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5

Dilemmas in Virulence Management

Minus van Baalen

5.1 Introduction

Both the patient who is infected with a communicable disease and the doctor treating the patient share a common interest: the eradication of the infection. That the treatment chosen by the doctor may have detrimental consequences for the population at large is not the primary concern of the doctor or the patient. Such matters are the concern of the larger-scale medical and political organizations that deal with the development of public health policies such as vaccination programs and possibly, as investigated in this book, "virulence management" strategies. Development of such policies is not only a complicated issue because of the intricacies of host–parasite interactions themselves, but also because the common aims of the public health authority and the population do not always overlap very well (Anderson *et al.* 1997). Of course, the community benefits when an individual ceases to be infective. However, parasites are not inert players in the game, and will adapt to any measures that are taken on a sufficiently large scale. Therefore, the development of some public health policies may not be beneficial to the community as a whole. The global resurgence of tuberculosis (TB) and the fact that many malaria parasites have become resistant against most preventive treatments are just two examples of the detrimental consequences of the large-scale application of individually beneficial medical treatment.

The insight that strategies to fight parasites should be based not only on short-term effects, but also on evolutionary considerations, is gaining ground (Ewald 1993, 1994a). For example, measures could be taken to counteract the development of resistance to antibiotics or other chemotherapeutic treatments (Baquero and Blázquez 1997; Bonhoeffer *et al.* 1997; Levy 1998; see Chapter 23). But other parasite traits evolve too. By working out how virulence may change in response to changes in the parasite's transmission cycle (Ewald 1994a; Van Baalen and Sabelis 1995b; see Chapter 2) one obtains an insight into the scope for such virulence management.

It has already been pointed out that measures taken to reduce the impact of a particular disease may involve ethical dilemmas. For instance, Anderson and May (1991) note that when a population is vaccinated against the poliomyelitis virus, the force of infection of this virus decreases. This means that fewer people will become infected, which is the desired beneficial effect. However, it also means that those who do become infected are likely to become so at a later age (polio was more commonly a childhood disease before vaccination); in the case of polio,

as with some other childhood diseases, an infection at a later age may have more serious consequences. Thus, vaccination effectively means sacrificing the interests of a few individuals for the benefit of the population. A similar ethical issue arises when the degree of infection varies and treatment can be directed to either the (few) heavily infected individuals or the lightly infected majority.

The ethical dilemmas associated with public health measures are further intensified when the evolutionary response of the parasites is taken into account. It is increasingly recognized that the evolution of resistance against antibiotics is becoming a serious problem, and that antibiotics should be used sparingly and carefully to restrain this development (Baquero and Blázquez 1997; Bonhoeffer *et al.* 1997; Levy 1998; see Chapter 23). However, less attention has been given to the associated ethical dilemma: to what extent should an individual's interest be sacrificed for the good of the community? Analyses tend to predict that vaccination campaigns should select for decreased virulence [through the decrease in multiple infection and, hence, within-host competition (Van Baalen and Sabelis 1995b; Chapter 11)]; but what if vaccination favors more virulent parasites? In this chapter, I discuss a very simple model that suggests adequate treatment may indeed be a mechanism that selects for increased virulence.

The original model was formulated to study the question of how much of its resources a host should invest to create an immune system that eradicates infections (Van Baalen 1998). This chapter is based on the insight that, on an elementary level, visiting a doctor and receiving medical treatment is exactly analogous to the effect of the immune system. The corpus of medical knowledge and the availability of doctors and health insurance all work toward the eradication of infection. Of course, the relation between benefits and costs is less straightforward than the model assumes, but other than this shortcoming, the analogy can be carried quite far.

The analysis yields some results that may not be intuitively apparent. For example, individually optimal antiparasite measures may not lead to extinction of the parasites, but rather the opposite. Combining optimum defense with optimum counterstrategies on the side of the parasites suggests the possibility of even more worrisome outcomes. That is, when medical treatment becomes too effective, an "arms race" may be triggered, during which more and more resources need to be invested into developing more effective treatments against increasingly rare but increasingly virulent parasites. Any high-level community body (a "public health authority") may then have to "decide" which outcome is more desirable: a mild disease that affects many people, or a virulent disease that affects only a few.

In this chapter, I discuss to what extent this outcome depends on who pays the cost of medical treatment and at what level choices are made. That is, I compare the outcome for two possibilities: one in which all costs are paid by the individual on a case-per-case basis, and another in which all costs are paid by the community (so that every individual is required to pay an average fixed "health tax"). Decisions as to the effectiveness of the treatment are made by the individual (or doctor,

assuming he or she does not balance the patient's interests against those of the community) or by the community.

This chapter is entirely speculative, and I make no attempt to analyze the results in terms of any real infectious disease. In fact, all the numerical examples have been chosen to demonstrate an effect rather than to give an indication of its likelihood or size.

5.2 Optimal Antiparasite Strategies

In this section, I compare the consequences of actions taken at different levels (i.e., at that of the individual or that of the community), while keeping parasite virulence constant. In Section 5.3, I allow the parasites to coevolve and respond to the antiparasite policies.

The basic points are illustrated by analyzing a simplistic susceptible–infected–susceptible (SIS) model for host–parasite dynamics. In the epidemiological literature, it serves as a reference base (e.g., see Anderson and May 1991) with which to contrast the consequences of more realistic extensions. This model also served as a framework to investigate coevolution of recovery rate and parasite virulence (Van Baalen 1998); here I present a reinterpretation of these results explicitly in terms of virulence management in which recovery is due to medical treatment.

The most important assumptions that underlie this model are that:

- The host population grows logistically in the absence of disease;
- The population is well-mixed so that overall transmission is a mass-action process;
- Treated hosts become immediately susceptible again (no period of immunity).

This set of assumptions leads to

$$\frac{dS}{dt} = b(N)N - dS - \beta SI + \theta I \ , \tag{5.1a}$$

$$\frac{dI}{dt} = \beta SI - (d + \alpha + \theta)I \ , \tag{5.1b}$$

with $N = S+I$. Here, S and I represent healthy and infected hosts, respectively; d is the background per capita mortality rate, β is the per capita transmission parameter of the disease, α is the disease-induced per capita mortality rate (virulence), θ is the per capita recovery rate, and $b(N)$ represents the inflow of susceptible hosts due to births, with

$$b(N) = b_0(1 - \kappa N) \ , \tag{5.2}$$

where b_0 is the per capita birth rate and κ measures the density-dependent reduction of the recruitment rate.

In an SIS model with recovery, individual hosts switch back and forth between the susceptible and the infected states. Usually it is assumed that recovery occurs because the immune system clears the parasite, but here I assume that recovery is the result of medical treatment. The value of θ then embodies the efficiency of

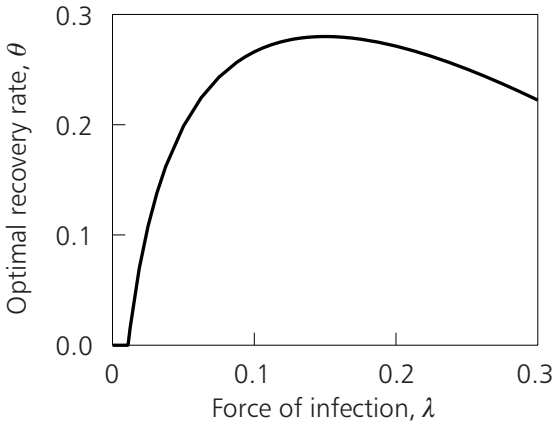


Figure 5.1 The relationship between individual optimal investment in recovery θ as a function of the force of infection λ (the risk per unit time of becoming infected). Parameters: $d = 0.02$, $\alpha = 0.3$, $c = 1$.

the entire public health system (i.e., the entire complex consisting of doctors, the availability of antibiotics, health insurance, etc.) in eradicating an infection.

Medical assistance is not free, of course. It is important to realize that the costs may be incurred at many levels, from the individual who pays a consultation fee to the community that finances the public health system (to train doctors, maintain hospitals, carry out research, etc.). There are two extreme cases: in the first individual hosts can pay for medical insurance – the quality of which determines their individual rate of recovery through treatment; in the second the rate of recovery is determined entirely by the community (through investment in a public health system).

Suppose an individual can increase his/her rate of recovery θ at the expense of a reduction in his/her rate of reproduction $b_0 = b_0(\theta)$, for example

$$b_0(\theta) = b_{\max} e^{-c\theta} \,, \tag{5.3}$$

where $b_{\max}$ is the maximum rate of reproduction and c is a measure (the cost) of how quickly the rate of reproduction decreases with a unit increase in θ. Of course, in reality this is more complicated, but, within the present simple framework, this is the most straightforward relationship. What is important to realize is that, in whatever way the costs are paid, the host population is involved in what is technically a "game." That is, the optimum strategy for the individual depends on the strategies that are adopted by the rest of the population (Maynard Smith and Price 1973; Maynard Smith 1982). In Van Baalen (1998), it is shown how the optimum investment in recovery rate depends on the risk of infection (see Figure 5.1). As can be seen, the optimal investment increases once the force of infection is greater than a threshold value, but decreases again for very high values of the force of infection. The reason for this is that if the force of infection is very high, hosts tend to become reinfected very quickly after they have recovered. No matter how quickly the infection is cleared, hosts spend most of their time in the infected state

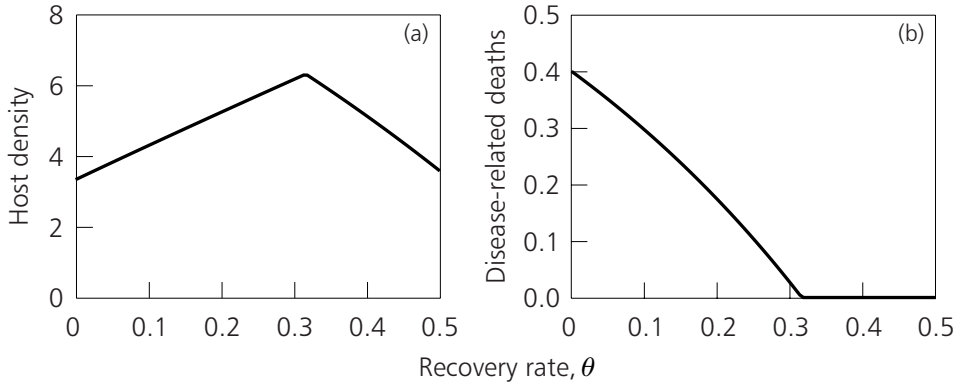


Figure 5.2. The relationship between tax-mediated investment in health care (leading to a recovery rate of θ) and total host population density (a) and proportion of disease-related deaths $p = \alpha I/(dN + \alpha I)$ (b). Note that host density decreases after the parasites have become extinct because the hosts keep paying their tax without accruing any additional benefit. Parameters: $b_{\max} = 0.04$, $d = 0.02$, $\kappa = 0.05$, $c = 1$, $\alpha = 0.3$, $\beta = 0.1$.

anyway. Under such conditions, a host could just as well economize on health care and invest its resources otherwise (Van Baalen 1998).

Without a doubt, this model is far too simplistic to describe human population dynamics in any detail, let alone account for the complicated political decisions and the micro- and macroeconomic processes that govern the quality of public health. Having stated this, the model captures at least two ubiquitous relationships. First, parasites suppress host fitness (and hence population growth). Second, resistance to parasites imposes a cost (whether it is borne by individuals or averaged out over larger communities).

When the entire population of hosts tries to adopt the individually optimal strategy, the results may appear counterintuitive: the force of infection does not decrease, but rather is *maximized*. If the population invests little in health, then the parasites are given free reign – under which conditions it pays to invest in health care. If the host population invests heavily in health care, the parasite population will decrease. As a consequence, hosts can individually afford to "cheat" and economize on health care. Thus, one wonders to what extent the population as a whole benefits when investment in health care is based on individual decisions.

Contrast this with the case in which the cost of health care is uniformly distributed over the entire population. This would require a public organization that levies some sort of health care tax and ensures that every individual is treated once that individual is infected. What would be the optimal strategy for such a public organization? Taking the same cost–benefit function as defined before, the optimal strategy for the community seems obvious. Whether the aim is to maximize population density (Figure 5.2a) or to minimize disease-related deaths (Figure 5.2b), the best strategy for the community is to invest just enough to render the parasite extinct.

Some remarks are appropriate here. Once the parasites are extinct, it no longer makes sense to fight them. In principle, therefore, investments can then be reallocated. However, this leaves the population susceptible to reinvasion by the parasite; thus, to protect the population against reinvasion, investments may have to continue. A second point is that for more realistic models (or with different cost–benefit relationships) the two criteria – maximizing mean wealth and minimizing parasite incidence – do not necessarily coincide. In that case, it must be decided what the most desirable outcome is – which may pose ethical dilemmas (see also Medley 1994).

5.3 Parasite Evolutionary Responses

Above, it was assumed that the parasites are evolutionarily inert. This, of course, is very unlikely. If health care becomes more efficient, then an elementary aspect of the parasites' environment changes – to which the parasites are expected to adapt. What will be the consequences?

A parasite's fitness is proportional to the product of its infectivity and the duration of the infection (Anderson and May 1982; Bremermann and Pickering 1983). It is very likely that it cannot maximize both at the same time. An increase in infectivity is detrimental to the host, who is likely to die sooner, thus reducing the duration of the infectious period. Conversely, prolonging the infectious period may require a reduction in infectivity. Thus, the parasite's "host-exploitation strategy" should strike the optimal balance between the intensity and duration of infectivity (Anderson and May 1982; Bremermann and Pickering 1983; see Box 5.1).

To a parasite, it is irrelevant whether it stops transmitting because its host dies or because it is knocked out by antibiotic treatment. Therefore, if the host is likely to seek antibiotic treatment, the parasite should respond by shifting its policy toward quicker exploitation of the host. Thus, the availability of effective antibiotics is likely to favor more virulent parasites.

Often, it is argued that the best strategy for the application of antibiotics is to use them such that all parasites are killed. Then, it is claimed, even those parasites that are less sensitive to the antibiotic leave no descendants, and, hence, no resistance against the antibiotic can develop (Baquero and Blázquez 1997; Bonhoeffer *et al.* 1997; Levy 1998). This may be true, but it should not be forgotten that resistance is not the only parasite trait that evolves. The present analysis suggests that parasites respond evolutionarily even to perfect "magic bullet" types of antibiotics. In fact, the more effective the drug is, and the more likely a host is to seek treatment (resulting in a greater recovery rate θ), the stronger the evolutionary response. And it is worth noting that the direction of this evolutionary response is not at all desirable. I am not aware of any studies that show that the use of antibiotics has led to increased virulence, but the analysis in this chapter serves as a warning that there are reasons to expect such an evolutionary response!

If the parasites respond to increased treatment efficacy by becoming more virulent, then the ethical dilemmas associated with public health become more intense.

Box 5.1 Evolutionary optimization under infectivity–virulence trade-offs

A parasite needs to balance the short-term benefit of increased transmission and the longer-term benefit of host preservation. Suppose, as explained in Box 2.2, that the parasite experiences a trade-off between its infectivity (measured by its transmission coefficient β) and its virulence (measured by its disease-induced morality rate α). We can describe such a trade-off by a constraint that links these two parameters

$$\beta = \beta(\alpha) \; . \tag{a}$$

Under these conditions, what is the optimal virulence, that is, that level of virulence favored by natural selection? Ignoring the possibility of multiple infection (see Box 7.1), we can consider the dynamics of the density of hosts J that are infected by a mutant parasite with virulence α_{mut}

$$\frac{dJ}{dt} = \beta(\alpha_{\text{mut}})S^*(\alpha_{\text{res}})J - (d + \alpha_{\text{mut}})J \; , \tag{b}$$

where d is the natural host mortality rate and $S^*(\alpha_{\text{res}})$ is the density of susceptible hosts, which, in turn, is determined by the resident parasite strain with virulence α_{res}. Whether or not the mutant invades depends on the sign of the right-hand side of Equation (b). This invasion condition is conveniently expressed in terms of the mutant's basic reproduction ratio

$$R_0(\alpha_{\text{mut}}, \alpha_{\text{res}}) = \frac{\beta(\alpha_{\text{mut}})}{d + \alpha_{\text{mut}}} S^*(\alpha_{\text{res}}) = Q(\alpha_{\text{mut}})S^*(\alpha_{\text{res}}) \; , \tag{c}$$

where $Q(\alpha_{\text{mut}})$ is the "per-host exploitation factor." Notice that here the mutant's R_0 is a function of both its own virulence and the resident's, because the latter determines the density of susceptible hosts. (The relation with the R_0 introduced in Box 2.2 is explained below.) Since at equilibrium the resident's R_0 must exactly equal one, $R_0(\alpha_{\text{mut}}, \alpha_{\text{res}}) = 1$, we have

$$S^*(\alpha_{\text{res}}) = \frac{d + \alpha_{\text{res}}}{\beta(\alpha_{\text{res}})} \; . \tag{d}$$

If the resident strain adopts a virulence α_{res} such that

$$Q(\alpha_{\text{res}}) > Q(\alpha_{\text{mut}}) \tag{e}$$

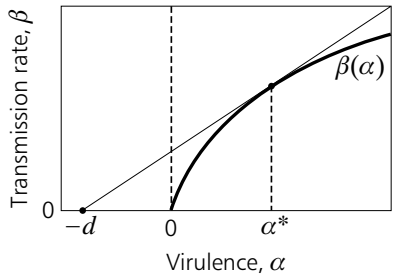
for all levels of virulence α_{mut}, it is evolutionarily stable.

The evolutionarily stable level of virulence therefore maximizes the per-host exploitation factor Q (Van Baalen and Sabelis 1995a). Note that Q is expressed entirely in terms of individual-level rate coefficients and does not involve any population-level quantities, such as the number of susceptible hosts that appear in R_0. The evolutionarily stable level of virulence can be found graphically by determining for which α_{mut} the tangent on the curve $[\alpha_{\text{mut}}, \beta(\alpha_{\text{mut}})]$ passes through the point $(-d, 0)$ (see figure).

Boxes 2.2 and 9.1 explain how the evolutionarily stable virulence can be calculated by "maximizing R_0." Importantly, the R_0 introduced there is a slightly different quantity from the R_0 introduced here, although the two quantities are closely

continued

Box 5.1 *continued*



Graphical method for finding the evolutionarily stable level of virulence α^*. The evolutionarily stable virulence maximizes the ratio $\beta(\alpha)/(d+\alpha)$ and thus occurs for the α at which the tangent of the curve α, $\beta(\alpha)$ passes through the point $(-d, 0)$.

related. In general, the R_0 of a certain type of individual is defined as the lifetime offspring production (in the case of a parasite, offspring are freshly infected hosts) in a certain reference environment. In Box 2.2 this reference environment is the parasite-free host population. By contrast, here the reference environment is a host population that is already infected with the resident parasite strain. Notice that, in the models under consideration in this box as well as in Boxes 2.2 and 9.1, the basic reproduction ratio R_0 in any reference environment with susceptible density S_0 is simply proportional to the "per-host exploitation factor" Q, $R_0 = QS_0$, but note that this no longer holds true if multiple infections occur. We can therefore choose any such reference environment to compare the basic reproduction ratios R_0 of a resident and mutant strain: this comparison gives the same result as one based on their per-host exploitation factors Q. The standard convention in the literature is to choose the disease-free environment to determine S_0. Yet, for models in which R_0 is always proportional to the density of susceptible hosts, environments with different S_0 can be chosen just as well. Nevertheless, it must be realized that models for which the evolutionarily stable virulence can be calculated through an optimization argument and for which the quantity to be optimized by a disease can be simply related to R_0 are special ones; unfortunately these two simplifying features do not apply to other, more general models (see Mylius and Diekmann 1995; Metz *et al.* 1996b; and Mylius and Metz, in press).

Consider again the case in which hosts individually decide on their health insurance. Now the game aspect involves not only the risk of infection, but also the consequences of being infected. For example, if the population is well-insured (resulting in a large population-wide value of the recovery rate θ), then the parasites may become rare but also very virulent. In fact, they may become so virulent that it pays an individual host to increase its own recovery rate even more. Thus, an arms race is triggered in which the hosts are forced to invest more and more resources in their defense, and the parasites become more and more virulent to counter this defense. Eventually a stable end result (i.e., a coevolutionarily stable strategy, or CoESS) may be reached, in which hosts pay heavily to defend themselves against a rare but serious disease.

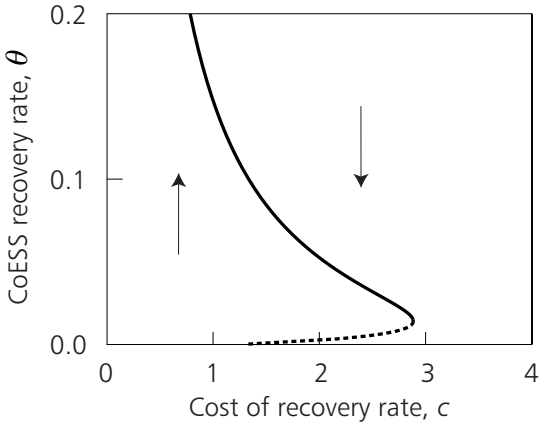


Figure 5.3 CoESS recovery rate θ as a function of relative cost c. For intermediate costs, there are two simultaneous CoESSs (one given by the full curve and one by $\theta = 0$, separated by the dashed curve). Arrows indicate the direction of selection. These results are based upon the assumption that parasite infectivity and disease-induced mortality are related through the constraint $\beta = \beta_{\max}\alpha/(\delta + \alpha)$. Parameters: $b_{\max} = 0.04$, $d = 0.02$, $\kappa = 0$, $\beta_{\max} = 0.1$, $\delta = 0.02$.

This is not always an inevitable outcome as for some parameter combinations a second CoESS is possible: hosts tolerate the parasite, while parasites respond by staying relatively benign (Van Baalen 1998). Van Baalen (1998) argued that if such bistability occurs naturally (i.e., as a consequence of immune system and parasite coevolution), reinforcement of the immune system with an external medical component might destabilize the tolerance–avirulence CoESS and trigger an arms race that escalates to the defense–virulence CoESS. Presumably, when antibiotics become available, the cost of increasing the recovery rate will be reduced (antibiotics are likely to be much less expensive than gearing up the immune system to obtain a similar result). Again, whether such bistable outcomes are a reality remains to be confirmed; but if they are, it raises worrying questions. As can be seen in Figure 5.3, if the cost c is reduced below a certain threshold, an arms race is triggered that may be difficult to undo due to the hysteresis effect.

Note that the present model is too simplistic to assess the likelihood that such bistability occurs. But if such bistability is a reality, "virulence management" acquires a whole new aspect. Which of the two outcomes is preferable? Once again, this cannot be answered without addressing ethical issues. The question then really is whether "we" (i.e., presumably some governmental organization) should strive for a common avirulent disease or for a rare but virulent disease. This is not an easy question to answer, and certainly falls outside of the scope of pure science.

5.4 Discussion

There exists a very basic conflict of interest among the individuals of a population who are infected by parasites. Taking into account the evolutionary response of

parasites against measures to fight them (whether on the level of individual treatment or of large-scale public health measures like vaccination) only intensifies this conflict of interest. Individuals profit from antibiotic treatment, but the community suffers from the evolution of resistance or increased virulence that follows.

In whatever form, defense against parasites is costly. Among the hosts there is an incentive to reduce these expenses. Moreover, there is a game-theoretical aspect to such defense. If the host population strongly defends itself, herd immunity creates opportunities for "cheats" to economize on defense. The end result (evolutionarily stable strategy, or ESS) is not the strategy that minimizes parasite load on the community – on the contrary. Rather, parasites effectively mediate competition among the hosts; the strategy that creates the highest parasite load while maintaining itself will outcompete any other (Mylius and Diekmann 1995). This scenario would create a bleak world. It is clear that under these conditions, a communal defense strategy may pay off for the community as a whole. That is, every host profits from the efforts of a public health authority that provides general health insurance. (An associated moral system, and possibly a judicial system to impose it, may be necessary to prevent cheats.)

Assuming that all hosts have ceded the most important decisions to such a public health authority, the problems are still far from over. The highest priority of such an authority would be, of course, to fight the parasites in the short term, such as by implementing public health measures, vaccination campaigns, provision of adequate medical care, etc. The decisions that must be taken at this level are complicated and must take into account all the effects of age structure, temporary or life-long immunity, multiple infection, cross-immunity, social structure, etc. (see Anderson and May 1991).

The purpose of this book is to discuss the possibilities of virulence management – that is, that set of public health measures that takes into account not only the short-term effects, but also the long-term evolutionary effects. The point of this chapter is that the design of such virulence management strategies may have to be developed in light of the partially conflicting interests between the individual and society, and, therefore, such strategies may require Machiavellian choices about whom to protect and whom to sacrifice. This may not be a welcome message, but turning a blind eye to it may present us with dire consequences. To end on a more positive note, virulence management allows us to exploit the forces that keep society together to improve the conditions for all. As such, virulence management may help the human society in its ongoing struggle to escape from its parasites (McNeill 1976).

Acknowledgments The author thanks John Edmunds for his valuable comments on a draft version of this chapter.

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