the *B. bronchiseptica* clade as ancestral (Parkhill et al. 2003; Cummings et al. 2004). They cause an acute respiratory infection lasting for 2–4 weeks that is followed sometimes by longer-lasting mild symptoms and eventually by complete systemic clearance. According to the World Health Organization, these two bacteria caused >40 million cases of whooping cough in 2002. We

ask why acute infections are favored in some hosts whereas more commensal infections are favored in others. What evolutionary advantage can these acute strains possess that compensates for the reduction in infectious period they have suffered? Bjørnstad and Harvill (2005) hypothesized that the invasion-persistence trade-off may be of consequence in the evolution of the acutely infecting *B. pertussis* and *B. parapertussis* from their chronic *B. bronchiseptica*-like ancestors.

Our approach is to first construct models of within-host dynamics in order to derive the trade-off between infectious period and transmission rate. We then combine this with a between-host model to study the consequences of pathogen life-history strategies on invasion and persistence at the population level. The main insights are as follows: (1) the invasion-persistence trade-off can be important for life-history evolution, (2) the shape of the dose-response curve (relating transmission rate to within-host pathogen load) is a key determinant of the outcome of pathogen evolution, and (3) only in host populations above a critical threshold is robust persistence of acute pathogens possible.

Modeling

We begin by setting up a within-host model that captures the transient interaction of the pathogen with the host's immune system and that is flexible enough to describe both chronic and acute infections. We then scale up the dynamics at the within-host level to the between-host level via a dose-response function, and we use the between-host model to compute epidemic curves at the population level. This allows us to explore the consequences at the population level of the pathogen strategy at the within-host level. In particular, it enables us to determine which features of within-host models lead to emergent trade-offs. In the following, we describe the three parts of our modeling approach: (1) within-host models of pathogen dynamics, (2) dose-response functions that determine how transmission rates depend on within-host pathogen load, and (3) the between-host epidemic model.

Within-Host Model

At the within-host level, we model the course of infection in the most basic terms: we are interested in the mechanisms that determine the parasite load, P , as a function of the age of infection, a , defined as the time elapsed since inoculation. Our main objective here is to use a model that (1) captures basic features of within-host growth and clearance of the pathogen, (2) is formulated in terms of biologically meaningful parameters that are subject to evolutionary pressures, and (3) is more realistic than SIR-type models that assume a constant level of infectiousness in an infected host and an exponentially distributed infectious period.

A slightly modified version of the model of Pilyugin and Antia (2000) suits this purpose. These authors proposed a simple model for the within-host interaction of pathogen with the host's specific immunity. In this model, the parasite grows exponentially at the rate r but is killed on encounter with immune cells. The kill rate of the immune response is k . Immune cells are produced at a baseline rate α and have a mean lifetime $1/d$. Immune cells proliferate at a rate proportional to the current rate of killing: the constant of proportionality is γ . Our model is slightly simpler than that of Pilyugin and Antia (2000) in that we assume

that handling time associated with pathogen-immune cell interactions is negligible. Our results are not sensitive to the model details: inclusion of more realism such as, for example, handling time in the immune response (which results in a maximum rate of immune response) or a programmed immune response (which entails an overshoot following pathogen clearance; Kaech and Ahmed 2001), does not change our conclusions. The model consists of a pair of differential equations for pathogen load P and specific immune response X ,

$$\begin{aligned}\frac{dP}{da} &= rP - kXP, \\ \frac{dX}{da} &= \alpha - dX + \gamma kXP.\end{aligned}\quad (1)$$

We integrate the differential equations from the initial condition $P = 1$, $X = 0$. The model possesses only two dynamic regimes. When $d/k < \alpha/r$, there is a stable equilibrium at $P = 0$, $X = \alpha/d$. When $d/k > \alpha/r$, the parasite load exhibits damped oscillations to a nonzero equilibrium, $P = 1/\gamma(d/k - \alpha/r)$, $X = r/k$. En route to this equilibrium, however, the pathogen load falls to extremely low values. In particular, for all parameters we have examined, P falls to less than its initial value of 1, indicating pathogen clearance. Moreover, this equilibrium must be interpreted as a pitched battle between pathogen and immune system, an outcome that is not found in the class of infections with which we are concerned. Accordingly, we assume the infection has been cleared when P drops below its initial level. In both regimes, therefore, the infection is ultimately cleared, but its duration and severity—that is, the cumulative parasite load generated—depend on the parameters. In particular, low values of r produce long-lasting infections that are less acute than those produced by larger values of r (fig. 1A). This feature of the model captures the continuum between acute and chronic infections. We denote by a_c the age of infection at which clearance occurs, and we assume $P = 0$ for $a > a_c$.

Transmission Models

The within-host dynamics determine the parasite load $P(a)$ and immune response at different infection ages. To integrate these dynamics into the between-host model, we assume a relationship between parasite load and transmission. In particular, we will assume that the instantaneous transmission rate β is a function of age of infection and parasite load. We explore three families of dose-response functions.

Linear β —The almost invariable assumption in the literature is that between-host transmission rate is simply proportional to within-host parasite load, $\beta(a) = q_1 P(a)$.

Delayed β —Because transmission may depend on the expression of symptoms (e.g., coughing) that typically do not manifest immediately on infection but only after some time has passed, we consider a delayed-onset model of transmission. In this model, $\beta(a) = q_2 P(a)/\{1 + \exp[-s(a - a^*)]\}$; transmission is negligible until a certain time, after which it becomes proportional to parasite load.

Saturating β —It is likely that the transmission rate depends nonlinearly on parasite load, at least at very high values of the latter. In particular, the probability of a contact resulting in

infection may saturate at high inoculum sizes. To investigate the effects of this saturation effect, we consider a nonlinear dose-response curve, $\beta(a) = q_3 [1 - \exp(-P(a)/P^*)]$.

Between-Host Model

At a population level, we model the age-specific spread of disease using the McKendrick–von Foerster equations. To derive these equations, let $\int_{\alpha_1}^{\alpha_2} i(t, a) da$ denote the fraction of the host population at time t consisting of individuals who were infected between times $t - \alpha_2$ and $t - \alpha_1$. Conservation of individuals implies that

$$\begin{aligned} \frac{\partial i}{\partial t} + \frac{\partial i}{\partial a} &= -\mu(a)i, \\ i(t, 0) &= \lambda(t)(1 + \varepsilon \sin 2\pi t)S(t), \end{aligned} \quad (2)$$

where $\mu(a)$ is age-specific mortality, $\lambda(t)$ is the force of infection, the sinusoidal factor models seasonality in transmission, and $S(t)$ is the fraction of the host population susceptible to infection at time t . Transmission is assumed to be frequency dependent so that the force of infection is

$$\lambda(t) = \int_0^{a_c} \beta(a) i(t, a) da = \int_0^{a_c} \beta(a) l(a) i(t-a, 0) da. \quad (3)$$

Here, $l(a) = \exp(-\int_0^a \mu(a') da')$ denotes the probability that an individual infected a time units ago has not yet died. Note that, although we assume frequency-dependent transmission, the dynamics under density dependence are identical as long as the host population size is constant. For the remainder of the article, we will assume that infections are nonlethal; this amounts to assuming a constant death rate: $l(a) = e^{-\mu a}$.

To complete the system of equations, we need an equation for the susceptible fraction $S(t)$. We assume that the susceptible pool is replenished by births and that the total host population size remains constant in time. We therefore assume that $S(t)$ obeys

$$\frac{dS}{dt} = \mu(1-S) - \lambda(t)(1 + \varepsilon \sin 2\pi t)S. \quad (4)$$

The all-important basic reproductive ratio is given by

$$R_0 = \int_0^{a_c} \beta(a) l(a) da.$$

Equations (2)–(4) can be solved numerically to predict the population-level dynamic consequences of a particular set of assumptions at the within-host level. For all simulations, we assumed that 1% of the host population was initially infected.

Numerical Methods

The within-host pathogen load is determined by the within-host models (eq. [1]). We numerically integrate these ordinary differential equations to obtain the trajectory of the pathogen load, $P(a)$. Having computed $P(a)$, each of the transmission models translates this into between-host transmission rate $\beta(a)$ and basic reproductive ratio R_0 . With $\beta(a)$ in hand, we integrate equations (2)–(4) to obtain the epidemic curve. We use a simple backward Euler scheme for this purpose.

Quantifying Extinction Risk

Other things being equal, immunizing pathogens that give rise to more violent epidemic fluctuations are less likely to persist over the long term. This is because extinction risk is greatest immediately following an outbreak, when the fraction of infected hosts,

$$H(t) = \int_0^{a_c} i(t, a) da,$$

is at a minimum, and therefore the expected number of transmission events is smallest and the probability of failure of transmission is most appreciable.

Even when $R_0 > 1$ —that is, the endemic equilibrium is, deterministically speaking, stable—stochastic extinction may occur. Extinction is most likely to occur in the deep trough immediately following a novel pathogen's introduction. If the pathogen survives this trough, extinction risk decreases with time as H approaches equilibrium via damped oscillations (fig. 1). Seasonal variation in transmission, however, results in sustained oscillations. In seasonal environments, therefore, the trough following each outbreak is associated with elevated risk of extinction. In both cases, the depth of the trough following an outbreak gives an indication of the magnitude of this risk. To determine how extinction risk depends on model parameters, we examined the depth of predicted troughs in two scenarios: (1) a virgin epidemic in a nonseasonal environment and (2) recurrent epidemics in a seasonal environment. Specifically, we defined H^* to be the minimum value of H in each scenario: higher values of H^* correspond to lower risk of extinction.

What is the exact connection between H^* and the critical community size (Bartlett 1956, 1957, 1960; Keeling and Grenfell 1997)? A definitive answer to this question would require a fully stochastic treatment with concomitant loss of analytical tractability. Na°sell (2005) derived an approximate formula for the critical community size under a standard, nonseasonal SIR model with demographic stochasticity. Comparison of our H^* with the critical community size obtained in this way reveals that the two quantities give essentially the same qualitative picture of how persistence depends on the epidemiological parameters.

Results

In this section, we derive and compare the population-level consequences of the assumptions on within-host pathogen dynamics and transmission described above. We focus on the pathogen's optimal life-history strategies, holding the host biology fixed. Given perfect

cross immunity among strains of pathogens, the pathogen strategy with the highest R_0 value is the evolutionarily stable strategy. The landscape of R_0 , therefore, tells us the likely direction of pathogen evolution. However, not all regions of this landscape are accessible. For a given host population size, certain parameter combinations will, with high probability, lead to local extinction of the pathogen. These regions of parameter space are therefore effectively inaccessible to the pathogen. We use the quantity H^* to circumscribe the accessible region of parameter space.

Figure 1A shows the within-host pathogen dynamics. A key parameter of this model is the parasite growth rate r . Higher values of r lead to more acute infections, which stimulate stronger immune response and therefore more rapid pathogen clearance. Figure 1B–1D shows the corresponding population-level dynamics under the various transmission models. In all models, increasing r eventually results in deeper postepidemic troughs (lower H^*).

By varying r and another parameter (in this case, γ), we build up surfaces showing pathogen fitness (R_0) and relative stochastic fade-out risk (H^*). Figure 2A shows the contours of R_0 and H^* under the linear-transmission model. Not surprisingly, R_0 increases as we increase the parasite growth rate r and/or decrease the immune-cell recruitment rate γ . Because, under this model, more acute infections generate stronger immune responses, the infectious period decreases as r increases. Nevertheless, the cumulative pathogen load produced over the course of an infection increases with r so that the net effect is to increase R_0 . It follows that, under the assumptions of this model, a pathogen maximizing R_0 will evolve toward ever greater acuteness.

Under these circumstances, limits to the tendency toward acute infection arise at the level of the host population. From figure 2A we see that, for a given host population size, the accessible region is bounded above by some H^* contour. Thus, a pathogen evolving to maximize R_0 will increase its growth rate to the maximum value compatible with the host population size. In other words, the pathogen should evolve to the brink of its own local extinction, an effect similar to that observed by Rand et al. (1995) in a spatially explicit, individual-based model. Moreover, as host population increases, the accessible region expands and allows the evolution of more acute infections (fig. 2B). Thus, a trade-off between invasion and persistence emerges.

In figure 2C, 2D, we show the analogous results based on the delayed-transmission model. Here, contours of H^* are similar to those in figure 2A, but the contours of R_0 bend down at the right, an indication that, for a given γ value, R_0 is maximized at an intermediate value of r . The consequences of increasing host population size are illustrated in figure 2D: as population size increases, the optimal acuteness initially increases. Beyond a threshold, although the maximum supportable acuteness continues to increase, the optimal acuteness does not. This is due to the fact that, under the delayed-transmission model, increasing r eventually leads to clearance of the pathogen before transmission can occur. The same effect is observed under the saturating-transmission model (fig. 2E, 2F). Here, increases in pathogen load beyond a certain point no longer lead to increases in transmission intensity. These diminishing returns, combined with decreasing infectious period, reduce the fitness of extremely acute pathogens. Under both of the more realistic transmission models, greater

acuteness leads to increased transmission only up to a point; beyond that point, the reduction in infectious period associated with increased acuteness erodes the value of R_0 .

To summarize, we find that, for each of the transmission models considered, increased host population size favors the evolution of more acute infections. An additional effect arises when transmission is not simply proportional to pathogen load: infections of a pathogen with intermediate acuteness may then be favored. Put another way, under realistic models of transmission, when the host population size is sufficiently large, the population-level dynamics cease to constrain the acuteness of infection. Under these conditions, only within-host mechanisms determine optimal life-history strategies.

This situation contrasts with that obtained using the more phenomenological SIR model. Figure 3 shows that, under the SIR model, H^* increases (and critical community size decreases) as R_0 increases. No trade-off between invasion and persistence arises under this simple model. The emergent trade-off becomes evident only when fitness and extinction risk are related to pathogen life history via a model of within-host dynamics.

Figure 4 shows that the conclusions above continue to hold for recurrent epidemics in seasonal environments. The contours of H^* show a similar pattern under all transmission models: in more seasonal environments, troughs are deeper and extinction is more likely. As in the non-seasonal case, R_0 increases with r under the linear-transmission model, and pathogens maximizing R_0 should evolve to the edge of their own extinction. When transmission is delayed until the onset of symptoms or is saturating with pathogen load, the maximum R_0 is attained at an intermediate value of r and the optimal pathogen strategy is buffered from the edge of extinction.

Although we have used a crude, deterministic quantification of extinction risk to derive these results, the patterns remain in stochastic simulations of the model. Specifically, in work to be reported elsewhere (S. Shrestha, E. T. Harvill, O. N. Bjørnstad, and A. A. King, unpublished manuscript), we show that an identical qualitative picture emerges in an individual-based model in which within-host dynamics are given by equation (1) but between-host transmission and host demography are stochastic.

Discussion

A variety of mathematical models predict that the optimal pathogen life-history strategy depends on the mode of transmission, the biology of the host, and the contact structure of the host population (e.g., Frank 1996; Eames and Keeling 2006). Here we formulate models of within-host infection dynamics and then scale these models up to derive their between-host dynamic consequences and evolutionary implications. An important insight is that the optimal life history may also depend on the size of the local host population through an emergent invasion-persistence trade-off. In particular, evolution will tend to favor increasing acuteness to push immunizing pathogens toward the edge of their own extinction. Only when transmission depends on pathogen load in a nonlinear fashion or, more generally, when mechanisms acting at the level of the individual host constrain fitness—and then only

in host populations above a threshold size—is robust persistence of highly acute pathogens possible.

This result has been derived in the context of a well-mixed population, that is, mass-action kinetics. How might more realistic assumptions regarding host population structure change our conclusions? The simplest approach here is to consider a host population with two levels of mixing, that is, a metapopulation. Preliminary simulations of a stochastic metapopulation model show that subdivision of a population into local patches always effectively increases the critical community size. This effect is modest until the degree of connectivity among patches becomes quite small; for very small connectivities, the effective critical community size grows rapidly as connectivity decreases. The effect of metapopulation structure, then, at least within this simple one-strain model, appears to be entirely quantitative; the qualitative picture remains as we have described. Interesting spatial effects may arise in models with explicit competition among strains. This is scope for future work.

The transmission model is crucial in determining how and when the invasion-persistence trade-off sets in. Under the linear-transmission model that is so favored in the literature, the constraint is active at every population size. The pathogen's growth rate r and, consequently, R_0 , can increase monotonically with population size. Under the more realistic models, the effects of the trade-off may be less clear-cut when selection acts both within and between hosts. This highlights two critical points. First, at large population sizes, selection at the within-host level is more important than at the between-host level. Second, in small populations, selection at both levels combines—potentially in a nonadditive way—to shape the evolutionary landscape.

We have focused on the case of a completely avirulent (i.e., nonlethal) family of pathogens. As we have shown, under realistic transmission functions and when the population size is sufficiently large, the invasion-persistence trade-off is not enforced. In such a regime, then, one expects that, other things being equal, virulence is one factor that will influence pathogen evolution. When the host population is small, however, the evolutionary forces acting on a virulent pathogen will depend on the intricate constraints among transmission, infectious period, and virulence: constraints imposed, again, by the interaction of the pathogen with the host's immune system.

Although our focus has been on the evolution of acuteness per se and not on virulence, to the extent that these are correlated, one can view our results as an addition to the list of mechanisms whereby larger populations support more virulent pathogens. Other studies have noted that, when transmission is density dependent, higher population densities lead to higher contact rates, which in turn support strains of higher virulence (Ewald 1994). Also, higher per-host contact rates lead to higher levels of superinfection; the enhanced within-host competition among pathogens can then lead to higher virulence (May and Nowak 1995; Frank 1996; Mosquera and Adler 1998). The mechanism we describe here—enhanced persistence of aggressive pathogens in larger populations—is unique among these alternatives in that it operates even in the frequency-dependent case, that is, even when the per-host contact rate does not increase with population size or density. It is worth noting that

available evidence suggests that transmission of childhood diseases such as whooping cough scales in a frequency-dependent manner (de Jong et al. 1995; Bjørnstad et al. 2002).

Whereas theoretical models of pathogen evolution abound, empirical support is available only in a relatively small number of case studies. This may in part be because conspicuous shifts in life-history optima will happen only in the face of rapid changes in host population structure (or invasion into a new host, as in the case of myxomatosis in European rabbits; Fenner 1983). The Neolithic revolution in human societies some 10,000 years ago may offer an interesting “historical experiment” of relevance. This was marked by rapid increase in the sizes and densities of human settlements (Eshed et al. 2004). In an intriguing recent review, Mira et al. (2006) argue that the evidence for dramatic changes in the genomes of human-associated bacteria represents the signature of rapid evolution in the face of the altered host community structure; our theoretical exploration is motivated by the independent emergence of two epidemic strains of *Bordetella* (*Bordetella pertussis* and *Bordetella parapertussis*) that cause acute whooping cough and whooping cough-like illness in humans. The ancestor of these, *Bordetella bronchiseptica*, causes chronic, nonlethal infection in a wide range of non-human mammals (Bjørnstad and Harvill 2005). Although the timing of the emergence of these acute pathogens is not fully known, Mira et al. (2006) argue that intense genomic changes can be dated to around the time that human community sizes increased radically. The acute strains that currently circulate may therefore be the evolutionary response to the larger population sizes—and concomitantly enhanced opportunities for more acute life-history strategies—of the human host: this may be a case where the invasion-persistence trade-off is shaping life-history evolution.

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Figure 1.

A, Within-host pathogen dynamics for three different r values. Also shown are the corresponding nonseasonal epidemic curves for the linear-transmission model (B), delayed-transmission model (C), and saturating-transmission model (D). Parameters α , d , and k are set to the values shown in table 1; $\gamma = 10^{-4}$ and $\varepsilon = 0$. In general, increasing acuteness eventually leads to elevated risk of stochastic extinction.

Figure 2.

On the left, the R_0 (black contours) and H^* (gray) surfaces under the Pilyugin-Antia model with linear (A), delayed (C), and saturating (E) transmission models, respectively. On the right, $-\log_{10} H^*$ versus optimum r for fixed $\gamma = 10^{-4}$ corresponding to the models at left. The solid gray line shows the maximum r compatible with a given value of H^* ; the dashed line represents the value of r that maximizes R_0 . As host population size increases, pathogens with higher $-\log_{10} H^*$ are able to persist. Under the linear-transmission model (B), the optimal r is always at the boundary of persistence. Under the delayed and saturating models (D, F), by contrast, when the population size increases above a threshold value, the optimal acuteness r is no longer on the boundary of persistence.

Figure 3.

Contours of H^* (gray gradient) and R_0 (black contours) under the standard SIR model.

Darker shades correspond to lower critical community sizes and thus to pathogens that are more persistent at the population level. Note that no trade-off emerges in this case: by increasing infectious period, transmission rate, or both, a pathogen can increase its fitness and its ability to persist.

Figure 4.

Effect of seasonality on H^* (the gray gradient shows $-\log_{10} H^*$) in the epidemics for the Pilyugin-Antia model with linear-transmission (A), delayed-transmission (B), and saturating-transmission (C) models; R_0 (black contours) is independent of the amplitude of the seasonal forcing, 3 . Under the linear-transmission model, R_0 increases monotonically with r ; under the delayed-transmission and saturating-transmission models, it reaches a maximum at an intermediate value of r . With strong seasonality and extreme acuteness (hatched region), equations (2)–(4) can display complex dynamics, including multiannual (sub-harmonic) attractors that coexist with the annual attractor. In such long-period cycles, H can reach extremely low values.

Table 1

Model parameters

Model, parameter	Symbol	Value
Within-host model:		
Parasite growth rate	r	10–130
Kill rate of the immune response	k	3.5
Baseline production rate of immune response	a	1
Death rate of immune response	d	.5
Immune response recruitment rate	γ	$.5\text{--}1.5 \times 10^{-4}$
Transmission models:		
Transmissibility factor, linear model	q_1	10^{-3}
Transmissibility factor, delayed model	q_2	1.5×10^{-3}
Transmissibility factor, saturating model	q_3	10^3
Delayed-transmission coefficient	s	25
Delay constant	a^*	.1
Saturation constant	P^*	5×10^5
Between-host model:		
Host mortality rate	μ	.02
Seasonality amplitude	ε	0–1