The scope for virulence management: A comment on Ewald's view on the evolution of virulence

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The scope for virulence management: a comment on Ewald's view on the evolution of virulence

Minus van Baalen and Maurice W. Sabelis

Parasites exploit their hosts to accomplish transmission to new hosts. Whether the purpose is to release infective particles or to promote their chances of transport by vectors, they must reproduce in their host. As this requires exploitation of the resources and physiological machinery of the host, the host is likely to experience detrimental effects that reduce the reproductive rate or increase the death rate. Parasite 'virulence' is therefore an inevitable consequence of pathogen reproduction. Indeed, the term is generally used to refer to both the cause – parasite reproduction – and its effect – reduced host fitness.

Increased infectivity is advantageous to a parasite, but its associated effect, disease-induced mortality, is not. If the parasite depends on direct transmission, it must not prevent its host from meeting new susceptible hosts. Parasites that are transmitted by vectors may be little impaired when their host is immobilized, but will only be taken up by the vector as long as their host remains alive. Natural selection therefore favours those strains that strike the optimal balance between intensity and duration of infectivity.

Is it possible to manipulate the situation such that the parasites become less harmful to their hosts? In a recent book, Paul Ewald[1] argues that by manipulating the efficiency of transmission, natural selection might be made to favour less-virulent parasite strains. The idea is that the more difficult it is to infect new hosts, the more it 'pays' a parasite to be less harmful to the host in which it resides. Ewald discusses several cases where suppression of parasite transmission (by general methods, such as increased hygiene or the introduction of public sanitation) was indeed followed by a shift towards less-virulent strains.

However, there is a difficulty with this explanation. Natural selection will only favour one strain over another if strains are affected differentially. Yet, when transmission becomes more difficult, all strains are affected to the same extent, irrespective of the way in which they exploit their host. That it has become harder to reach new hosts does not, by itself, benefit avirulent strains. Reduced transmission will lead to a lower incidence of infection; desirable as this may be, it does not change the optimal host-exploitation strategy.

Or does it? If the incidence of infection decreases, so does the incidence of infection with multiple clones, reducing the likelihood of parasites sharing their host with other clones. If within-host competition affects optimal virulence, any change in the frequency of multiple infection has evolutionary consequences.

Within-host competition

For singly infected hosts, virulence is the outcome of the struggle between single hosts and single parasite clones, and this favours an optimal compromise between parasite production and host survival[2,3]. Multiple infection means that the conflict is not merely between host and parasite, but also among different parasite clones, and this favours increased virulence[3–6]. To predict the evolution of virulence under conditions of multiple infection, within-host competition should be taken into account, but population dynamics of hosts and parasites must beconsidered explicitly, because the frequency of multiple infection depends on the state of the entire host–parasite system.

Population dynamics

The first insight into the situation was provided by Levin and Pimentel's classic model[7] for the interaction of two parasite strains differing in virulence. This model is based on the assumption that within doubly infected hosts, virulent parasites quickly outgrow avirulent parasites (relative to the length of the infectious period), so that virulent parasites instantaneously 'take over' hosts infected with avirulent parasites. Virulent and avirulent parasites may nevertheless coexist in the population at large. When both virulence types are rare, avirulent parasites have the benefit that they use their hosts more efficiently. However, when avirulent parasites become common, the balance shifts to favour virulent pathogens. But then, as the virulent pathogens become prevalent, less-efficient use of the host reduces their abundance, and avirulent parasites can regain lost ground. In Levin and Pimentel's model[7], it is this negative feedback that allows the coexistence of virulent and avirulent parasites. Such coexistence implies that neither very high nor very low virulence is evolutionarily stable[8].

What will happen if intermediate strains arise? If multiple infection

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always results in the most virulent parasite expelling the least virulent, highly polymorphic parasite populations may result with complex dynamics[9]. However, instantaneous replacement of one strain by another is unlikely to occur if parasites differ very little in virulence. If the prolonged simultaneous presence of more than one parasite clone in a host (that is, host sharing) is taken into account, monomorphic populations will result instead of polymorphic ones[10]. Yet whether the within-host interaction is correctly represented by 'superinfection' (more-virulent pathogens eliminate less-virulent pathogens from a host[9]) or 'co-infection' (host sharing[9]), the outcome is increased average virulence compared with the optimum for single parasite clones. To predict the evolutionary consequences of changes in transmission efficiency, we give an example that assumes co-infection.

Evolutionarily stable virulence

How the interaction between population dynamics and evolution, termed 'ecogenetical feedback' by Eshel[4], determines virulence is shown in Fig. 1a. Suppose the parasites are very virulent. Then, under conditions of population dynamical stability, the risk of becoming infected (force of infection) is low. In consequence, the incidence of multiple infection is also low, and mutant parasites that are less virulent are favoured. Thus, the parasite population becomes less and less virulent. However, at some point this process stops. Were virulence to decrease below the point where the two curves intersect, the force of infection would increase to such an extent that within-host competition would favour more-virulent strains. Eventually, an equilibrium is reached. The level of virulence that results, called evolutionarily stable because no mutant parasite can invade, is determined both by competition within hosts (small scale) and by competition for hosts (large scale).

'Virulence management'

Given the hypothesis that virulence will settle at a compromise between efficient use of the host and within-host competition, what are the consequences of interventions in parasite transmission cycles? Campaigns to suppress parasite transmission are very likely to lead to a reduction in the force of infection. This will diminish within-host competition, so that less-virulent strains are favoured (Fig. 1b). Changes in within-host competition among the parasites may well account for the evolutionary responses in virulence that Ewald[1] ascribes solely to changes in transmission.

As can be deduced from Fig. 1b, for 'virulence management' to be effective, two conditions must be met. Within-host competition must affect optimal virulence, because otherwise changes in the force of infection would have no effect. The equilibrium force of infection must depend on transmission efficiency, because otherwise changes in transmission efficiency would

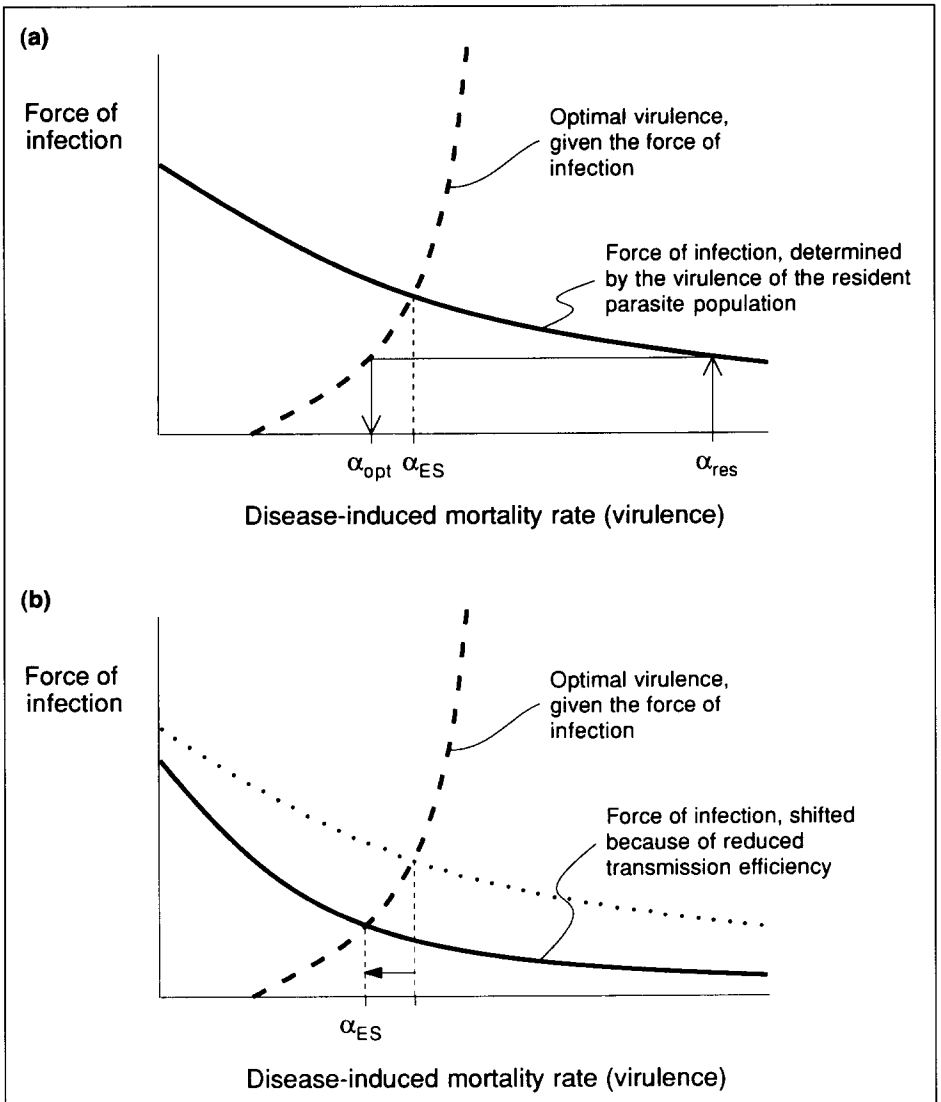

Fig. 1. Feedback governing the evolution of virulence. **(a)** Through its effect on host–parasite dynamics, the virulence of the parasite population determines the force of infection, the risk of becoming infected (solid curve). The force of infection determines the strength of within-host competition, so that optimal virulence (dashed curve) depends in turn on the force of infection. If the parasite population is very virulent (α_{res}) the force of infection is low (under population dynamical equilibrium), and avirulent mutants (α_{opt}) are favoured. The evolutionary equilibrium (evolutionarily stable virulence, or α_{ES}) is at the intersection of the two lines. **(b)** Shows the effect of decreased transmission efficiency on evolutionarily stable virulence, assuming that reduced transmission efficiency leads to a reduced force of infection. The dotted curve shows the original position of the solid curve. (Adapted from Ref. 10 with permission; copyright University of Chicago, 1995.)

not result in changes in the intensity of within-host competition. If either condition is not met, the evolutionarily stable level of virulence will not shift at all.

Contrary to Ewald's predictions, suppressing parasite transmission may even result in the opposite of what was intended. For example, antibiotic therapy also reduces transmission, but this is actually likely to favour increased virulence. The parasites lose their host anyway, and their only chances for transmission are in the time between infection and the administration of antibiotics[3]. As another example, eradication of mild strains that can monopolize their host (for example, by exploiting the immune system) might create opportunities for more-virulent strains that lack this ability. Thus, there might be situations in which it is advisable to tolerate mild strains.

Developing a science of 'evolutionary epidemiology' might well offer new insights, but at present much of the necessary information is lacking. We know how parasites cause disease and are transmitted, but we have little insight into the alternatives that are open to the parasites, and even less into how these alternatives affect within-host competition. Until we know more of the frequency of co-infection, the intensity of within-host competition remains obscure. Yet it must be stressed that the evolution of virulence cannot be understood from studying transmission alone, and that investigating within-host competition is a prerequisite for gaining further insight.

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Response from Ewald

Minus van Baalen and Maurice Sabelis err in their portrayal and interpretation of my arguments. They state "The idea is that the more difficult it is to infect new hosts, the more it 'pays' a parasite to be less harmful to the host in which it resides. ... Natural selection will only favour one strain over another if strains are affected differentially. Yet, when transmission becomes more difficult, all strains are affected to the same extent, irrespective of the way in which they exploit their host."

The first part of this quotation is inaccurate. The idea is not that harmfulness is negatively associated with the difficulty of infecting new hosts. Parasite harmfulness might be positively or negatively associated with this difficulty. In the second part of this quotation, they assume that an environmental change affects variants to the same extent. According to the framework that I present in my book[1], the virulent and mild variants are affected differentially by the particular environmental changes that I consider. Consider waterborne transmission. According to my hypothesis, waterborne transmission differentially affects the success of mild and severe variants. A protected water supply favors mild variants because mild variants allow host mobility, which is needed for direct transmission. When social and environmental conditions allow waterborne transmission from immobilized hosts, the competitive balance shifts to favor the more exploitative variants, which can, under these conditions, gain the reproductive benefits of their higher level of exploitation without incurring the reduction in transmission that would otherwise result from host immobilization.

In an effort to generate an alternative to such arguments, van Baalen and Sabelis state 'Multiple infection means that the conflict is not merely between host and parasite, but also among different parasite clones'. Even without multiple infection, the conflict is not merely between host and parasite. Clones that are in different hosts still compete with each other for entrance into susceptible hosts. A clone that enters a susceptible host first may, for example, stimulate an immune response that makes that host unavailable for the competing clone. In this case, multiple infection may not occur because the late-arriving clone is knocked out before it generates an infection or after the early-arriving clone has been eliminated by the immune system. Considering the previous example, a preponderance of waterborne transmission should favor interpersonal transmission of the more virulent clones, whereas reliance on person-to-person transmission should favor interpersonal spread of the milder clones.

Van Baalen and Sabelis also misrepresent my arguments about hygienic improvements. I do not argue that virulence would be reduced by 'general methods, such as increased hygiene or the introduction of public sanitation', or general 'suppression of parasite transmission'. Rather, I identify several specific interventions that should reduce virulence. To restrict my analysis to realistic possibilities, I focus in my book on those interventions that would be considered socially acceptable. Some kinds of improvement in hygiene often fall into this category, but others do not. The importance of this distinction is illustrated in my chapter on hospital-acquired infections, where I suggest that the virulence of neonatal pathogens might be lowered not only by increases in the hygienic standards of attendants, but also by some