

On the evolution of virulence and the relationship between various measures of mortality

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Smallpox causes roughly 20% mortality whereas chickenpox causes less than 0.1%. Most ‘verbal’ (i.e. non-mathematical) discussions using a mortality definition of virulence would therefore label smallpox as more virulent. Indeed, the virulence of many diseases is measured using such case mortalities, χ , or related measures such as expected host lifespan, T , or lethal dose, LD_x . But χ , T and LD_x are only indirectly related to parasite-induced instantaneous mortality rate, α , which is the mortality measure used in much of the theory developed to explain virulence evolution. Here I point out that relatively deadly pathogens can actually have lower values of α than benign pathogens, demonstrating that α does not, by itself, reflect the extent to which a parasite causes host mortality. I present mathematical relationships between α and χ , T and LD_x , and use these to demonstrate that predictions about virulence evolution can be qualitatively altered depending upon which measure is used as the definition of virulence. Two simple examples are presented to illustrate this point, one of which demonstrates that the well-cited prediction that virulence should evolve to be higher when disease-independent host mortality increases need not hold. This prediction has been made in terms of parasite-induced instantaneous mortality, α , but if virulence is measured using case mortality (or T or LD_x) then this prediction can easily be reversed. Theoretical and empirical researchers must use compatible mortality measures before a productive exchange between the two can take place, and it is suggested that case mortality (or lethal dose) is best suited as a single (mortality) measure of parasite virulence.

Keywords: lethal dose; case mortality; expected lifespan; parasite; pathogen; disease

1. INTRODUCTION

In the absence of co- or super-infection (Nowak & May 1994; May & Nowak 1995), many epidemiological models have revealed that the basic reproduction ratio (Diekmann *et al.* 1990; Frank 1996) is an important determinant of parasite evolution. In particular, the parasite strain with the largest reproduction ratio is able to exclude all other strains; i.e. it is evolutionarily stable. For many models, this ratio takes the form (Frank 1996)

$$R_0 = \frac{\beta}{\alpha + \gamma + \delta}. \quad (1.1)$$

Here β is the transmission rate per unit time of the parasite from infected to susceptible hosts, δ is the disease-independent host mortality rate, γ is the rate of parasite clearance by host defence mechanisms and α is the parasite-induced mortality rate. Note that all parameters in equation (1.1) are instantaneous rates, and that this formulation assumes all these rates are constant.

Theory on virulence evolution often uses parasite-induced instantaneous mortality rate, α , as the definition of a parasite’s virulence (Bull 1994; Read 1994; Frank 1996; Levin 1996). This is often justified by arguing that it represents the extent to which the parasite causes mortality in its host. One of the dominant paradigms in the study of virulence evolution is that trade-offs between α and other parameters in equation (1.1) dictate the level of α that we expect to evolve, and therefore dictate the extent to which we expect a parasite to cause mortality in its host. In particular, it is often assumed that α , β and γ all depend on the underlying host exploitation strategy, ε , employed

by the parasite (which might be measured by parasite replication rate or density within the host). Indeed, an increasing body of evidence (Anderson & May 1982; Ebert 1994; Ebert & Mangin 1997; Lipsitch & Moxon 1997; Mackinnon & Read 1999; Messenger *et al.* 1999) suggests that α , β and γ do in fact differ for different exploitation strategies (i.e. different parasite genotypes). For example, parasite-induced instantaneous mortality rate, α , is often thought to increase with exploitation, ε , as is the transmission rate, β . Therefore, in principle this framework can be used to predict the level of virulence that evolves by finding the value of ε that maximizes R_0 , and then determining the level of α to which this corresponds.

There are, however, some important difficulties with using α as the definition of virulence. From an evolutionary standpoint, the term ‘virulence’ usually refers to the extent to which a parasite reduces its host’s fitness (Bull 1994; Read 1994). This can involve changes in host fecundity and/or mortality, but it is the effect on host mortality that perhaps has received the most attention. Importantly, there are several ways in which parasite-induced mortality can be quantified, in addition to the instantaneous mortality rate α . Three of the most common alternatives are: (i) case mortality (i.e. the probability of parasite-induced host death once infected)—larger values represent higher virulence; (ii) expected time until death from infection—smaller values represent higher virulence; and (iii) lethal dose—smaller values represent higher virulence. As will be argued below, α does not actually correspond to the measure of parasite-induced mortality that is often used in ‘verbal’ discussions of virulence

evolution, nor does it correspond to the mortality measure of virulence used in many empirical studies directed towards testing theory. In fact, as will be seen, α is not actually, by itself, a measure of the extent to which a parasite causes mortality in its host. Therefore, its use as an evolutionary definition of virulence is, to some degree, questionable.

The main purpose of this article is to determine the extent to which predictions about virulence evolution using α as the mortality measure correspond, qualitatively, to predictions about virulence evolution when using these other mortality measures. This is an important question because, if predictions from different mortality measures are qualitatively at odds, then a fruitful exchange between theoretical and empirical research will be possible only if both use compatible mortality definitions of virulence. The results presented below indicate that, to a large extent, this is not the case. Some well-cited predictions about virulence evolution can be qualitatively incorrect according to the mortality measures that are used in many empirical studies. For example, the vast majority of theory predicts that virulence should evolve to be higher if disease-independent host mortality rate, δ , increases (Anderson & May 1982; Sasaki & Iwasa 1991; Kakehashi & Yoshinaga 1992; Lenski & May 1994; Ebert & Weisser 1997; Day 2001; but see Williams & Day 2001). Importantly, this prediction has been made in terms of α , while many data on virulence are quantified as case mortality, expected lifespan or lethal dose. The results below demonstrate that this prediction about the relationship between virulence and δ can easily be reversed if virulence is quantified using these other mortality measures. In fact, what turns out to be critical in all of the results below is the relationship between the instantaneous mortality rate that a parasite induces on its host, the transmission rate, and the rate of clearance of the parasite by the host's defence mechanisms.

2. MORTALITY MEASURES OF VIRULENCE

Several mathematical models have explored how various host and/or parasite factors affect the evolutionarily stable level mortality that a parasite imposes on its host (i.e. virulence). A great deal of this theory uses α as the measure of virulence. To determine the extent to which predictions about virulence evolution using either case mortality, expected lifespan or lethal dose as the mortality measure differ from these results, I begin by supposing that we have a model specifying the dependence of the evolutionarily stable exploitation strategy, ε^* , on some parameter of interest, σ .

Because the parasite-induced instantaneous mortality rate, α , depends on the exploitation strategy, when σ changes, the evolutionarily stable value of α (i.e. α^*) will change as well. In fact, α^* might change for two reasons: (i) because α depends on ε , and ε^* changes when σ changes, and (ii) because α might depend on σ directly. This latter dependence will not always be of interest, but it might occur if, for example, σ represents some feature of the host (e.g. age). In this case, even for a fixed exploitation strategy, the mortality rate induced by the parasite might change as this feature of the host is varied. Therefore, in general we can denote these dependences as

$\alpha(\varepsilon, \sigma)$. Similar considerations hold for the clearance rate γ ; i.e. $\gamma(\varepsilon, \sigma)$. As a result, if σ is increased by a small amount, we can differentiate α with respect to σ to obtain an expression specifying how the evolutionarily stable value of α will change:

$$\frac{\partial \alpha}{\partial \varepsilon} \frac{d\varepsilon^*}{d\sigma} + \frac{\partial \alpha}{\partial \sigma} \quad (2.1)$$

This expression simply reflects the two different ways in which an increase in σ can affect α : indirectly through a change in ε^* (which gives $(\partial \alpha / \partial \varepsilon)(d\varepsilon^* / d\sigma)$) and directly through a potential dependence of α directly on σ (which gives $\partial \alpha / \partial \sigma$). Note that typically ε is defined so that $\partial \alpha / \partial \varepsilon > 0$, and therefore in the absence of a direct dependence of α on σ , α^* changes in a direction given by the sign of $d\varepsilon^* / d\sigma$.

I now consider how the evolutionarily stable value of case mortality, expected lifespan and lethal dose are expected to change with an increase in σ , and compare these with equation (2.1).

(a) Case mortality

Case mortality, χ , seems to be the measure of virulence that most 'verbal' discussions implicitly assume. It is also one of the most common measures of virulence for human infectious diseases and quantifies the likelihood of death due to disease (once infected). As such, case mortality does reflect the degree to which a parasite causes mortality in its host, and therefore it fits well within the broader evolutionary perspective on virulence. For the simple epidemiological model of § 1, we have the relationship (Appendix A)

$$\chi(\varepsilon, \sigma) = \frac{\alpha(\varepsilon, \sigma)}{\alpha(\varepsilon, \sigma) + \gamma(\varepsilon, \sigma)} \quad (2.2)$$

Note that equation (2.2) holds, conditional upon the host not dying of natural causes. Without such conditioning we have the relationship $\chi = \alpha / (\alpha + \gamma + \delta)$.

From equation (2.2) we can immediately see that the relationship between case mortality and α can be positive or negative. In particular, given a χ , the corresponding α can be either high or low depending on the magnitude of the clearance rate, γ . This illustrates the simple but often under-appreciated fact that α is not actually, in itself, a measure of the extent to which a parasite causes mortality. Indeed, if we focused only on α as a measure of virulence, diseases that significantly reduce host fitness by causing relatively high mortality (i.e. high χ) would be considered less virulent than those that cause relatively low mortality (i.e. low χ) if they also have a clearance rate that is low enough. Of course, it is possible to identify such cases as those having a high case mortality that results from a low α acting over a long duration (because the rate of host recovery is also low). Nevertheless, it is clear that information other than α is necessary to do so (e.g. Fenner & Ratcliffe 1965; Anderson & May 1982). Consequently, attempts to explain why some parasites cause high host mortality by focusing solely on the evolution of α are, in general, inadequate.

These considerations make it clear that, in order to predict the evolutionarily stable level of case mortality, we need to know how α and γ are interrelated through ε . For example, neglecting the direct dependence of α and γ on

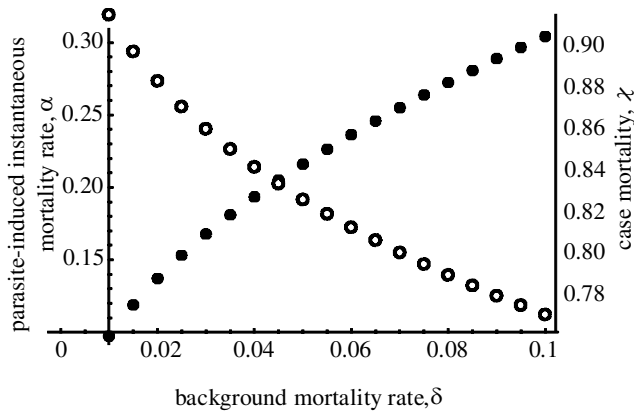


Figure 1. The evolutionarily stable instantaneous mortality rate and case mortality as a function of disease-independent host mortality rate, δ . Filled circles, α : the well-cited prediction that increases in δ lead to the evolution of higher virulence (when measured as α). Open circles, χ : increases in δ can easily lead to the evolution of lower χ even though α increases. Results were obtained by maximizing R_0 in equation (1.1) for different values of δ , where $\beta(\varepsilon) = 1 - e^{-0.1\varepsilon}$, $\alpha(\varepsilon) = \varepsilon$ and $\gamma(\varepsilon) = \varepsilon^2$, and then plotting $\alpha(\varepsilon^*)$ or $\alpha(\varepsilon^*)/(\alpha(\varepsilon^*) + \gamma(\varepsilon^*))$ against δ .

the parameter σ , and assuming that ε is defined such that α increases with ε , we can see from equation (2.2) that if γ decreases with ε (or is independent of ε), then larger values of α^* (which correspond to larger values of ε^*) will correspond to larger values of χ^* ; i.e. predictions about virulence evolution will be qualitatively the same using either measure. This need not be true if γ increases with ε (figure 1), and if there is a direct dependence of α and γ on the parameter σ , the relationship between predictions using α and those using χ is even more complex. By differentiating equation (2.2) with respect to σ , we see that, if σ is increased by a small amount, the evolutionarily stable level of χ will change in a direction given by the sign of

$$\frac{\partial \alpha}{\partial \varepsilon} \frac{d\varepsilon^*}{d\sigma} + \frac{\partial \alpha}{\partial \sigma} - \frac{\alpha}{\gamma} \left(\frac{\partial \gamma}{\partial \varepsilon} \frac{d\varepsilon^*}{d\sigma} + \frac{\partial \gamma}{\partial \sigma} \right). \quad (2.3)$$

A comparison of equation (2.3) with equation (2.1) reveals that, in general, we do not expect predictions about α^* to correspond to predictions about χ^* since the sign of equation (2.3) can easily differ from that of equation (2.1).

Equation (2.2) is derived assuming that the instantaneous rates, α and γ , are constants, but this is probably rarely true. If these rates vary during an infection, then case mortality is given by (Appendix A)

$$\chi(\varepsilon, \sigma, p_0) = \frac{\int_0^{\infty} \alpha(\varepsilon, \sigma, p_0; t) l(t) dt}{\int_0^{\infty} \alpha(\varepsilon, \sigma, p_0; t) l(t) dt + \int_0^{\infty} \gamma(\varepsilon, \sigma, p_0; t) l(t) dt}, \quad (2.4)$$

where

$$l(t) = \exp \left[- \int_0^t \{ \alpha(\varepsilon, \sigma, p_0; s) + \gamma(\varepsilon, \sigma, p_0; s) + \delta \} ds \right]$$

(which is the probability that the infection lasts until time t) and $\alpha(\varepsilon, \sigma, p_0; t)$ and $\gamma(\varepsilon, \sigma, p_0; t)$ are the instantaneous mortality and clearance rates at time t during the infection for a parasite with exploitation strategy ε and inoculum size p_0 . The dependence of α and γ on the inoculum size reflects the fact that the dynamics of the mortality and clearance rates during an infection will probably be affected by the initial parasite density. Moreover, p_0 plays a central role in measures of virulence based on lethal dose as explained below.

With this more realistic model, parasite-induced instantaneous mortality rate, α , varies during an infection, but it can still be used as an index of virulence. Of course now it is even less clear how predictions about the evolutionarily stable level of χ will compare with those for the time course of α during an infection. Moreover, the pattern of variation in both α and γ during the infection (as well as their relative magnitudes) has a large influence on the case mortality rate (figure 2a). Quite generally, however, as σ increases, the evolutionarily stable level of χ changes in a direction given by the sign of

$$\frac{\partial \chi}{\partial \varepsilon} \frac{d\varepsilon^*}{d\sigma} + \frac{\partial \chi}{\partial \sigma}, \quad (2.5)$$

which clearly need not bear any correspondence to the sign of equation (2.1).

(b) Expected lifespan

Another measure of virulence is the expected lifespan of a host given that it dies from infection. The reasoning is that a shorter expected lifespan corresponds to higher virulence. If α and γ are constant during the infection then we have (Appendix A)

$$T(\varepsilon, \sigma) = \frac{1}{\alpha(\varepsilon, \sigma) + \gamma(\varepsilon, \sigma) + \delta}. \quad (2.6)$$

As with case mortality we can see that the relationship between α and T can be positive or negative. Even if both α and γ do not depend directly on the parameter σ , T can either increase or decrease as ε (and therefore α) increases depending upon how the clearance rate γ changes with host exploitation. It is only when γ increases with ε that we are guaranteed that T will behave in a way that corresponds to the behaviour of α (i.e., T decreases as α increases). In fact, by differentiating equation (2.2) with respect to σ , we see that if σ is increased by a small amount, the evolutionarily stable level of T will change in a direction given by the sign of

$$- \left\{ \frac{\partial \alpha}{\partial \varepsilon} \frac{d\varepsilon^*}{d\sigma} + \frac{\partial \alpha}{\partial \sigma} \right\} - \left\{ \frac{\partial \gamma}{\partial \varepsilon} \frac{d\varepsilon^*}{d\sigma} + \frac{\partial \gamma}{\partial \sigma} \right\}. \quad (2.7)$$

If predictions about virulence evolution using T were to correspond, qualitatively, to predictions when using α , then the sign of equation (2.7) would have to be the opposite to that of equation (2.1); higher virulence corresponds to a lower expected lifespan. Clearly this need not be the case. In general, we do not expect predictions about α^* to correspond to predictions about T^* . More generally, if the rates α and γ vary during an infection, then we have (Appendix A)

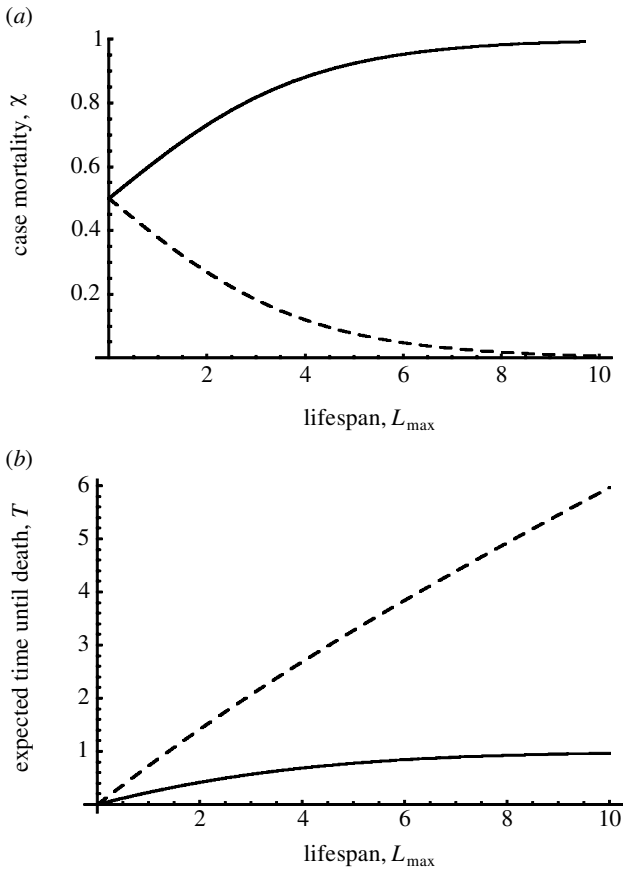


Figure 2. (a) A simple example of the effect of the timing of mortality rate, α , and clearance rate, γ , on case mortality. Average instantaneous mortality and clearance rates over the infection are the same (one-half), and for simplicity the host has a fixed maximal lifespan of L_{max} . Also, the times at which clearance or mortality occurs during the infection do not overlap. Solid line (mortality first): $\alpha = 1, \gamma = 0$ from 0 to $L_{max}/2$ and $\alpha = 0, \gamma = 1$ thereafter. Dashed line (clearance first): $\alpha = 0, \gamma = 1$ from 0 to $L_{max}/2$ and $\alpha = 1, \gamma = 0$ thereafter. Case mortality was calculated using equation (2.4). For any fixed lifespan, L_{max} , case mortality, χ , differs depending on the timing (i.e. whether mortality or clearance happens first). Also note that $\chi \rightarrow 1$ as L_{max} gets large if mortality happens first and $\chi \rightarrow 0$ if clearance happens first. (b) Expected infection lifespan, T , for the same parameter specifications as in (a) (i.e. the average lifespan of an infected host). T can differ dramatically depending on the timing of α and γ . Also, the behaviour of T and χ as a parameter (e.g. L_{max}) increases can agree (dashed lines) or disagree (solid lines) depending on the timing of α and γ . Results for T were calculated using equation (2.8).

$$T(\varepsilon, \sigma, p_0) = \frac{\int_0^\infty \alpha(\varepsilon, \sigma, p_0; t) l(t) t dt}{\int_0^\infty \alpha(\varepsilon, \sigma, p_0; t) l(t) dt}, \tag{2.8}$$

where, again,

$$l(t) = \exp \left[- \int_0^t \{ \alpha(\varepsilon, \sigma, p_0; s) + \gamma(\varepsilon, \sigma, p_0; s) + \delta \} ds \right].$$

Quite generally, when σ is increased, the evolutionarily stable value of T will change in a direction given by the sign of

$$\frac{\partial T}{\partial \varepsilon} \frac{d\varepsilon^*}{d\sigma} + \frac{\partial T}{\partial \sigma} \tag{2.9}$$

which need not bear any correspondence to the sign of equation (2.1). Also note that, in general, it is not clear that predictions using T will bear any correspondence to predictions using χ either. Moreover, the pattern of variation in both α and γ during the infection (as well as their relative magnitudes) has a large influence on T , as well as on the relationship between T and case mortality (figure 2).

(c) **Lethal dose**

Lethal dose, LD_x , has often been used as a mortality measure of virulence in empirical studies, particularly those involving experimental manipulations. LD_x is the size of the parasite inoculum required to produce a case mortality of $x\%$. Obviously this measure is closely related to case mortality, χ , but theoretical predictions about the evolution of LD_x can be made only if the theory explicitly incorporates within-host dynamics of the parasite. The reason is that there must be a mechanistic link between the inoculum size, p_0 , host mortality and recovery during the infection (e.g. Diekmann *et al.* 1990; Anderson & May 1991, ch. 11; Sasaki & Iwasa 1991; Antia *et al.* 1994; Levin *et al.* 1996; Day 2002). Doing so necessitates allowing β, α and γ to vary over the course of an infection, and thus we must use equation (2.4) for calculating case mortality. LD_x is then the value of p_0 satisfying the equation

$$\chi(\varepsilon, \sigma, p_0) = x. \tag{2.10}$$

By implicitly differentiating equation (2.10) with respect to σ , we can determine that, when σ is increased, LD_x will change in a direction given by the sign of

$$- \left\{ \frac{\partial \chi}{\partial \varepsilon} \frac{d\varepsilon^*}{d\sigma} + \frac{\partial \chi}{\partial \sigma} \right\}. \tag{2.11}$$

Equation (2.11) is simply the negative of that for case mortality, equation (2.5); a parasite strain that causes a higher case mortality requires a lower inoculum size to achieve a given case mortality level. This indicates that lethal dose and case mortality are just different ways of measuring the same thing. I stress, however, that there is a subtle reason why χ and LD_x can behave differently with respect to an increase in σ . Remember that χ depends upon p_0 and therefore the two terms in equations (2.5) and (2.11) depend on p_0 as well. In general, there is no reason to expect that each term will have the same magnitude or even the same sign for all values of p_0 . The inoculum size, p_0 , used to determine case mortality will probably often be close to that of a natural setting, and this is the value that would be used in equation (2.5). The inoculum size used to determine LD_x , however, will depend on the mortality level, x , chosen. If x is substantially larger than the typical case mortality in a natural setting, then the value of p_0 required will be larger than that of the natural setting as well. In this case χ and LD_x might well behave differently as σ increases. The model

of virulence evolution presented in Ganusov *et al.* (2002) is an interesting example that illustrates this point very well. If the mortality level, x , chosen is one that is comparable with natural case mortality levels, however, then we are guaranteed that predictions using χ or LD_x will be the same.

To close this section, I should also point out that, while equations (2.2) and (2.6) illustrate how to calculate χ and T if α , γ and δ are known (assuming these are constant), it is possible to do the reverse and calculate α and γ given that we know χ , T and δ . Equations (2.2) and (2.6) can be used to derive the relationships

$$\alpha = \frac{\chi}{T}(1 - \delta T) \quad (2.12)$$

and

$$\gamma = \frac{(1 - \chi)}{T}(1 - \delta T). \quad (2.13)$$

If instead we calculate case mortality without conditioning on the host not dying of natural causes, then we have

$$\alpha = \frac{\chi}{T} \quad (2.14)$$

and

$$\gamma = \frac{1 - \chi}{T} - \delta. \quad (2.15)$$

These equations might prove useful as a way to indirectly quantify α and γ if χ , T and δ are easier to measure. It should be emphasized, however, that in the more realistic scenario in which both α and γ vary during an infection, knowing both χ and T does not allow one to calculate these instantaneous rates.

3. DISCUSSION

The amount of effort directed towards understanding the evolution of virulence has increased substantially over the past 20 years, both by theoretical and empirical researchers (Anderson & May 1991; Ewald 1994; Stearns 1999; Dieckmann *et al.* 2002). This topic is clearly of great interest from an academic standpoint, but it is also of interest from a more pragmatic standpoint. One hope is that ultimately we will be able to use this knowledge to manage the evolution of parasite virulence in the future (Dieckmann *et al.* 2002). Of course, doing so will require a close feedback between theory and experiment, and the results presented here will hopefully help in that regard.

The relationship between parasite transmission rate and parasite-induced host mortality rate across different parasite genotypes has become the focus of considerable attention in studies of virulence evolution because it plays a key role in predicting how parasite-induced host mortality rate should evolve (Anderson & May 1982; Ebert 1994; Ebert & Mangin 1997; Lipsitch & Moxon 1997; Mackinnon & Read 1999; Messenger *et al.* 1999). The results presented here argue that instantaneous parasite-induced host mortality rate does not, by itself, determine the extent to which a parasite will actually cause mortality in its host, but rather we require information on the clearance rate of the parasite by host defences as well. Therefore, consider-

able attention should also be directed towards this aspect of host–parasite interactions in addition to that of the transmission–mortality-rate relationship. It is the interrelationships between parasite transmission rate, parasite-induced mortality rate and parasite clearance rate across different parasite genotypes that determine how parasite-induced mortality, as measured by case mortality, lethal dose or expected lifespan, should evolve. Previous work has highlighted the importance of parasite clearance by the host as a factor in the evolution of parasite-induced instantaneous mortality rate, α (Anderson & May 1982, 1991; Frank 1992, 1996; Antia *et al.* 1994; Ebert & Herre 1996; Van Baalen 1998). The results presented here complement this earlier work by illustrating that not only is the evolution of α strongly affected by such factors, but the expected relationship between α and more commonly used empirical measures of virulence such as χ , LD_x and T cannot be predicted without considering the effects of clearance as well. Moreover, it is these latter measures of mortality that more accurately reflect the degree to which a parasite reduces its host's fitness through an increase in mortality, and therefore it is these that are probably the most suitable evolutionary definition of virulence.

In fact, there are several reasons why case mortality in particular (or lethal dose) is a good choice for a general, single measure of parasite-induced mortality (i.e. virulence). Case mortality is probably the mortality measure that many people have in mind when thinking about virulence evolution, as, from a human health perspective, we want to know the chance of dying from various parasites (once infected). Moreover, case mortality appears to be the (mortality) measure of virulence that is implicitly assumed in many 'verbal' discussions of virulence evolution. From a more conceptual standpoint, case mortality is probably a good choice for unifying theory on virulence evolution. Instantaneous mortality rate is useful mostly in models for which it is constant during an infection, whereas lethal dose is useful only for models that explicitly incorporate within-host dynamics. Case mortality, however, can be defined for both types of models and it provides a clear and relevant way to compare theoretical predictions. Moreover, when testing theory empirically, the results presented here demonstrate that experiments can use either LD_x or χ (subject to the caveats mentioned earlier) depending on which is easier, and obtain compatible results. Of course, a more complete description of the reduction in host fitness due to mortality would also include the timing of death (i.e. the expected lifespan, T), but as a single quantity, case mortality seems like a good choice. Additionally, it is worth noting that some experiments use surrogate measures of mortality such as cumulative weight loss when testing theory (e.g. Mackinnon & Read 1999). This is probably more closely related to case mortality than to instantaneous mortality rate, but it would be worthwhile exploring the relationship between these measurements in more detail.

It should be stressed, however, that although focusing on the evolution of α is not in general enough to understand why some parasites cause great mortality whereas others cause very little, this focus nevertheless provides the foundation from which further elaborations involving case mortality, expected lifespan or lethal dose can be made. Moreover, the interrelationships between parasite clear-

ance rate, transmission rate and parasite-induced mortality rate for some parasite species might well be such that focusing on the evolution of instantaneous mortality rate is sufficient. For instance, figure 1 shows that increases in disease-independent host mortality can actually lead to the evolution of lower virulence as measured by case mortality, in contrast to results using parasite-induced instantaneous mortality rate as the definition of virulence (Anderson & May 1982; Sasaki & Iwasa 1991; Kakehashi & Yoshinaga 1992; Lenski & May 1994; Ebert & Weisser 1997; Day 2001; Williams & Day 2001). This occurs because parasite clearance rate by host defences, γ , is assumed to increase with host exploitation as does parasite-induced mortality rate, α (figure 1). For example, this might occur if more extensive host exploitation (and thus a higher instantaneous mortality rate) also induces a stronger immunological response. Thus, although α evolves to higher levels under higher disease-independent mortality (as predicted by the studies cited above), so does γ , and the combined effect is a lower case mortality, χ . But if γ decreases with increased host exploitation, then these seemingly contradictory predictions will not occur because larger α 's will always be associated with larger χ 's (e.g. there is some suggestion that this is true for the myxomatosis–rabbit system (Fenner & Ratcliffe 1965; Anderson & May 1982), but see Fenner & Fantini (1999) for a discussion of potential methodological problems with these data). Similar issues arise when comparing predictions using α versus T as well (T. Day, unpublished results), but the conditions under which predictions from α correspond, qualitatively, to those using χ need not be the same as the conditions for correspondence between α and T . Therefore, it remains an open empirical issue as to whether focusing on α alone will be sufficient for any given parasite species. At the very least, however, predictions using lethal dose should always correspond to those using case mortality (subject to the caveats mentioned earlier).

The results presented here illustrate how we expect various measures of parasite-induced mortality to evolve given that we know how a parasite's host exploitation strategy evolves. Importantly, I have used only information from an underlying model's predictions about ε^* to derive these results. It is usually the case, however, that any model will impose additional constraints on various parameters that might thereby restrict the range of possible predictions. For example, in the simple epidemiological model of § 1, in which α , γ and δ are constant during an infection, it can be seen that predictions about virulence evolution using α will usually correspond to predictions using T . The reason is that, regardless of how α and γ change as the host exploitation strategy increases, $T = 1/(\alpha + \gamma + \delta)$ must decrease as ε increases if there is to be an intermediate evolutionarily stable exploitation strategy as $R_0 = \beta T$ and β is assumed to increase with ε . Therefore, assuming that α increases with ε , predictions about virulence evolution using T will correspond to those using α . Of course this is not true if α and γ vary during an infection, but it does serve to illustrate the point that there can be additional constraints placed on these various measures of mortality that restrict the range of possible predictions. Which constraints one should incorporate, however, depends on

what is deemed biologically reasonable for the parasite species in question.

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APPENDIX A

Here I derive an expression for case mortality. The following results are based on an underlying epidemiological model presented in Day (2001). Suppose that parasite-induced death, parasite clearance through an immune response, and disease-independent death are (mutually exclusive) events that happen stochastically during an infection, with rates α , γ and δ . I will suppose that α and γ might change during the infection as a result of changes in parasite density within the host. The probability that a host is still infected at infection age t is then given by

$$\exp\left[-\int_0^t \{\alpha(s) + \gamma(s) + \delta\} ds\right], \quad (\text{A } 1)$$

(infection age here refers to the time since the infection began—it is not host age (see Day 2001)). Therefore, the probability that a host has died of the disease by any given infection age (denoted by p_d) satisfies

$$\frac{dp_d}{dt} = \alpha(t) \exp\left[-\int_0^t \{\alpha(s) + \gamma(s) + \delta\} ds\right]. \quad (\text{A } 2)$$

Similarly, the probability that the host has cleared the disease, p_c , satisfies

$$\frac{dp_c}{dt} = \gamma(t) \exp\left[-\int_0^t \{\alpha(s) + \gamma(s) + \delta\} ds\right]. \quad (\text{A } 3)$$

As a result, we have

$$p_d(a) = \int_0^a \alpha(t) \exp\left[-\int_0^t \{\alpha(s) + \gamma(s) + \delta\} ds\right] dt, \quad (\text{A } 4)$$

$$p_c(a) = \int_0^a \gamma(t) \exp\left[-\int_0^t \{\alpha(s) + \gamma(s) + \delta\} ds\right] dt. \quad (\text{A } 5)$$

and thus case mortality (conditional upon the host not dying of natural causes) is given by

$$\chi = \frac{p_d(\infty)}{p_d(\infty) + p_c(\infty)}, \quad (\text{A } 6)$$

which is equation (2.4). If the rates α and γ are constant over the infection, then this simplifies to equation (2.2). One can also derive an expression for the expected lifespan of the host, given that it dies from infection, using these results. In particular, equation (A 4) is the probability that the host has died of infection by infection age a , and there-

fore we immediately get equation (2.8). Equation (2.6) can then be derived from this by assuming that rates α and γ are constant.

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