

Challenging the trade-off model for the evolution of virulence: is virulence management feasible?

Dieter Ebert¹ and James J. Bull²

¹Ecologie et évolution, Département de biologie, Université de Fribourg, Chemin du Musée 10, CH-1700 Fribourg, Switzerland

²Section of Integrative Biology, University of Texas, Austin, TX 78712, USA

Progress in understanding the evolution of infectious diseases has inspired proposals to manage the evolution of pathogen (including parasite) virulence. A common view is that social interventions that lower pathogen transmission will indirectly select lower virulence because of a trade-off between transmission and virulence. Here, we argue that there is little theoretical justification and no empirical evidence for this plan. Although a trade-off model might apply to some pathogens, the mechanism appears too weak for rapid selection of substantial changes in virulence. Direct selection against virulence itself might be a more rewarding approach to managing the evolution of virulence.

The last quarter of the 20th century witnessed an increase in the interest of evolutionary biologists in understanding and controlling infectious diseases. Phylogenetics became the mainstay in tracking infectious diseases, and fears of the evolution of drug resistance in pathogenic microorganisms inspired news headlines and garnered Pulitzer Prizes. In the midst of this was another realization, implying a longer-term use for evolutionary biology: humans themselves might be in a position to manipulate the evolution of infectious diseases toward harmless ends. This proposal offered the possibility that an evolutionary-minded public health programme could render some diseases benign.

Lured by the possibility of such ‘virulence management’, the virulence of infectious diseases gained respect as a topic for evolutionary study. From the invariant lethal outcome of AIDS to the non-lethal consequences of colds, the optimal virulence hypothesis was advocated as being a kind of ‘new-age’ tool to fight the consequences of infectious diseases [1–6]. The idea was that with appropriate public health measures and treatment protocols, we could not only reduce the incidence of infectious diseases and cure them when they do occur, but we could also cause the parasites to become avirulent. In some of the more extreme claims, warnings were offered of impending plagues if we ignored the evolutionary message, and suggestions were put forth in broad outline of how to avert these calamities both in human populations and in agriculture. These arguments were extended to suggest that genetically

engineered, highly virulent bioweapons might not be a long-lasting threat, because evolution would work quickly against high virulence [7], that the spread of the Ebola virus is strongly limited because it is too virulent, and that imperfect vaccines would lead to higher levels of virulence for unvaccinated people [8]. The possibilities were far reaching.

Although there could be many ways in which the evolution of virulence could be influenced by human intervention, the dominating concept behind most arguments of virulence management is rapid response to indirect selection based on the trade-off model. We question the generality and applicability of this model. We suggest there are a few basic reasons why virulence management based on this simple trade-off model is far less powerful than expected. This is not to say that virulence cannot evolve as a consequence of human intervention, and indeed, virulence does appear to have evolved in response to human intervention (although not explained within the trade-off framework). To manage virulence, other aspects of specific diseases appear more promising than those suggested by the limited scope of the trade-off model.

We question the generality and applicability of [the trade-off model].

The trade-off model

The motivating question is why parasites harm their hosts if a live and healthy host is beneficial to their transmission. The now-conventional answer to this fundamental question is that the reduction in host survival (this equals virulence in the strict sense) is an unavoidable consequence of parasite reproduction within the host [9,10]. This association between transmission and host survival (and thus parasite survival) represents an evolutionary trade-off for the parasite: a low level of reproduction has little impact on host longevity but results in little transmission, whereas a high level of reproduction yields high transmission but only during the brief tenure of the diseased host (Fig. 1). The optimal solution for the parasite is to balance virulence and reproduction such that its

Corresponding author: Dieter Ebert (dieter.ebert@unifr.ch).

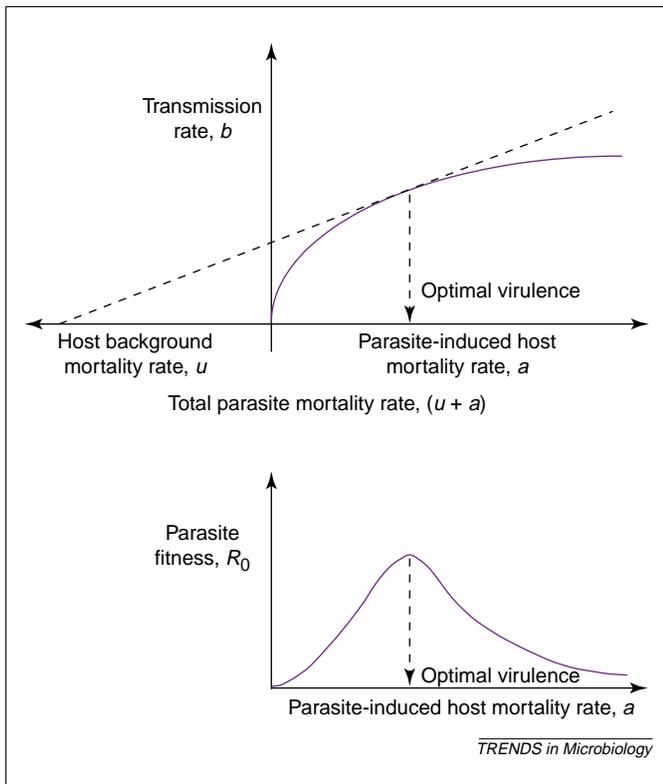


Fig. 1. The trade-off model for the evolution of virulence. The model assumes a decelerating functional relationship between transmission rate, b and parasite-induced host mortality (virulence), a (top panel). Because early host death curtails parasite transmission, the life time transmission success (R_0 , the total number of secondary infections produced by a primary infection in a population of susceptible hosts) of a parasite is maximal at intermediate levels of a (bottom panel). In a simple model $R_0 = b/(u + a)$, where u is the parasite-independent host mortality rate. Note: for other (non-decelerating) functional relationships between b and a (e.g. linear or accelerating), R_0 has no intermediate optimum. For simplicity, this graphical model does not include the effects of multiple infections. Modified, with permission, from [59].

transmission success is maximized over the lifetime of the infection [9]. Thus, the trade-off model makes the strong assumption (as did the former conventional wisdom) that everything else being equal, host mortality is detrimental for the parasite, that is, virulence is an important component of parasite fitness. Theoretical studies suggest that the virulence optimum is sensitive to the abundance of susceptible hosts, the intrinsic host lifespan, and the rate of clearance of the infection by the host's immune system, as well as other factors [11–13].

This basic trade-off model was developed and applied by Anderson and May [9] and by Ewald [10]. These early applications assumed between-host competition among parasites – that parasites competed through their maximal lifetime transmission success and thus evolved toward an optimum along the transmission–virulence trade-off. Many mathematical models calculating the evolution of virulence under this model and many elaborations of it have since been published (see papers in [5] for a representative overview). The modification of these basic models that received most attention was the effect of multiple strains infecting the host concurrently, leading to within-host competition among pathogens. A common prediction of multiple infection models was increased virulence above the level that evolved under single

infection, a result that rests on an additional assumption, namely that the more successful parasite during within-host competition is also more virulent [14–16].

Despite the considerable attention to the conceptual bases of virulence evolution, there are several difficulties with empirical applications of the trade-off model. First, some suggestions were based on faulty intuition, such as the widespread idea that reducing the opportunities for parasite transmission favours lower virulence because high virulence would kill the host too quickly (as noted in [17] and [18]). Second, even for concepts with sound theoretical logic, models merely make qualitative predictions about optima and do not enable quantitative predictions about magnitudes and rates of change. Virulence management is specifically about ways to cause rapid and meaningful changes in virulence, thus rates as well as magnitudes are crucial. For example, the foundation of virulence management is that virulence will evolve in response to indirect selection: changes in opportunities for parasite transmission will select changes in virulence. However, this field has not confronted a basic difficulty with indirect selection. In quantitative genetics terms, indirect selection attempts to generate a response in trait X (virulence) to selection for the correlated trait Y (transmission). If the genetic regression between them is low (i.e. a noisy or shallow trade-off), the response of X to selection on Y will be slow and small in magnitude – in the right direction but not necessarily useful for the short timescale of virulence management [19]. The models do not address the crucial importance of the covariance between virulence and transmission. Third, a trade-off does not necessarily lead to a virulence optimum. The trade-off function has to be saturating, that is, virulence increases more rapidly than transmission rate. In the basic trade-off model, linear or accelerating trade-off functions would not lead to intermediate levels of virulence. This condition for the existence of a virulence optimum has rarely been noted nor been supported with empirical data.

Testing the trade-off model

The optimal virulence perspective offered the promise of explaining variation in virulence across parasites as well as predicting changes in virulence over time. A variety of existing data could be used to test this model and, in addition, it was relatively easy to conduct experiments with model parasites to test the model directly. Although many existing data were consistent with trade-offs in the broad sense, they were in fact equivocal with respect to the more narrow application of virulence management.

Experimental tests

Virulence management and trade-off models are well suited to experimental verification with model parasites, and a variety of such experiments have already been carried out [20–35]. A trade-off between transmission and some measure of virulence has been supported in many but not all systems (e.g. not in [33–35]). Surprisingly, however, (indirect) selection for changes in virulence often failed to obey the expected response even when a trade-off was evident. Many of these studies revealed a complex, often

system-specific pattern of pathogen evolution that did not agree with simple models of virulence management. The results of these studies were sometimes explained post-hoc by meaningful evolutionary arguments, but they show that the predictions derived from the trade-off model were not broadly supported and that specific details of the biology of the systems had to be invoked. The reliance on post-hoc explanations and outright failures in these studies are especially disappointing to hopes for virulence management, because the investigators used well-known systems with which they had previous experience.

Not everything was a failure, however. Some studies observed the predicted direction of virulence evolution in response to selection. Yet most of those studies either employed extreme conditions (e.g. contrasting pure vertical transmission with high levels of horizontal transmission [28,29]) or observed relatively weak responses. For example, one study observed the expected relative change in virulence, but the response was small for the selection applied and even then was apparent only after carefully removing the extensive assay-to-assay variation [27]. Collectively these experiments challenge the premise that the trade-off model is a powerful determinant of virulence evolution under realistic conditions. Applying the trade-off model to infectious diseases under natural conditions appears suspect because of the large number of unmeasured variables.

A similar concern about extreme conditions applies to the famous myxoma virus 'experiments'. The release of a highly lethal myxoma virus into wild rabbits of Australia and Europe was quickly followed by a decline in virulence [36]. Subsequent mathematical analysis suggested that viruses with intermediate levels of virulence did indeed have the greatest transmission success [9]. The interpretation of this example to support the trade-off model for virulence management is difficult, however, as the virus was released to control a species that was not its natural host, and the virulence of the virus at the time of release was chosen to be unnaturally high (the virus was outside the bounds of natural evolution). Thus, we witnessed selection against an unnatural strain with extreme characteristics. Whether selection can act in a similar manner within the natural range of virulence and transmission is unclear.

Rapid evolutionary adaptation of pathogens in the laboratory was taken as an encouraging sign that similar rapid evolution of virulence might be possible under natural conditions. In particular, serial passage experiments with horizontally transmitted parasites and pathogens often led to a strong and rapid increase in pathogen growth rate [37]. In its classical form, pathogens were transferred at regular intervals from one animal to the next, disregarding their virulence and ability to transmit naturally. This favoured increased pathogen growth rates and increased virulence, supporting the idea that virulence is usually held in check by selection for transmission between hosts. The increase in virulence under conditions in which virulence has no cost for the pathogen seems consistent with the trade-off model, which predicts that a reduced cost of virulence should lead to an increase in

virulence. However, it also predicts an increase in transmission rate. By contrast, transmission is often even impaired in the evolved lines [37–39]. Thus, a positive correlation between within-host growth rate and virulence during serial passage experiments in animals does not necessarily translate into a positive correlation between virulence and transmission. These experiments merely show the effect of relaxed selection for transmission and are possibly confounded by an altered effective population size for the pathogen (experimental infection could transfer many more parasites than would be transferred with natural infection).

Correlational and comparative studies

Further apparent support for the trade-off model came from comparative studies, indicating that different modes of transmission are associated with variation in virulence. For example, vertically, airborne- and sexually transmitted diseases are less virulent than horizontally, vector-borne and non-sexually transmitted diseases, respectively [10,40,41]. However, the amount of variation in virulence that can be attributed to these factors is typically low, and confounding factors are difficult to exclude. Even if the variation in virulence could be attributed to the mode of transmission, the question remains whether a quantitative change in transmission (as opposed to a change in the mode of transmission) would effectively influence the evolution of virulence and how rapidly virulence could respond to a change in transmission, because the parasite species in these comparative studies are separated by long evolutionary times.

A finding cited by Ewald [1,6] to support evolutionary changes in virulence is strain replacement – a new strain, differing in virulence, replaces the former strain in circulation. This type of evidence also suffers strongly from confounding factors. Unless the genomes of the two strains are found to be virtually identical except for virulence, such data are equivocal, because the strain replacement could occur for reasons other than differences in virulence. One of the most devastating strain replacements in history was the 1918 influenza ('Spanish flu'). Ewald speculated that its high virulence evolved in the poor sanitary conditions in the trenches of the Western Front of World War I, where the high density of soldiers became an incubator for the quickly lethal virus [1,6]. However, these were also the first influenza strains of the H1N1 serotype, hence were invading a population lacking in protective antibodies. It is also unclear why this event has not occurred again in regions of the world where poor sanitation and high population density are part of everyday life. Thus, it is not clear whether the high virulence of the Spanish flu was adaptive to the virus.

Virulence of pathogens of human

Consideration of pathogens of humans could yield the most relevant insights to the feasibility of virulence management. One of the most obvious difficulties facing the hopes for virulence management is that an evolved change in virulence has rarely been documented, despite massive human interventions and social changes over the past century.

The trade-off model might not apply to one of our most notorious diseases. Infection by HIV-1 is considered nearly 100% fatal if untreated, but mortality peaks ten years after infection. It could well be that virulence is, in some complex way, associated with transmission (higher viral loads might be associated with more transmission and more rapid disease progression [42,43]), but this does not mean that transmission of HIV is limited by virulence, as assumed by the trade-off model. There is in fact considerable (but indirect) evidence that although the disease is epidemic, the epidemiologically relevant transmission of HIV-1 occurs soon (months) after infection and hence years before mortality [44]. If selection for increased transmission leads to a decrease in time to death of infected patients, as predicted by the trade-off model [11,45,46], then the current epidemic spread of HIV in many parts of the world (also now endemic in some populations) has grim prospects. However, to our knowledge there has been no acknowledged change in the disease progression of HIV infections in the two decades since its discovery. Admittedly, it is also not obvious whether a change in the rate of disease progression would have been detected in the countries where the disease is most rampant and devastating.

Polio virus infects the human gut, where it does no obvious harm, and >99% of infections are asymptomatic. Disease occurs when the infection passes into the blood and then into the central nervous system. As is typical of many diseases, virulence is greater (i.e. disease is more likely) with the age of the host. Contrary to expectations based on the trade-off model, improved social hygiene is thought to have increased the virulence of polio infections by increasing the average age of first exposure. However, the increased virulence appears not to be an evolved outcome, but merely to be a consequence of the altered epidemiology [47]. Despite almost complete worldwide eradication of polio virus through use of a vaccine, there has been no recognized decline in virulence as would be expected from the trade-off model.

The bacterial disease diphtheria constitutes one of the few documented cases of an evolved decline in virulence, which is now being reversed in the former Soviet Union. This decline occurred in response to human intervention, but the standard version of the trade-off model does not provide us with the correct understanding. The bacterium *Corynebacterium diphtheriae* inhabits the throats of humans in either of two forms, one benign and the other pathogenic. The pathogen secretes a toxin that inflames tissues and thereby presumably improves its local growth conditions and ultimately improves its transmission. A vaccine engenders immunity against the toxin per se, so the pathogenic bacterium no longer inflames the tissues. Widespread vaccination has been followed by decreased incidence of the pathogenic form, and relaxation of vaccine coverage has led to subsequent increases [48,49]. This decline in virulence does not fit the standard trade-off model – which predicts that the optimal virulence should increase when the cost of virulence is removed [8]. Lower virulence seems to have evolved because of direct selection against virulence instead of through indirect selection via host mortality. An extended version of the trade-off model,

with an altered fitness function for the pathogen, did indeed show that this can be predicted if the biology of the system is accurately taken into account [50]. A similar mechanism has been proposed to explain the post-vaccination (inducing antitoxin immunity) decline in the virulence of pertussis [50,51]. Both examples illustrate that virulence management can be effective, but specifically when virulence per se is the direct, rather than indirect, target of intervention.

Why the difficulty?

The trade-off model is based on two assumptions: (1) parasite-induced host mortality is costly for the parasite; and (2) transmission and virulence are inextricably coupled. Although these assumptions do apply in some cases, they are not general. In addition to the limitations of this model evident in many of the examples we have discussed, there are further grounds for questioning one or both assumptions, suggesting that virulence has little or no selective consequence for many pathogens. First, virulence is not always a simple function of parasite reproduction, but has many different causes, including the host immune response, specific tissues invaded by the pathogens (which often challenges the naive view that levels of parasite reproduction are directly correlated with virulence) or specific interaction among hosts and parasite genotypes [52,53]. In some diseases, virulence results from infection of tissues that are dead-ends for the parasite, from which no transmission occurs [54]. Without understanding what causes virulence, what the alternative virulence phenotypes are, and how virulence impacts parasite fitness, it could be impossible to predict how virulence will evolve. Second, even if virulence is embedded in a trade-off with transmission, the trade-off might involve more than just two dimensions, and any attempt to reduce it to two dimensions could give misleading results [55].

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Virulence is not a fixed property of an infectious agent. By far the largest variance in virulence is observed among infected host individuals. For example, in polio, tuberculosis and malaria, the effects of infection range from asymptomatic to severe disease. The factors that can contribute to this strong variation are diverse and include genetic variation and interactions among hosts and parasites, environmental effects such as dose dependence, host nutrition and age at first exposure, and interactions with other infectious diseases [53,56,57]. The virulence–transmission trade-off has so far been considered across pathogen genotypes, but hardly across host conditions, host genotypes or environmental conditions. It could well be that within the complex settings in which infectious diseases evolve, only a small fraction of patients account for the majority of transmission and that this is independent of virulence.

A change in perspective

This paper offers a devil's advocate view against the contemporary incarnation of optimal virulence models, which are based on a transmission–virulence trade-off. Indeed, we go so far as to suggest that the predictions for virulence management generated by such models are doomed to fail, although we acknowledge that our view is conjectural. To put virulence management in a more positive light, we suggest that the current paradigm is an unnecessarily narrow view of virulence, a view that might hinder progress in this exciting field by channelling research along one narrow track. We believe that there are more promising avenues to explore. First, we think that any programme of virulence management must understand how virulence relates to parasite fitness, and cannot assume that virulence follows a naive trade-off model. Second, as exemplified by the diphtheria case, virulence management can be more successful when targeting virulence directly rather than when targeting a correlated trait.

Many of the most successful studies of the evolution of parasites and pathogens did not focus on parasite-induced host mortality (the common definition of virulence), but instead addressed other traits more directly linked to parasite fitness. This approach might lack the apparent generality of the trade-off model because it is embedded in the specific biological details of the parasite, but by acknowledging specific biological details, it provides a broader foundation for controlling transmission and virulence. The evolution of many traits can be more easily predicted when there is a direct connection to parasite fitness – successes and promising examples include drug resistance, infectivity, and evasion from the immune system. Further, there are long lists of diverse behavioural alterations of infected hosts that have been directly shown to be linked to parasite fitness (in same cases to host fitness) (see [58] for a recent review). Likewise, studies of the evolution of benevolence of vertically transmitted parasites (where parasite fitness is strongly linked to host reproduction) offer an unmatched series of successes [28,29,40]. For exclusively horizontally transmitted parasites, no study of the evolution of virulence is equally convincing as those involving vertical transmission. The reason for these latter successes could be that during vertical transmission virulence is more closely linked to parasite fitness and thus more strongly subject to selection than in the case of horizontal transmission.

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This leads to our second suggestion for an altered perspective of virulence evolution: how to manage virulence. We suggest that virulence management should be based on identifying ways to select against virulent forms of parasites and pathogens directly, rather than selecting

on correlated traits (P. Ewald suggested a similar idea to J.J.B., pers. commun.). Direct selection against virulent forms makes virulence a key component of parasite fitness and a response to selection is much more likely. The best-known examples for the evolution of virulence can be explained with direct selection against virulent pathogens – as with the antitoxin vaccines used against pertussis and diphtheria. Even the evolution of benevolence in exclusively vertically transmitted parasites fits this category, because selection operates directly against virulence in this design. Direct selection is very powerful to change trait means rapidly, in particular when the trait under selection has a high heritability. As this seems to be the case for virulence in many pathogens and parasites, we expect that this form of virulence management could have a promising future.

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The virulence–transmission trade-off and virulence management

Sam L. Elliot

NERC Centre for Population Biology, Imperial College London, Silwood Park Campus, Ascot, Berkshire, SL5 7PY, UK

In a recent article in *Trends in Microbiology*, Ebert and Bull [1] question the generality of the classic trade-off model between parasite virulence and transmission. They queried the management of one trait (virulence) by the management of a supposedly correlated trait (transmission) when that correlation could be unproven or weak. While I agree that the trade-off model might not be universal, I see this more as an incentive to understand better where and when the model does apply, and to develop alternatives where it does not. Also, their critique of virulence management overlooks the fact that many interventions could affect virulence indirectly and we do not always have the option to select directly for reduced virulence. We would do well to understand patterns of selection on virulence both to manipulate virulence and to understand the consequences of other interventions.

Ebert and Bull cite vertically transmitted parasites as the only case where empirical observations of the classic trade-off model fit the theoretical predictions. Perhaps, in this case, the answer was found at the first attempt, and we must work towards similarly satisfying explanations for other cases. Many systems will be imperfectly served by this model, but extensions have been suggested for: (1) parasites that must kill their hosts to effect transmission [2]; (2) parasites that castrate or sterilize their hosts [3,4]; and (3) parasites that are virulent by means of toxins [5,6]. For example, Ebert and Bull cite AIDS and poliomyelitis as cases in which virulence has little to do with transmission, and diphtheria as an instance where intervention resulted in a change of virulence that was inconsistent with the classic trade-off. Their explanation is that high virulence results from an (potentially maladaptive) infection of ‘dead-end’ host tissue. This has been approached in a ‘two-bag’ model of virulence of veterinary diseases [7], in which virulence in one ‘bag’ of host tissue might obey the classic trade-off but, in the other bag, it does not. Suggestions for veterinary disease management arise and the model might be applicable for some human diseases.

Ebert and Bull describe the management of one trait to effect a change in another as naive. However, they miss one of the aims of virulence management, which is not to manage virulence *per se*, but to understand how other interventions might affect virulence. Thus, while Gandon

et al. [8] could be criticized for proposing management of malarial virulence via a vaccination programme, they were in fact investigating some of the potential consequences of an intervention that is liable to happen anyway. Ebert and Bull criticize the famous myxoma case as too extreme to develop meaningful predictions. However, the release of a virulent natural enemy (such as the myxoma virus) to control a pest organism is commonplace and it would be useful to predict the path of that natural enemy’s virulence [9].

I believe that Ebert and Bull are right to warn against assuming a general applicability of the classic trade-off model. Understanding that biological detail for a given system, however, allows us: (1) to attempt to manage virulence directly, as they propose; (2) to predict the consequences of our other interventions; and (3) to attempt to manage virulence via a correlated trait, once we are confident of that correlation and, as they suggest, the strength of that correlation.

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Understanding and managing pathogen evolution: a way forward

Sylvain Gandon¹ and Troy Day²

¹Centre d'Etudes sur le Polymorphisme des Microorganismes, Unité Mixte de Recherche CNRS/IRD 9926, Institut de Recherche pour le Développement, 911 avenue Agropolis, 34394 Montpellier Cedex 5, France

²Departments of Mathematics and Biology, Jeffery Hall, Queen's University, Kingston, ON, K7L 3N6, Canada

Ebert and Bull [1] challenged the trade-off model for the evolution of virulence. What they term the trade-off model 'is based on two assumptions: (1) parasite-caused host mortality is costly for the parasite; and (2) transmission and virulence are inextricably coupled'. With such a narrow description of the adaptive theory of virulence evolution, it is easy to find many parasites that do not fit these assumptions, and to question the use of this theory for virulence management. Of course, this 'standard model' has only a heuristic value, showing that intermediate virulence can be evolutionarily stable. But the general theory is not as naïve as they portray, with recent models accounting for many life history complexities [2,3] and host heterogeneities [4,5]. These details matter for virulence evolution, but that does not imply that such a theory is doomed to fail. We disagree with several points made by Ebert and Bull, but here we focus on the question raised in the title of their article: is virulence management feasible?

Ebert and Bull fail to distinguish between a satisfying theory of virulence evolution and successful virulence management policies. These are two distinct issues. A successful theory of virulence evolution can be an ineffective tool for virulence management. First, if we do not know the details of the life cycle of the organism, then few predictions can be made. We recognize that we know little about the life cycle of many parasites and, worryingly, of many human pathogens. This applies for nearly all predictions in evolutionary biology, and it does not imply that theory is invalid. Rather, it suggests that current biological information is insufficient to adequately test the theory or for the theory to be applied usefully. This calls for further empirical studies of pathogens. One potentially useful approach is to measure the genetic variance–covariance matrix between traits, such as transmission and virulence, to infer short-term predictions on the direction of evolution [3]. Second, even if all this knowledge is available, the theory might predict that the speed of evolution after an intervention is slow. In this case, such intervention might have little useful impact. We agree that current research virtually ignores this issue (but, see Ref. [4]), however, this point also calls for more research because it raises both a theoretical problem (what are the conditions under which the speed of evolution will be fast?), as well as an empirical challenge (measurement

of the variance–covariance matrix would indicate if there is enough genetic variation for rapid changes in virulence).

The only alternative proposed by the authors for virulence management is to target virulence directly. They refer to the pertussis and diphtheria cases where vaccines appear to have selected against the strains that produce high levels of toxin. Certainly, imposing direct selection against virulence (if possible) might work. But, the case of antitoxin vaccines remains an exception where it is easy to identify the cause of virulence. In many situations, the cause of virulence is unknown and such a strategy is impractical. Moreover, even if a vaccine could be produced against toxin producers, Gandon *et al.* [6] demonstrated that, because toxin production is also associated with some benefit (resource acquisition within the host, and thus transmission), this strategy can yield unexpected results, such as evolution towards higher virulence (i.e. higher levels of toxin production). In any event, a strong argument for the use of direct selection in virulence management does not constitute a strong argument against the validity or generality of the trade-off hypothesis.

Finally, it is noteworthy that there is the possibility of there being benefits to targeting transmission directly, rather than (or in addition to) targeting virulence. Any intervention will have to balance costs and benefits of the resultant evolutionary response, as well as the epidemiological response that occurs. For example, certain approaches to targeting transmission might reduce disease incidence, regardless of what happens to it evolutionarily. This is clearly desirable, particularly if the disease can be reduced to the point of eradication, but these benefits must be balanced with the evolutionary risks involved. The ideal situation would be to design interventions that have positive evolutionary and epidemiological effects, and it is far from clear that these will always involve the targeting of virulence alone.

Current theory is not as naïve as Ebert and Bull suggest. They recommend abandoning the simplest version of the trade-off model and, instead, suggest looking at the relationship between virulence and fitness, and targeting virulence directly. Our primary disagreement with their view stems from the fact that both of these suggestions remain within the current theoretical framework of pathogen evolution. It is recognized that more work is required to yield both a completely satisfying theory for the evolution of pathogen life histories, and to



Response to: Eliot and Gandon and Day: Revisiting virulence management

Dieter Ebert¹ and James J. Bull²

¹Ecologie et Évolution, Département de Biologie, Université de Fribourg, Chemin du Musée 10, CH-1700 Fribourg, Switzerland

²Section of Integrative Biology, University of Texas, Austin, TX 78712, USA

Virulence management is the proposal to manipulate human activities in order to direct the evolution of parasites towards lower virulence. Our article [1] criticized proposals for virulence management on the grounds that current data do not support such proposals. We further suggested that models underlying many of those proposals are too distinct from biology to warrant such proposals.

It is important to distinguish virulence management from virulence evolution. The premise of virulence management is the promise of large and rapid evolutionary changes in virulence. By contrast, studies of virulence evolution can address virulence changes over any scale of time and magnitude. We had specifically challenged virulence management.

Our pessimism on current views of virulence management began from two lines of observation that are not challenged by either Gandon and Day's or Elliot's letters. First, the literature does not support the view that many infectious agents have evolved new levels of virulence in recent years, despite profound changes in intervention and cultural practices (e.g. use of vaccines, modern hygiene, medical treatment). Some of these changes should have selected large changes in virulence if the theory was correct. We hope that our article will encourage researchers to determine whether the general impression is true or that virulence might instead have changed over time (e.g. nutrition has also changed and could mask changes in virulence). Second, experiments to test predictions of the trade-off model have not been supportive or have resulted only in weak effects. These two lines of argument led us to doubt whether approaches based on present theories will be widely successful. We suggested some reasons why the theory might be problematic, chiefly that current models might not incorporate sufficient biology.

Virulence management proposals assume that high levels of virulence curtail parasite transmission, an assumption known as a trade-off. Explicit trade-off models usually assume that virulence is manifested as host mortality, and transmission stops only when the host dies. We think that virulence management based on this simple trade-off model is unlikely to succeed because the rapid and profound virulence evolution needed to justify virulence management requires extreme and unrealistic trade-off functions (i.e. that small changes in transmission cause large changes in host mortality). By

contrast, long-term processes of virulence evolution can be explained without extreme trade-offs and is thus more likely to succeed. A more realistic view of trade-offs should include not only host mortality, but also the immune response, the time course of infection and perhaps tissue tropisms of infection. Recent papers that identify pitfalls of, or provide useful extensions to, the trade-off model take an important step in this direction [2–4]. A greater realism should benefit both bodies of theory, but is especially relevant to understanding the potential for virulence management.

Adding greater realism to the models could have its downsides. When studying two-species systems (here, a host and a parasite), researchers invariably discover that much of the system's behaviour is due to interactions, which are often highly specific to the host and to the parasite. If the outcome of an interaction is system-specific, generalized models might perform poorly in predicting the course of virulence evolution in the short term (relevant for virulence management), even if the underlying basic model for virulence evolution is correct and useful in the long term. For a powerful and satisfactory management of virulence, it might be necessary to construct system-specific models, which take the details into account and thus do not generalize. Just as we use specific drugs for different parasites, and even different variants of the same parasite, we might need different models to understand how to manage virulence in different infectious diseases. This view is not at variance with either letter; instead, it challenges many of the earlier proposals to manage virulence.

We share the view that more work is warranted to understand virulence evolution and virulence management, and we acknowledge that many studies of virulence evolution and some of virulence management have been appropriately cautious. We would be delighted to be wrong in our doubts, but we feel that at least some balance is needed in discussions of virulence management, because the evidence does not yet offer much promise.

We hope that our article inspires broader approaches to studying virulence evolution and management. There are demonstrated applications of evolutionary theory in medicine and biology that warrant considerable enthusiasm for extending theory to other problems. At the same time, we need to discuss where our efforts are best applied.

Corresponding author: Dieter Ebert (dieter.ebert@unifr.ch).

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