A CONSIDERATION OF PATTERNS OF VIRULENCE ARISING FROM HOST-PARASITE CO-EVOLUTION

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Abstract.--
In this article we explore how host survival and fecundity are affected by host-parasite co-evolution. We examine a situation in which hosts can mount a defensive response upon being infected in order to clear the infection, but where 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 co-evolutionary 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 co-evolved host and parasite strategies. In particular, despite the fact that the parasite imposes only a mortality cost on the host, co-evolution 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 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.

Keywords.—case mortality, immunological up-regulation, fecundity, pathogen, infection, clearance
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 of that system when infection occurs. While the benefits of such defenses to a host are obvious, empirically determining the costs of these defenses has proven difficult (Lochliller and Deerenberg 2000). In particular, it has proven most difficult to adequately test for costs of physical defenses and immune system maintenance, while 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-Hemapel 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 co-evolve 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 co-evolution (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 co-evolution 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 co-evolutionary 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, $c$ (i.e., the probability of dying once infected), which is defined by $c = v / (v + c + u)$ 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; see Day 2002a for more general formulations). 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). Since these will have conflicting effects on case mortality, it remains unclear how host-parasite co-evolution 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. Here, however, 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), as 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 (Day and Burns, unpubl. results).

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

\[
\frac{dS}{dt} = b_S S + b_I(c) I \left[ uS + cI \right] - bSI
\]

(1)

\[
\frac{dI}{dt} = bSI \left[ u + v + c \right] I
\]

(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 $\beta$ 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, $\beta$, 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, in press).

System (1-2) has one non-trivial equilibrium. The conditions for its local stability are (Appendix):

\[
b_S > u \quad \text{(3)}
\]

and

\[
b_I < u + v \quad \text{(4)}
\]

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 co-evolutionarily 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:

\[
\frac{dS_1}{dt} = b_S S_1 + b_I (c) I_1 u S_1 + c I_1 \beta S_1 I_1 \beta S_1 I_2
\]

(5)
\[
\frac{dI_1}{dt} = bS_1I_1 + bS_1I_2(\mu + \nu + c)I_1 
\]

(6)

\[
\frac{dS_2}{dt} = b_S S_2 + b_S(\hat{c})I_2 \mu u S_2 + \hat{c}I_2 \mu S_2 I_1 \mu S_2 I_2 
\]

(7)

\[
\frac{dI_2}{dt} = bS_2I_1 + bS_2I_2(\mu + \nu + \hat{c})I_2 
\]

(8)

The subscripts 1 and 2 denote resident and mutant strains respectively. Hence, 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

\[
W(\hat{c},c) = \mu(\mu u b_S)\hat{c} + \mu u + \nu)(\mu + \nu b_S(\hat{c}) 
\]

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

\[
\frac{\partial W}{\partial \hat{c}} \bigg|_{\hat{c}=c} . 
\]

(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

\[
\frac{d}{dc} \left[ \frac{\partial W}{\partial \hat{c}} \right] \bigg|_{\hat{c}=c^*} < 0. 
\]

(11)

Additionally, this equilibrium is evolutionarily stable provided that

\[
\frac{\partial^2 W}{\partial \hat{c}^2} \bigg|_{\hat{c}=c^*} < 0. 
\]

(12)

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

\[
\frac{\partial W}{\partial \hat{c}} \bigg|_{\hat{c}=c} = (b_S \mu u) + \frac{(c + u + \nu)(b_S \mu) \frac{db_I}{dc}}{(u + \nu b_I)}. 
\]

(13)

From the form of equation (13), we can see that when the costs of immunological up-regulation are linear (e.g., \( b_I(c) = b_S \mu \mu c \)), there is no intermediate ESS since this
equation reduces to an expression proportional to \((u + v)(1 \square) \square b_S\), which is either positive or negative. Therefore, if the cost of up-regulation is large (i.e., \square 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., \(c = b_S / \square\)) 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 (Day and 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 non-linear costs such that \(b_I(c) = b_S (1 - c^2)\). The ESS clearance rate is then,

\[
c^* = \frac{(u + v) \square + \sqrt{(u + v) \square b_S + (u + v)^2}}{\square}.
\]  

Thus, the ESS clearance rate decreases as the cost of up-regulation, \(\square\), or the fecundity of susceptibles, \(b_S\), increases, and it increases as the host’ background mortality rate, \(u\), increases (Figure 1). Importantly, it increases as the parasite-induced mortality rate, \(v\), increases as well (Figure 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 \(\frac{\partial^2 W}{\partial v \partial c} > 0\) (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, $b$, are positively related to the level of host exploitation by the parasite, $e$. 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; see Lipsitch and Moxon 1997, for discussion).

Under this assumption, both $b$ and $v$ are treated as increasing functions of $e$. Therefore, to simplify the analysis we can capture the positive relationship between $b$ and $v$ (mediated through their mutual dependence on $e$) by simply treating $b$ 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 $R = b/(u + c + v)$ (Frank 1996). Therefore the ESS value, $v^*$, must satisfy

$$\frac{d}{dv} \left( b \right) \left( n + v + c \right) = 0.$$  \hspace{1cm} (15)

Throughout we will assume that $\frac{d^2}{dv^2} < 0$ 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; $b(v) = mv^n$, where $0 < n < 1$. In this case the ESS level of $v$ is

$$v^* = \frac{n}{1-n}(u + c).$$  \hspace{1cm} (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 $b - v$ 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, \( \square \) (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, \( \square \). Doing so reveals a very simple result:

\[
\square^* = n. \tag{17}
\]

Surprisingly, this reveals that the case mortality that is expected to evolve is completely determined by the shape of the trade-off between \( \square \) 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 (see Day 2002a for more general results of this sort).

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

\[
L^* = \frac{1}{c + u} \frac{\square n}{u}. \tag{18}
\]

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.

*Co-Evolutionarily 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 co-evolutionarily 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 \(b(v)\), 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 co-evolutionary dynamics of host and parasite, the case mortality of the host is not. Rather, case mortality is still simply \(n^* = n\), and therefore it is completely determined by the parasite’s transmission/mortality rate trade-off. As suggested by the previous sections, the co-evolutionary dynamics of host and parasite affect the degree of up-regulation that evolves, as well as the expected lifespan 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 co-evolutionary outcomes in terms of \(v^*\) and \(c^*\) might occur as a result of co-evolution 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 co-evolution 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 co-evolution 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 co-evolution 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 co-evolved. 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 co-evolved 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 \( \bar{b}(v) \), the conflicting effects of \( v \) and \( c \) on case mortality as a result of host-parasite co-evolution will likely still be true quite generally (Day 2002a). Therefore, even though formulations of the model using other functions for \( \bar{b}(v) \) 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 the transmission and virulence are related according to \( \bar{b}(v) = a_1 v / (a_2 + v) \), then the evolutionarily stable level of parasite-induced mortality is given by \( v^* = \sqrt[2]{a_2 \sqrt{a + c}} \), and thus case mortality at
the ESS is given by $c^* = \frac{a_2}{\sqrt{a_2 + \sqrt{u + c}}}$. 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 co-evolved hosts and parasites. Nevertheless, a potentially powerful approach at dissecting such co-evolved interactions is to cross infect different hosts with one another’s co-evolved 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 co-evolved host-parasite systems despite the fact that case mortality will not.

Our model was not designed to describe host-parasite co-evolution 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 co-evolution 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 co-evolution 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 develop models that incorporate such features to produce a more comprehensive theory for making predictions about how host-parasite co-evolution 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:

\[
S = \frac{c + u + v}{u + v}, \quad I = \frac{(b_S u)(c + u + v)}{(u + v b_I)} \quad \text{and} \quad S = 0, I = 0.
\] (A1)

The Jacobian matrix for this system is:

\[
\begin{pmatrix}
& b_I + c & S \\
& S & c & u & v
\end{pmatrix}
\] (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:

\[
\begin{pmatrix}
& b_I(c) + c & S_1 \\
& S_1 & c & u & v \\
& 0 & 0 & b_S u & I_1 \\
& 0 & 0 & I_1 & \hat{c} + \hat{c}
\end{pmatrix}
\] (A3)

This is an upper triangular matrix, so the eigenvalues are simply those of the two 2x2 block-diagonal elements. The upper left 2x2 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 2x2 block-diagonal element. The trace and determinant of the lower right quadrant are, respectively:

\[
\begin{align*}
\text{trace} &= b_S \hat{c} + 2u v < 0, \\
\text{determinant} &= (u b_S)(\hat{c} + u + v) + I(c)(u + v b_I \hat{c})< 0.
\end{align*}
\] (A4)

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). Since 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.
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Figure 1
The relationship between the evolutionarily stable level of up-regulation and parasite virulence (i.e. Equation 14) for a variety of different parameter values. (a) $b_S=5$, $u=0.5$. (b) $u=0.5$, $l=20$. (c) $b_S=5$, $l=20$.

Figure 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 $\bar{u}(v) = \frac{a_1 v}{a_2 + v}$.
(a)

(b)

(c)
Case mortality

\[ a_2 = 10 \]

\[ a_2 = 1 \]

\[ a_2 = 0.1 \]