BRIEF COMMUNICATIONS

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A CONSIDERATION OF PATTERNS OF VIRULENCE ARISING FROM HOST-PARASITE COEVOLUTION

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Abstract.—In this article we explore how host survival and fecundity are affected by host-parasite coevolution. We examine a situation in which hosts upon being infected can mount a defensive response to clear the infection, but in which there is a fecundity cost to such immunological up-regulation. We also suppose that the parasite exploits the host and thereby causes an elevated host mortality rate. We determine the coevolutionary stable strategies of the parasite's level of exploitation and the host's level of up-regulation, and illustrate the patterns of reduced host fitness (i.e., virulence) that these produce. We find that counterintuitive patterns of virulence are often expected to arise as a result of the interaction between coevolved host and parasite strategies. In particular, despite the fact that the parasite imposes only a mortality cost on the host, coevolution by the host results in a pattern whereby infected hosts always have the same probability of death from infection, but they vary in the extent to which their fecundity is reduced. This contrasts with previous results and arises from our inclusion of two important factors absent from previous theory: costs of immunological up-regulation and a more suitable measure of parasite-induced mortality.

Key words.—Case mortality, clearance, fecundity, immunological up-regulation, infection, pathogen.

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There are several layers to a host's investment in defense against parasites. Aside from the costs of physical defenses that prevent infection, there are costs to maintaining an immune system as well as costs of up-regulation (i.e., activation) of the immune response when infection occurs. Although the benefits of such defenses to a host are obvious, empirically determining the costs of these defenses has proven difficult (Lochmiller and Deerenberg 2000). In particular, it has proven most difficult to adequately test for costs of physical defenses and immune system maintenance, although recent advances are beginning to show that substantial amounts of both energy and anabolic resources are allocated to up-regulation of the immune response at the expense of growth and reproduction (e.g., Demas et al. 1997; Moret and Schmid-Hempel 2000).

Recently there has been growing interest in developing a comprehensive theory for the evolution of such host immunological defenses, particularly in determining how host-related defense mechanisms are expected to coevolve with parasite life histories. An extensive body of population-genetic theory exists exploring so called gene-for-gene and matching-allele models of host-parasite coevolution (e.g., Agrawal and Lively 2002, and references therein), but this theory usually makes predictions about how we expect infection-preventing mechanisms to evolve rather than infection clearing mechanisms such as immunological up-regulation. Moreover, the majority of this theory does not incorporate the effects of the epidemiological dynamics of parasite transmission, which are known to be important in host and parasite evolution (but see Gandon et al. 2002). Two recent exceptions include van Baalen (1998), who explored the coevolution of virulence and host immunological defenses when there is a cost to immune system *maintenance*, and Bowers (2001), who modeled the evolution of host defense within an epidemiological framework. Here we present a model that contains two important factors absent from this previous research and that provides a new perspective on this topic.

First, supposing that there is a substantial cost of immunological up-regulation, infected hosts will display a reduced fitness relative to uninfected hosts because up-regulation takes resources away from host survival and/or reproduction. Importantly, the cause of this infection-related reduction in host fitness contrasts that given by the large body of theory that treats such ''virulence'' as an unavoidable consequence of the parasite exploiting the host (Bull 1994; Read 1994; Ebert and Herre 1996; Frank 1996). The former takes the host's perspective and explains the level of reduced host fitness as having evolved to balance the costs and benefits of immunological up-regulation, whereas the latter takes the parasite's perspective and explains it as having evolved to balance the costs and benefits of the degree of exploitation of the host by the parasite. Of course, for most host-parasite systems, the reduction in host fitness due to infection is likely the result of a complex interplay between the costs of immunological up-regulation and the cost of the parasite exploiting the host (Hurd 2001). Moreover, because most host-parasite systems have coevolved to some extent, the precise nature of this interplay has likely been shaped by natural selection in both the host and the parasite population. Therefore, one of our goals is to determine what patterns of host fecundity and survival when infected are expected given this coevolutionary interaction between host and parasite.

Second, previous theory has used parasite-induced instantaneous mortality rate, v, as the definition of parasite virulence despite the fact that this does not actually represent the extent to which a parasite causes mortality in its host (Day 2002a). Rather, the mortality effects of a parasite are best

reflected by case mortality, χ (i.e., the probability of dying once infected), which is defined by $\chi = v/(v + c + u)$, where c is the clearance rate of the parasite through host defenses and u is the background host mortality rate (assuming these parameters are constant during an infection; for more general formulations, see Day 2002a). Importantly, previous theory has demonstrated that higher values of clearance, c, select for higher values of v, and vice versa (Frank 1996; van Baalen 1998). Because these will have conflicting effects on case mortality, it remains unclear how host-parasite coevolution will affect the extent to which parasites actually kill their hosts. Exploring this question is the second goal of our note.

The Model

A complete theory would incorporate the way in which immunological up-regulation affects host fecundity and survival, as well as how host exploitation by the parasite affects these host life-history attributes. However, here the theory we develop has a more modest goal. It is widely believed that immunological up-regulation must impose a cost on the host, both in terms of energy and anabolic processes, and that this in turn likely reduces growth and fecundity. This belief is supported by some recent studies (e.g., Demas et al. 1997; Moret and Schmid-Hempel 2000; Lochmiller and Deerenberg 2000) and therefore we restrict our attention to fecundity costs of immunological up-regulation. We note, however, that this issue has yet to be satisfactorily resolved (Sheldon and Verhulst 1996), because there exists conflicting evidence (e.g., Williams et al. 1999) suggesting that costs of up-regulation, if they do in fact exist, might well be exhibited in complex and subtle ways. Similarly, although parasites can impose both mortality and fecundity costs on hosts due to their utilization of host resources, we focus only on mortality costs because the vast majority of the existing theory on parasite virulence evolution does so. There is not yet enough empirical evidence to determine whether these restrictions are more prevalent in natural systems than other possibilities, but it makes sense to focus on these first since theory for the independent evolution of each of these is relatively well developed.

To develop the theory, an epidemiological model governing the underlying parasite transmission dynamics must be specified. For simplicity we will use a model in which the parasite controls the host population density (i.e., in the absence of the parasite the host population grows exponentially). Except where noted, all of the qualitative conclusions remain unchanged if instead the host is regulated by other density dependent mechanisms (T. Day and J. G. Burns, unpubl. results).

Letting S and I denote the density of susceptible and infected hosts, their epidemiological dynamics are given by

$$\frac{dS}{dt} = b_S S + b_I(c)I - uS + cI - \beta SI \tag{1}$$

$$\frac{dI}{dt} = \beta SI - (u + v + c)I, \tag{2}$$

where the degree of immunological up-regulation is represented as c, the infection clearance rate of the host. The birth rate by susceptible hosts, b_S, does not vary with c, but the birth rate by infected hosts, $b_I(c)$, is assumed to be a decreasing function of c, which imposes the fecundity cost of up-regulation (this formulation assumes an instantaneous switch in resource allocation once a host is infected). The parameter u is the natural or background host mortality rate, v is the additional host mortality rate due to infection, and β is the transmission rate of parasite from host to host. As with the majority of current theory on virulence evolution, we assume that the parasite transmission rate, β, and the parasite-induced host mortality rate, v, are both positively related to the level of exploitation of the host by the parasite (but see Day 2002b). This imposes a life history trade-off on the evolution of the parasite (Galvani 2003).

System (1–2) has one nontrivial equilibrium. The conditions for its local stability are (see Appendix):

$$b_S > u \quad \text{and} \tag{3}$$

$$b_I < u + v. \tag{4}$$

In the development of the theory below, we first determine the evolutionarily stable strategy (ESS) of the host's degree of immunological up-regulation, c^*. We then examine the ESS level of host exploitation by the parasite. Finally, we examine the coevolutionarily stable strategies (coESS) of exploitation by the parasite and host immunological up-regulation. Our approach closely follows that of van Baalen (1998), although he considered costs of immune system maintenance only. We will comment on the relationship between his and our results in the Discussion.

Evolutionarily Stable Immune System Up-Regulation

To determine the ESS clearance rate, we assume that the dynamics at the epidemiological time scale are fast relative to those at the evolutionary time scale. In particular, we suppose that system (1–2) has reached an endemic equilibrium, and then we consider the possibility of a host strain with a different clearance rate invading.

The dynamics of a mutant host strain can be obtained by augmenting system (1–2) to allow for this second host type:

$$\frac{dS_1}{dt} = b_S S_1 + b_I(c)I_1 - uS_1 + cI_1 - \beta S_1 I_1 - \beta S_1 I_2 \tag{5}$$

$$\frac{dI_1}{dt} = \beta S_1 I_1 + \beta S_1 I_2 - (u + v + c)I_1 \tag{6}$$

$$\frac{dS_2}{dt} = b_S S_2 + b_I(\hat{c})I_2 - uS_2 + \hat{c}I_2 - \beta S_2 I_1 - \beta S_2 I_2 \tag{7}$$

$$\frac{dI_2}{dt} = \beta S_2 I_1 + \beta S_2 I_2 - (u + v + \hat{c})I_2. \tag{8}$$

The subscripts 1 and 2 denote resident and mutant strains, respectively. Thus, the resident clearance rate is c and the mutant clearance rate is $\hat{c}$.

The Appendix shows that a mutant host with clearance rate, $\hat{c}$, can invade a population in which the hosts have a

clearance rate, c, provided that $W(\hat{c}, c) > 0$ where

$$W(\hat{c}, c) = -(u - b_S)(\hat{c} + u + v) - \beta I(c)[u + v - b_I(\hat{c})] \quad (9)$$

is a measure of the mutant host's fitness when rare, and $I(c)$ is the equilibrium density of infected hosts with clearance rate c (given in the Appendix). Therefore, supposing that mutant hosts have a clearance rate that is not very different from that of resident hosts, c, the clearance rate of hosts should evolve is a direction given by the sign of

$$\left.\frac{\partial W}{\partial \hat{c}}\right|_{\hat{c}=c}. \quad (10)$$

An evolutionary equilibrium, c^*, must satisfy expression (10) when set equal to zero, and this equilibrium is convergence stable (Eshel 1983; Taylor 1989; Bulmer 1994) provided that

$$\frac{d}{dc}\left[\left.\frac{\partial W}{\partial \hat{c}}\right|_{\hat{c}=c}\right]_{c=c^*} < 0. \quad (11)$$

Additionally, this equilibrium is evolutionarily stable provided that

$$\left.\frac{\partial^2 W}{\partial \hat{c}^2}\right|_{\hat{c}=c=c^*} < 0. \quad (12)$$

Using equation (9) and the equation for $I(c)$ from the Appendix, and calculating expression (10) gives

$$\left.\frac{\partial W}{\partial \hat{c}}\right|_{\hat{c}=c} = (b_S - u) + \frac{(c + u + v)(b_S - u)\dfrac{db_I}{dc}}{(u + v - b_I)}. \quad (13)$$

From the form of equation (13), we can see that when the costs of immunological up-regulation are linear (e.g., $b_I(c) = b_S - \lambda c$), there is no intermediate ESS since this equation reduces to an expression proportional to $(u + v)(1 - \lambda) - b_S$, which is either positive or negative. Therefore, if the cost of up-regulation is large (i.e., λ is large), no up-regulation is favored whereas if this cost is small (and the fecundity of susceptible hosts is also small), then maximal up-regulation (i.e., $c = b_S/\lambda$) is favored. Not too much significance should be placed on the lack of an intermediate ESS, however, since this is no longer true if there are density-dependent mechanisms other than the parasite that regulate the host population (T. Day and J. G. Burns, unpubl. results).

An intermediate value of c^* must satisfy expression (13) when set equal to zero, and for it to be a convergence stable ESS it must also satisfy conditions (11) and (12). It can be shown that both of these conditions are satisfied if (and only if) $d^2b_I/dc^2 < 0$, and therefore we will assume this is true throughout. As a simple example, suppose there are nonlinear costs such that $b_I(c) = b_S - \lambda c^2$. The ESS clearance rate is then,

$$c^* = \frac{-(u + v)\lambda + \sqrt{\lambda[u + v - b_S + \lambda(u + v)^2]}}{\lambda}. \quad (14)$$

Thus, the ESS clearance rate decreases as the cost of up-regulation, λ, or the fecundity of susceptibles, b_S, increases,

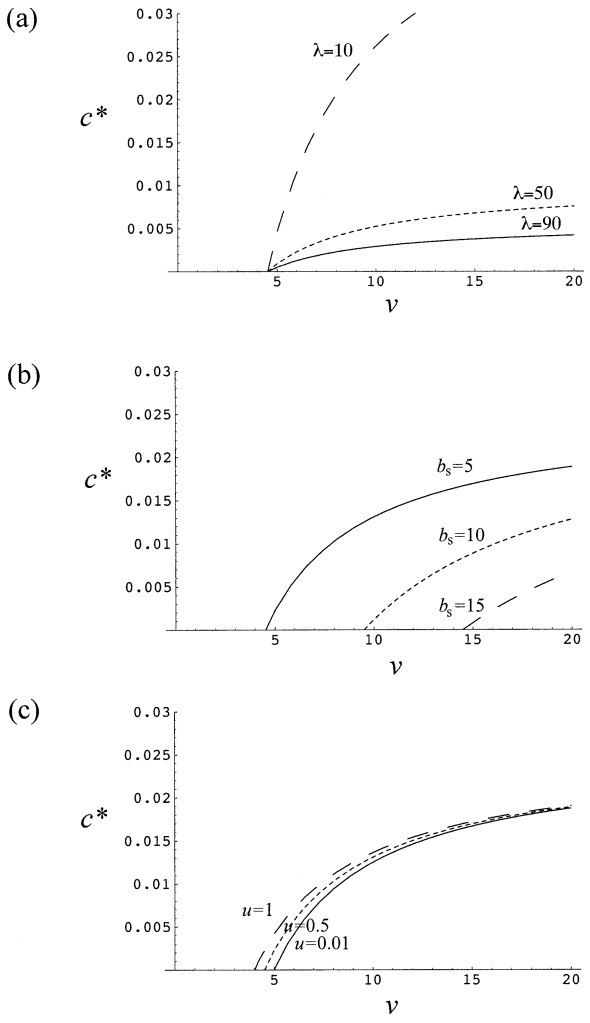

FIG. 1. The relationship between the evolutionarily stable level of clearance rate and parasite virulence (i.e., Equation 14) for a variety of different parameter values. (a) $b_S = 5$, $u = 0.5$. (b) $u = 0.5$, $\lambda = 20$. (c) $b_S = 5$, $\lambda = 20$.

and it increases as the host's background mortality rate, u, increases (Fig. 1). Importantly, it increases as the parasite-induced mortality rate, v, increases as well (Fig. 1). In fact, it can be shown by setting expression (10) equal to zero and implicitly differentiating with respect to v, that c^* increases with v whenever $\partial^2 W/\partial v \partial \hat{c} > 0$ (i.e., whenever the benefits of an increase in clearance rate are larger when parasites induce a higher host mortality rate). This is likely true quite generally (e.g., it is always true in the present model), and this is significant because evolutionary increases in v by the parasite will thereby select for evolutionary increases in the degree of up-regulation in the host. Next we explore the ESS level of v that is expected to evolve in the parasite, in the absence of host evolution.

Evolutionarily Stable Host Exploitation by the Parasite

There is a large body of theory in evolutionary epidemiology that attempts to explain the parasite-induced instantaneous mortality rate, v, that evolves by supposing that there are costs as well as benefits to a parasite as v increases. Most

of this theory supposes that both v and the transmission rate between hosts, β, are positively related to the level of host exploitation by the parasite, ϵ. There is growing evidence that parasites with increased transmission rate pay a cost in terms of quicker host death, leaving less time for the parasite to be transmitted, in support of this assumption (Bull et al. 1991; Herre 1993; Ebert 1994; Ebert and Mangin 1997; Mackinnon and Read 1999; Messenger et al. 1999; for discussion, see Lipsitch and Moxon 1997).

Under this assumption, both β and v are treated as increasing functions of ϵ. Therefore, to simplify the analysis we can capture the positive relationship between β and v (mediated through their mutual dependence on ϵ) by simply treating β as an increasing function of v. By doing so, numerous previous analyses have shown that the ESS level of v that evolves in the parasite, is that which maximizes $R = \beta/(u + c + v)$ (Frank 1996). Therefore the ESS value, v^*, must satisfy

$$\frac{d}{dv}\left[\frac{\beta(v)}{u + v + c}\right]_{v=v^*} = 0. \quad (15)$$

Throughout we will assume that $d^2\beta/dv^2 < 0$ as well, which guarantees that v^* is a convergence stable ESS.

To proceed further, we use a quite general form for the relationship between transmission and the parasite induced host mortality rate; $\beta(v) = mv^n$, where $0 < n < 1$. In this case the ESS level of v is

$$v^* = \frac{n}{1 - n}(u + c). \quad (16)$$

Note that the ESS level of v increases with the host's background mortality rate, u, as well as with the host's degree of up-regulation, c. Notice that v^* also decreases as n increases, because the $\beta - v$ relationship then plateaus for lower values of v.

Result (16) has been obtained previously, as have similar results that give the same qualitative predictions with regard to changes in u, c, and n (see Frank 1996 and Williams and Day 2001 and references therein). Typically v has been equated with a parasite's ''virulence'' in these earlier results, with the rationale being that v is a measure of the extent to which the parasite causes mortality in its host. There are many other ways to measure parasite-induced mortality, however, including case mortality, χ (the probability of a host dying once infected), as well as expected life span of those hosts who die from infection, L. Moreover, contrary to what is often assumed, v is not in fact a measure of the extent to which the parasite causes host mortality. The reason is that parasites inducing large values of v might nevertheless cause very little mortality if infected hosts have a high clearance rate through a high degree of immunological up-regulation (Day 2002a).

Interestingly, previous authors have not, to our knowledge, examined the predictions of the above model of parasite evolution in terms of case mortality, χ. Doing so reveals a very simple result:

$$\chi^* = n. \quad (17)$$

Surprisingly, this reveals that the case mortality that is expected to evolve is completely determined by the shape of the trade-off between β and v. The parameters u and c have no effect of the probability of an infected host dying. As a result, taking case mortality as our definition of virulence (which, we would argue, is more appropriate than v) produces a very different qualitative prediction about the effects of host background mortality and clearance rates on virulence evolution than that obtained by previous authors who have used v as a measure of virulence (for more general results of this sort, see Day 2002a).

Although the probability of a host dying once infected is not expected to change with changes in c or u, the expected amount of time until death occurs is affected. This quantity if defined as (Day 2002a) $L = 1/(u + v + c)$, and at the ESS value of v, this simplifies to

$$L^* = \frac{1 - n}{c + u}. \quad (18)$$

Therefore, hosts with high clearance and/or background mortality rates are expected to endure the same probability of death once infected as hosts with low such values, but the former will die more quickly than the latter.

Coevolutionarily Stable Host and Parasite Strategies

It is clear from the above analyses that the ESS level of up-regulation by the host is affected by the parasite's replication strategy, and that the ESS parasite replication strategy is also affected by the host's degree of up-regulation. What then, are the coevolutionarily stable strategies of the host-parasite system?

A co-ESS pair of values, (c^*, v^*), must simultaneously satisfy expression (10) set equal to zero and equation (15). With our choice of the function $\beta(v)$, we have already seen that equation (15) can be solved explicitly for v^* to give equation (16). Therefore, the co-ESS pair is given by this value of v^*, along with the corresponding value of c^* obtained by solving expression (10) set equal to zero for this particular value of v^*.

Our primary interest here is in determining how the host's fitness is reduced by infection at this co-ESS. It should be clear from the results of the previous section (i.e., that case mortality depends only on n) that, although v^* is affected by the level of up-regulation that evolves, and therefore by the coevolutionary dynamics of host and parasite, the case mortality of the host is not. Rather, case mortality is still simply $\chi^* = n$, and therefore it is completely determined by the parasite's transmission/mortality rate trade-off. As suggested by the previous sections, the coevolutionary dynamics of host and parasite affect the degree of up-regulation that evolves, as well as the expected life span of an infected host that evolves, but the extent to which a parasite actually kills its host (i.e., case mortality) remains constant. Thus, although a wide range of coevolutionary outcomes in terms of $v^*$and c^* might occur as a result of coevolution under different conditions in different host-parasite systems, these results suggest that the extent to which the parasite kills its host will nevertheless remain constant (provided n remains constant).

Discussion

These results have interesting implications for comparisons of host-parasite systems that have evolved under different

conditions. For example, suppose we compared a system in which a high background host mortality rate led to the coevolution of high immunological up-regulation by the host as well as a high rate of exploitation by the parasite, with one in which a low background mortality led to the coevolution of low up-regulation and low exploitation. A naïve researcher studying these systems would witness a pattern in which infection resulted in identical levels of mortality in the two systems, but infected hosts in the former system would have their fecundity reduced much more than those of the latter system. Interestingly, someone taking a ''parasite's view'' might mistakenly be led to conclude that the evolution of virulence in these systems mainly involves reductions in host fecundity through the parasite exploiting the host, despite the fact that this parasite does not, in itself, impose any fecundity cost on the host. Rather, the coevolution of host immunological up-regulation has essentially transferred the mortality cost of exploitation by the parasite into a fecundity cost through the evolution of expensive, fecundity-reducing defense mechanisms. This contrasts sharply with previous theory that has used v as a measure of parasite-induced mortality, and is due to the fact that the actual mortality experienced by the host (i.e., the probability of death once infected) is a result of the combined action of the host's clearance rate and the parasite's level of exploitation that has coevolved. This also illustrates an inherent difficulty in trying to ascribe virulence (i.e., reduced host fitness of infected hosts) to either the host or the parasite. The pattern of virulence exhibited is a result of the interaction between host and parasite, and it is this interaction that is shaped by natural selection.

Case mortality is predicted to be constant across differently coevolved host-parasite systems (provided that n remains constant) because the evolution of a high clearance rate in the host selects for the evolution of a high level of exploitation by the parasite. These produce conflicting effects on host case mortality that exactly cancel, leaving it unaffected. It should be noted that, although this exact cancellation need not hold for other functional forms of $\beta(v)$, the conflicting effects of v and c on case mortality as a result of host-parasite coevolution will likely still be true quite generally (Day 2002a). Therefore, even though formulations of the model using other functions for $\beta(v)$ predict that case mortality *will* vary across co-evolved systems, it often changes very little due to these conflicting effects. For example, if instead we suppose that transmission and virulence are related according to $\beta(v) = a_1 v/(a_2 + v)$, then the evolutionarily stable level of parasite-induced mortality is given by $v^* = \sqrt{a_2}\sqrt{u + c}$, and thus case mortality at the ESS is given by $\chi^* = \sqrt{a_2}/(\sqrt{a_2} + \sqrt{u + c})$. Figure 2 reveals that, even under this scenario, case mortality changes very little across most of the values of $u + c$.

Our results suggest that it will often be difficult to accurately ascribe the fitness reductions of infected hosts to either the costs of immunological up-regulation or parasite evolution from the study of coevolved hosts and parasites. Nevertheless, a potentially powerful approach at dissecting such coevolved interactions is to cross infect different hosts with one another's coevolved parasite strains (e.g., Perlman and Jaenike, submitted). This would allow a more detailed understanding of which components of reduced host fitness result from each of the two parties. It should also be noted, however, that data other than case mortality and fecundity reductions can be gathered that provide important information about host parasite co-evolution. For example, in our model expected host lifespan, L, will vary across differently coevolved host-parasite systems despite the fact that case mortality will not.

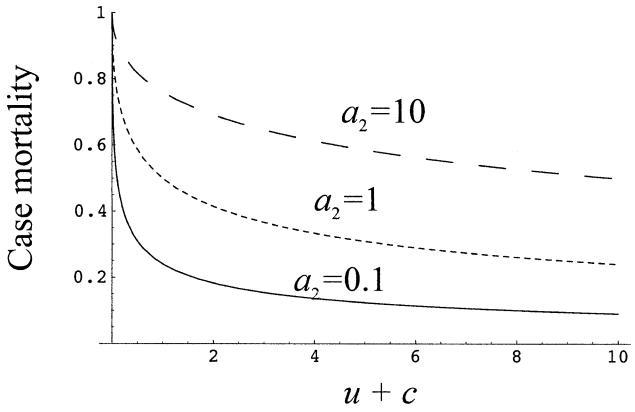

FIG. 2. The relationship between case mortality and host mortality plus clearance rate (i.e., $u + c$) at the evolutionarily stable level of virulence, assuming that transmission and virulence are related according to the function $\beta(v) = a_1 v/(a_2 + v)$.

Our model was not designed to describe host-parasite coevolution in general, but rather to illustrate two important factors in this process that have not yet garnered much attention. One of these is that host-parasite coevolution will often produce conflicting effects on case mortality thereby leaving it relatively constant. The other is that, despite the fact that a parasite might, in itself, induce only a mortality effect on its host, the coevolution of immunological up-regulation by the host can result in a pattern that appears as though the parasite causes only a fecundity reduction instead. The previous theory to which ours is most directly comparable is that of van Baalen (1998). He followed most previous theory in taking v to be a measure of the extent to which a parasite kills its host. Thus, cases in which very different values of v were expected to evolve were taken as ones where we expect parasites to induce very different levels of mortality. However, our results show that this need not be true if we look at case mortality. Van Baalen (1998) also focused on costs of immune system maintenance, and therefore did not explore how the evolution of up-regulation can impose fitness costs on the host that combine with parasite exploitation in potentially complex ways to produce patterns of ''virulence.''

We have focused on host-parasite systems in which the parasite induces a mortality cost on the host, and immunological up-regulation induces a fecundity cost. Although this formed a logical starting place, more generally we might expect mortality and fecundity costs to result from both exploitation by the parasite, as well as by immunological up-regulation. For example, costs of the immune system might not only lower reproductive rate but also increase the natural mortality rate, such as was found in bumblebees by Moret and Schmid-Hempel (2001). It would be worthwhile to de-

velop models that incorporate such features to produce a more comprehensive theory for making predictions about how host-parasite coevolution is expected to affect the fitness costs endured by infected hosts.

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Appendix

Equilibrium levels of S and I for equations 1 and 2 are:

$$S = \frac{c + u + v}{\beta}, \qquad I = \frac{(b_S - u)(c + u + v)}{(u + v - b_I)\beta} \quad \text{and} \quad \begin{matrix} S = 0, \\ I = 0. \end{matrix} \tag{A1}$$

The Jacobian matrix for this system is:

$$\begin{bmatrix} b_S - u - \beta I & b_I + c - \beta S \\ \beta I & \beta S - c - u - v \end{bmatrix}. \tag{A2}$$

Therefore, the non-trivial equilibrium is locally stable provided that $b_S > u$ and $b_I < u + v$. The ability of the mutant to invade can be determined from the eigenvalues of the Jacobian matrix of the augmented system when S_2 and I_2 are zero:

$$\begin{bmatrix} b_S - u - \beta I_1 & b_I(c) + c - \beta S_1 & 0 & -\beta S_1 \\ \beta I_1 & \beta S_1 - c - u - v & 0 & \beta S_1 \\ 0 & 0 & b_S - u - \beta I_1 & b_I(\hat{c}) + \hat{c} \\ 0 & 0 & \beta I_1 & -\hat{c} - u - v \end{bmatrix}. \tag{A3}$$

This is an upper triangular matrix, so the eigenvalues are simply those of the two 2×2 block-diagonal elements. The upper left 2×2 block diagonal element is identical to the Jacobian matrix from the original system (A2), and since we are only interested in resident host populations that are at a stable endemic equilibrium, the two eigenvalues of this sub-matrix must have negative real parts. Thus, the stability depends only on the eigenvalues of the lower right 2×2 block-diagonal element. The trace and determinant of the lower right quadrant are, respectively:

$$b_S - \hat{c} - 2u - v - \beta I \tag{A4}$$

$$(u - b_S)(\hat{c} + u + v) + \beta I(c)[u + v - v_I(\hat{c})]. \tag{A5}$$

The equilibrium is stable when the trace is negative and the determinant is positive. It can be shown that the trace, (A4), is negative, and therefore stability is determined by the determinant, (A5). Because this must be negative for the mutant to invade, multiplying this expression by -1 produces equation (9) of the text for the mutant's fitness.