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Epidemiology meets evolutionary ecology

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The rapid expansion and increasing mobility of human populations make understanding the evolution of parasite virulence a public health priority. The potential for the swift evolution of virulence in response to changes in host ecology has motivated the integration of evolutionary ecology with epidemiological theory, as part of the emerging field of evolutionary epidemiology. Virulence is the product of complex interactions among evolutionary, ecological and epidemiological processes. Recent models that incorporate ideas from both evolutionary ecology and epidemiology generate predictions that could not be made by either discipline alone. These models predict that the ecological or evolutionary changes affecting population dynamics of disease, such as spatial structuring, within-host dynamics, polymorphism in host resistance, host longevity and population size, impose selection on virulence. As disease incidence increases, it becomes particularly important to take into account the implications of infection by multiple parasite strains. Evolutionary epidemic models also identify the potential importance of immune evasion and optimal virulence for the selection of sex in parasites. Thus, merging epidemiology with evolutionary ecology has widespread potential to help us answer evolutionary questions and to guide public health policy.

The threats of bioterrorism and emerging diseases, such as HIV, ebola and yellow fever, provide a compelling reason to study the evolution of VIRULENCE (see Glossary). Merging epidemiological theory with an understanding of the evolutionary ecology of parasites and the behavioral ecology of their hosts has now improved the realism of predictive models of parasite virulence [1–8]. Research into the evolution of virulence has moved from insightful verbal arguments to explicit modeling and experimentation. Modeling is necessary to understand the complex interactions among the ecological, evolutionary and epidemiological processes governing virulence evolution, and to direct empirical research. Integrating these disciplines will help to guide public health policies that guard against the evolution of heightened virulence.

Here, I examine the life-history tradeoffs that maximize parasite transmission and hence determine optimal levels of virulence, and discuss how the epidemiological realism of virulence models is enhanced by distinguishing horizontal versus vertical and direct versus indirect transmission. Changes in human behavioral ecology that alter these transmission patterns affect the evolution of virulence, and incorporating ecologically realistic spatial-structuring of disease transmission into models of virulence evolution also influences optimal virulence. Furthermore, taking into account interactions among multiple strains within individual hosts can dramatically alter predictions of virulence levels. Phylogenetic analysis reveals the epidemic potential of emerging strains, and new evolutionary epidemic models (which incorporate both evolutionary and epidemiological dynamics) help predict the impact of different vaccines on the evolution of virulence. Additionally, recent epidemiologically realistic models demonstrate that sex and recombination in parasites can facilitate the evolution of immune evasion and virulence. Thus, such models provide insight into fundamental problems in evolutionary ecology, whilst an evolutionary perspective enhances our understanding of epidemiological public health issues.

Optimal virulence

Virulence is a fundamental trait of parasite life histories (Box 1). A long-standing myth is that the parasite does not harm its host; however, this fails to recognize the adaptive tradeoff among different fitness components of parasite and

Glossary

Directly transmitted diseases: transmission via direct contact between hosts (e.g. sexually transmitted diseases).
Endemic disease: persists over a long time in a host population.
Epidemic disease: refers to an outbreak of disease.
Horizontal transmission: any form of transmission that is not maternal, including vector-borne, airborne transmission and direct contact.
Indirectly transmitted diseases: vector-borne diseases, such as malaria, are transmitted indirectly between humans via at least one (often insect) vector; water-borne diseases, such as cholera, are disseminated indirectly through water contact.
Transmissibility ($\beta_{N\alpha}$): rate at which an infected host spreads infection (either directly or indirectly) to susceptible hosts. Usually depends on the density of hosts (N) and the virulence of the parasite population α.
Vertical transmission: maternal transmission from mother to offspring.
Virulence: an emergent property of host–parasite interactions that arises from host exploitation [68,69]. From an evolutionary perspective, virulence is the extent of parasite-induced reduction in host fitness. Although this definition encompasses effects on both fecundity and mortality, attention is given predominately to the latter. Furthermore, mortality-related virulence has been quantified in different ways. Usually modelers employ a parasite-induced instantaneous mortality rate, α (Box 1). However, this does not correspond to definitions used in most verbal arguments or in empirical studies, which tend to focus on the probability of parasite-induced host death rate once infected (i.e. case mortality rather than instantaneous mortality). In some cases, model predictions can be altered qualitatively by the precise definition used [70–72].

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host life histories [9–11] (Box 1). Parasites face a life-history tradeoff between persistence (i.e. host survival) and fecundity, given that greater host exploitation is likely to increase transmission rate but to reduce host survival and, hence, the time available for transmission [10,12] (*c.f.* [13], Box 1). Simultaneously, hosts face a life-history tradeoff between the cost of resistance and the risk of infection.

May and Anderson advanced research into virulence evolution by defining the fitness of the parasite explicitly in realistic ecological and epidemiological terms [9] (Box 1), rather than assigning arbitrary fitness functions. These parameters in turn depend on the ecology of the parasite and its host. Recent models extend this framework to incorporate increased evolutionary, ecological and epidemiological realism.

Transmission patterns

Horizontal versus vertical transmission

Ewald suggests that the behavioral ecology of human populations, particularly sexual behavior, plays a significant role in determining transmission patterns, including the relative importance of HORIZONTAL versus VERTICAL TRANSMISSION [14,15]. All else being equal, vertical transmission tends to reduce virulence, relative to horizontal transmission, because vertical transmission depends on host survival and reproduction [14]. For example, the greater opportunities for horizontal transmission in hospitals might contribute to outbreaks of highly virulent strains of *Escherichia coli*, salmonella, staphylococcus and streptococcus bacteria [14].

Ewald points out that host behavior might be paramount for diseases transmitted both sexually and maternally, such as HIV and HTLV-1 (human T-cell lymphotropic virus-1) [14,16]. He suggests that in promiscuous communities, transmission of EPIDEMIC DISEASES is maximized by high virulence. Therefore, reducing the rate of exchange of sexual partners generates an immediate reduction in transmission and also an evolutionary reduction in the virulence of epidemic diseases [17].

Mathematical models indicate that the generalization that virulence increases with the horizontal: vertical transmission ratio might have greater applicability to epidemic than to ENDEMIC DISEASES [10]. Moreover, greater horizontal transmission increases infection prevalence, which simultaneously increases vertical transmission; therefore, it is difficult to disentangle these modes of transmission [18].

Indirect versus direct transmission

Ewald argues that transmission of DIRECTLY TRANSMITTED DISEASES is limited by host illness because of an associated reduction in the mobility of hosts [14]. However, host mobility is not important for the transmission of vector-borne diseases, resulting in greater virulence in such diseases relative to directly transmitted diseases [14]. Again, the generality of this hypothesis has been questioned [19,20]. Other factors, including inoculum size [20] and spatial structuring of transmission [21] might provide alternative explanations for differences in virulence between directly and INDIRECTLY TRANSMITTED DISEASES. Nonetheless, Ewald's hypotheses [14–16] emphasize the value of applying host behavioral ecology to epidemiological problems. Building on this, recent models show that nonlinear dynamics of disease transmission have ecological consequences that are much more complex than was originally assumed [19–21].

Spatial structuring of disease transmission and dispersal mechanism

Traditional models of virulence evolution assume homogeneous mixing of host populations and global

Box 1. Life-history theory and tradeoff models

A life-history strategy is a solution to an ecological problem that maximizes reproductive success within the constraints of a specific environment. Thus, life-history strategies are assumed to optimize tradeoffs between fitness components. Parasite life-history strategies are selected to maximize lifetime transmission, but there is a tradeoff between the rate of transmission, β, (expected to increase with virulence) and duration of transmission (expected to decrease with virulence).

The application of life-history theory to epidemiological modeling has aided predictions about how changes in human behavior or public health policy will act on parasite life-history strategies [a,b]. Many aspects of epidemiology and disease transmission influence the evolution of parasite life-history. In turn, parasite life-history strategy will affect the optimal life-history strategy of hosts.

In spite of the progress that evolutionary ecologists have made in furthering our understanding of virulence, the misconception that parasites will ultimately evolve towards avirulence has only been dispelled gradually from the medical literature (reviewed in [c]). A crucial advance in our understanding of virulence was made by defining the fitness advantage of virulence to parasites explicitly in terms of the basic reproductive ratio (R_0), a parameter that forms the foundation of epidemic theory [d] (Eqn I):

$$R_0 = \frac{\beta_{N\alpha}}{\alpha + \mu + \nu_\alpha} \qquad \text{[Eqn I]}$$

where α is the virulence or infection-related mortality rate, $\beta_{N\alpha}$ is the rate of transmission of disease (a function of host population size, N, and α), μ is the average mortality rate of uninfected hosts and ν is the rate of recovery from infection, which can also depend on α. R_0 is defined as the average number of secondary infections produced from a single infected host in the absence of density-dependent constraints [e]. Parasites are predicted to evolve to maximize R_0, provided that certain assumptions are met, which is not necessarily so in all parasite species, limiting the usefulness of R_0 maximization. For example, estimates of R_0 do not generally take into account vertical transmission or multiple infections. Additionally, R_0 assumes no density dependence, although it does play a role in ecological and epidemiological processes that affect the evolution of virulence.

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infection probabilities. However, spatial and social structuring is fundamental to many epidemiological and ecological interactions. Recent models demonstrate that incorporation of spatially explicit dynamics of disease transmission predict lower levels of virulence than do those that ignore this realism [21–23].

Boots and Sasaki analyze a model in which highly virulent, transmissible parasites sweep rapidly through a local cluster of hosts [22]. If a parasite cannot disperse to another host cluster before it goes extinct locally, it does not persist. The dispersal mechanism of a parasite determines the connectivity between clusters. Thus, parasites with long-ranging dispersal (including water-borne, airborne and vector-borne parasites and those with persistent propagules) are able to sustain greater virulence than are directly transmitted parasites [21–23]. Unfortunately, the increasing mobility of humans increases connectivity between clusters and thus might select for greater virulence.

Bonhoeffer *et al.* suggest that propagule longevity does not affect optimal virulence [24]. However, when propagule production is mediated by host mortality, traits that increase virulence and induce host mortality, such as toxin production, are favored [13]. Thus, the standard tradeoff between virulence and transmission is unnecessary for virulence to evolve in propagule-producing parasites [13]. The current lack of consensus about the relationship between dispersal mechanism and virulence evolution calls for further modeling of this topic.

Host heterogeneity

Selection for virulence is a composite of evolutionary pressures arising from the life histories of both parasites and their hosts [2,7,25–27], as demonstrated by the rapid coevolution between myxoma virus and the European rabbit *Oryctolagus cuniculus* in Australia. Changes in virulence associated with cross-species transmissions also testify to the importance of host life history, of which heterogeneity in resistance is a component. If a parasite that is optimally adapted to one host resistance genotype is suboptimally adapted to other genotypes, host heterogeneity selects for lower virulence [28–32] and for heterogeneity in virulence [32,33]. This highlights the importance of heterogeneity within agricultural and livestock populations for guarding against outbreaks of virulent diseases.

Host heterogeneity can impose a tradeoff between the exploitation of different host genotypes. Regoes *et al.* propose that there is a dichotomy of evolutionary stable states: parasites either evolve a generalist strategy and infect different genotypes equally well, or specialize in infecting one genotype exclusively but better than would a generalist [31]. However, Ganusov *et al.* find that stochastic heterogeneity that does not impose a tradeoff between the infection of different host genotypes increases virulence [33]. In reality, Regeos *et al.*'s deterministic host heterogeneity [31] and Ganusov *et al.*'s stochastic heterogeneity are likely to act simultaneously, an interaction that remains to be modeled. Different measures of parasite-induced mortality employed by Regoes *et al.* [31] and Ganusov *et al.* [33] might also contribute to the discrepancy of their results regarding the effect of host heterogeneity on virulence levels.

The dynamic feedback of coevolutionary processes can shift a system from a single evolutionary stable level of virulence to a system of multiple stable states [34,35], or even chaotic dynamics [36]. Multilocus gene-for-gene interactions between hosts and parasites promote cyclical genetic heterogeneity of virulence that inhibits the spread of virulent genotypes [37]. Thus, feedback arising from the interaction between host–parasite coevolution and epidemiological processes can have a major impact on the dynamics of virulence evolution [26,35]. It is therefore becoming clear that the relationship between parasite virulence and host resistance is more complex than was originally assumed.

Competition between strains and within-host dynamics

Within-host interactions among strains can profoundly influence selection for virulence. Competing strains simultaneously infecting the same host are selected to rapidly exploit the host before resources are depleted [38], escalating to greater virulence [10,33,39–41]. Consequently, within-host competition does not necessarily select for a level of virulence that optimizes transmission. Levin and Bull propose that within-host dynamics might be even more important than is the transmission/persistence tradeoff for determining the virulence of diseases such as meningitis, poliomyletis and HIV [42]. Mathematical models support the hypothesis that within-host evolution of competing HIV strains contributes to the increased virulence associated with the onset of AIDS [41,43].

Although competition between strains increases virulence, kin selection between related strains is predicted to reduce it [10,39,44]. For example, there is evidence for conditional virulence strategies in lizard malarial parasite *Plasmodium mexicanum* based on the relatedness of competing strains [45]. In turn, the relatedness of strains within individual hosts is affected by ecological factors, such as dispersal, climatic influences on propagule longevity and the mobility, heterogeneity and size of the host population.

Interstrain competition could account for empirical observations of greater parasite replication in mixed (versus single-strain) infections [44,46], and might explain the continued increase in parasite replication of *P. mexicanum* even as transmission rate plateaus [47]. Competition between parasite strains within the same host could also account for excessive replication, analogous to the overproduction of sperm generated by male–male competition for transmission of genes to offspring [48].

As TRANSMISSIBILITY declines, the likelihood of multiple-strain infection (and hence within-host competition) is reduced, resulting in selection for lower virulence [49]. The interplay between these epidemiological and evolutionary processes could lead to unstable dynamics: greater transmission increases the prevalence of multiple-strain infection, which in turn increases virulence, and hence transmission, perpetuating a cycle of escalating virulence [50]. Consequently, medical intervention that generates an initial shift in virulence could drive the

system into a spiral that results in further change in virulence, limited ultimately by the level of parasite strain diversity (and hence multiple-strain infection). Reciprocally, a reduction in transmission, for instance because of improved hygiene or vaccination, might have a greater effect than is predicted by models that neglect within-host dynamics.

Evolutionary processes that determine parasite virulence depend on the interaction between selection acting on transmission between hosts and that acting within individual infections. The duration of infectiousness, spatial structuring, transmission patterns, host immune response and natural longevity of hosts all influence the relative importance of within-host and between-host dynamics to virulence evolution. The specific ecological conditions that affect these factors are only beginning to be deciphered [6,19].

Phylogenetic analysis

Phylogenetic analysis provides information about the location, timing and mechanisms of the emergence of virulent strains, which can help in the design of public health policies that reduce opportunities for virulent strains to arise. Phylogenetic patterns of within-host evolution of HIV strains indicate that the most virulent strains are not usually transmitted between hosts, but emerge in the final stages of HIV progression to AIDS [6], consistent with the hypothesis that HIV virulence arises as a by-product of within-host infection dynamics [42]. Conversely, phylogenetic analysis of virulent *E. coli* strains [51] and the high nonsynonymous:synonymous mutation ratio in genes that control virulence in *E. coli* [52] indicates that virulence is under positive selection in this pathogen.

Bush *et al.* reveal that the lineage with the highest proportion of nonsynonymous substitutions in key antigenic sites is most likely to dominate the epidemic [53]. Divergence in key antigenic sites enables escape from pre-existing immunity, thereby enhancing both transmission and virulence of the virus. Furthermore, Bush *et al.*'s model can be used to predict the progenitors of future epidemics. Thus, evolutionary models based on phylogenetic analysis can guide the development of vaccines against influenza viruses with epidemic or pandemic potential.

Public health policy

Public health officials face an ethical dilemma if the optimal treatment strategy for an individual patient is not optimal for the community. The resurgence of TB, the emergence of drug resistance in malaria, and the heightened virulence of pathogen populations result from intervention that has short-term epidemiological benefits but deleterious long-term evolutionary repercussions. Evolutionary epidemic models help us to evaluate the effect that different public health policies are likely to have on virulence evolution. Therapeutic agents shorten the infectious period, while vaccination reduces the number of susceptible hosts. These different forms of intervention could have qualitatively different effects on transmission dynamics and hence different evolutionary outcomes, which evolutionary epidemic models would help to identify.

The effects of drugs and antibiotics on virulence are not straightforward [10]. In a community with access to treatment, a dichotomy of pathogen strategies is favored. Reduced virulence is adaptive to the extent that patients do not seek treatment. Alternatively, increased virulence enhances transmission in the period before treatment. The latter effect might be minimized if treatments are used prophylactically.

Vaccines of imperfect efficacy can select for changes in virulence [5]. Gandon *et al.* predict that vaccines that reduce parasite replication and/or toxicity select for greater virulence, but vaccines that lower either transmission or host susceptibility select for lower virulence [5]. Vaccines that reduce the opportunities for transmission select for lower virulence, because persistence becomes increasingly important relative to transmission as opportunities for transmission decline. Therefore, vaccines that target host susceptibility could be responsible for a greater reduction in disease, through an evolutionary influence on virulence levels, than would be predicted from immediate epidemiological effects alone.

Models used to assess vaccines could be further enhanced by considering that the evolution of both virulence and vaccine resistance might be controlled by the same antigenic locus [54], and by taking into account concomitant changes in within-host dynamics of multiple infections. In addition to evolutionary equilibria, it is also important to evaluate transient dynamics, as these can be relatively long-lived, and will determine the sustainability of different public health policies. Seasonal fluctuations in host ecology have the potential to prevent evolutionary dynamics from reaching equilibrium.

These results highlight the importance for public health officials to prioritize policy that has beneficial short-term epidemiological effects and beneficial long-term evolutionary consequences. Intervention that reduces transmission and hence the likelihood of multiple-strain infection, and intervention that targets virulent strains could help reduce virulence in both the short- and long-term. For example, vaccines that target virulent strains were highly successful in the control of *Corynebacterium diptheriae* and *Haemophilus influenzae*, as well as bringing about a reduction in virulence [55]. It is important for public health officials to bear in mind that the most virulent strain is not necessarily the most prevalent (e.g. malarial strains), so careful selection of target strains is crucial.

Sex and virulence

A long-standing enigma in evolutionary biology is the widespread occurrence of sex, in spite of its twofold cost [56]. It has been widely recognized that parasite evolution might be a major factor in the selection for sex in hosts [57]. A new perspective on the evolution of sex can be provided by considering sex in parasites [58–60]. As in models of virulence evolution, realistic assumptions about epidemiology, immunology and evolution are necessary to assess accurately the selective value of sex in both hosts and their parasites [9]. Such models demonstrate that sexual reproduction in helminth parasites can more

Table 1. General effects of different factors acting on virulence evolution

Factor	Evolutionary response	Refs
Transmission factors		
Horizontal versus vertical transmission	Virulence is generally thought to increase as horizontal versus vertical transmission increases, but generalization can be misleading	[10,14,15,18]
Spatial structuring	Decreases virulence	[21–23]
Indirect transmission	Increases virulence, but tradeoff between transmission stages remains to be modeled	[14]
Propagule production	Increases virulence, although propagule longevity may not have an affect	[13,24]
Host ecology		
Heterogeneity in host resistance	Decreases or increases virulence, depending on the type of heterogeneity	[28–31]
Increase in rate of exchange of sexual partners	Increases virulence of sexually transmitted diseases	[17]
Increase in size of host population	Increases virulence for epidemic, but not endemic diseases	[10]
Host longevity	Consensus has been that virulence declines with increasing host longevity, but depends on the definition of parasite-induced mortality employed	
Coevolutionary dynamics	Can shift the system from a single evolutionary stable level of virulence to a system of multiple stable states	[34]
Parasite ecology		
Within-host competition between strains	Increases virulence, although effect is mitigated by relatedness between strains	[10,33,39–41,44]
Density dependence of parasite replication	Increases virulence if the relationship between parasite replication and reduction to host fitness is greater than linear	[11]
Sex	Sex in parasites increases virulence, whereas sex in hosts reduces virulence	[28,61]
Medical intervention		
Vaccines that reduce parasite growth and/or toxicity	Increases virulence	[5]
Vaccines that reduce parasite transmissibility or host susceptibility	Decreases virulence	[5]
Antibiotics	Either evolves lower virulence that makes treatment unnecessary or greater virulence that increases transmission before treatment	[10]

easily produce and maintain strain diversity than can asexual reproduction [58–60]. Parasites that can generate novel antigenic strains are able to escape pre-existing immunity, and are also likely to exhibit greater transmissibility and virulence. Thus, sex might be selected for in parasites to facilitate the evolution of immune evasion [58,60] and optimal virulence [61]. For example, outbreeding in the helminth *Schistocephalus solidus* increases transmissibility and the range of hosts that can be infected [62].

The establishment of infection within vertebrate hosts requires parasites to overcome host adaptations that have evolved to resist highly mutable parasites, such as viruses. Although many pathogens generate sufficient diversity through a high mutation rate, this strategy would cause the accumulation of deleterious mutations in helminth parasites, with their large genomes and relatively small within-host population sizes. Instead, the sexual reproduction of helminth parasites facilitates the evolution of immune evasion. Consequently, the sexual reproduction of helminths facilitates their adaptive radiation into the parasitic niche, because it enables long-lived helminth parasites to keep pace with the rapid evolution of other pathogens competing for the parasitic niche and with the rapid evolution of host defenses. Indeed, similar immunological mechanisms can act against parasites with very different biologies. For instance, T-helper lymphocytes are involved in the immune response against both HIV and helminth parasites.

Coevolutionary dynamics between hosts and parasites are clearly fundamental to the evolution of virulence and have also been proposed to drive the selection of sex [57]. Wedekin recently suggested that sex in parasites increases virulence [61], whereas sex in hosts reduces virulence [28]. Field data and analytical predictions both indicate that selection for virulence in schistosomes infecting snail hosts can generate fluctuating epistasis [63]. In turn, fluctuating epistasis is suggested to be fundamental to the evolution of sex [57]. Similarly, Sasaki proposes that the sustained cycles of host resistance and parasite virulence polymorphism exhibited by his model favor sex [37]. There is also empirical evidence to suggest that mate choice might occur in some helminths [64], which could facilitate the production of genetic diversity and the evolution of virulence.

Combining evolutionary theory of sex, virulence and immune evasion might yield insights about empirical observations of parasite reproduction. Robert *et al.* predict that maximal parasite fecundity, and hence transmission, is achieved by a heavily biased female sex ratio, given that a male can fertilize multiple females [65]. However, empirical studies of *Plasmodium* contradict this simple relationship [47]. These contradictions might be resolved by taking into account immunity-mediated competition among parasite strains. A balanced sex ratio facilitates the production of genetically diverse offspring [66]. In turn, diversity could aid evasion of immunity against

Box 2. Further research questions and topics

Modeling approaches

Epidemiological realism

- Explore virulence evolution using models that merge population genetics and epidemiological dynamics of transmission to complement traditional optimality models.
- Employ individual-based models to investigate the relationship between the distribution of parasite burden between hosts and virulence. Empirical studies have repeatedly demonstrated that helminth parasite burdens are aggregated in their host populations.
- Use dynamic optimization models to assess the importance of variation in transmission during the infection period [a].

Evolutionary realism

- Use stability analysis to examine the conditions under which selection for virulence drives a system towards regions of stability, perpetual fluctuation or turning points in the dynamics.
- Explore transient dynamics. Epidemics are, by definition, not in a state of equilibrium.

Coevolutionary realism

- Investigate whether host–pathogen genotype specificity reduces virulence by decreasing the probability of multiple strain infection.
- Develop quantitative genetic models of host resistance and parasite virulence to compare rates of the evolution of the parasite population in response to medical intervention or changes in host behavioral ecology when virulence is controlled by polygenic expression versus single genes of major effect.
- Model the tradeoff between different transmission stages of indirectly transmitted helminth parasites. Empirical studies of schistosomes have suggested that optimal virulence is different in vector versus final host species [b].

Ecological realism

- Develop stochastic models to assess the role that stochasticity plays in the evolution of virulence, and the maintenance of virulence polymorphism. Stochasticity is likely to be particularly important at the emergence of new strains when population numbers are low.
- Employ spatially explicit models to investigate the influence of local versus global transmission on the relative importance of within-host and between-host dynamics to the evolution of virulence.
- Take into account seasonal fluctuations that affect transmission and/or selective regimes using seasonally forced models.
- Formulate epidemiologically realistic models to capture the relatively complex biology of helminth parasites, which have been largely neglected in virulence models. For example, it is necessary to introduce quantitative aspects of the parasite burden when modeling helminth infection.
- Incorporate density dependence of parasite fecundity. This is particularly important when examining the evolution of virulence of helminth parasites. Increased parasite burdens might result in higher virulence but with lower parasite fecundity per capita.

Empirical research

- Explore the relationship between genetic exchange in parasites, antigenic diversity, immune evasion and virulence evolution both empirically and theoretically.
- Use comparative studies between closely related parasites to identify key ecological factors affecting the evolution of virulence.
- Carry out ecological correlation studies to improve understanding of variation in virulence between different diseases. Such studies should help to verify model assumptions and to clarify contradictions in model predictions.
- Perform experimental studies to identify the empirical relationship between virulence and transmission for specific diseases.

Public health policy

- Develop models to identify the types of disease that are most likely to respond favorably to evolutionary control of virulence, such as epidemic versus endemic diseases and horizontally versus vertically transmitted diseases. Simple models can be very powerful, but abstraction can be counterproductive when designing intervention strategies for specific diseases with life-history strategies that have evolved in the context of different ecologies.
- Develop models that compare the sensitivity of virulence evolution to prophylactic drugs versus vaccines versus behavioral changes.
- Establish more interaction and collaboration between modelers and public health officials.

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pre-existing parasite genotypes. Consistent with the immune-evasion value of sex for parasites is the recent observation that the sex ratio of the malaria parasite *Plasmodium gallinaceum* switches from predominately female early in infection to 1:1 later in infection [67]. This suggests that the production of genetically diverse offspring becomes particularly important later in infection, once immunity has developed against the parental strains.

Conclusion

Understanding the interplay between the ecology, evolution and epidemiology of host and parasite populations will lead to more accurate predictions of the evolution of virulence. The complex interactions of these processes can make simple predictions elusive, necessitating case-by-case modeling of specific diseases, complemented by empirical verification. However, more realistic virulence models that incorporate host behavioral ecology, spatial structuring of disease transmission, within-host infection dynamics and insights from parasite phylogeny are now available (Table 1).

Virulence models can be used to guide public health policy by helping to explain epidemiological and ecological complexity, particularly when interactions with selection imposed by human intervention are nonintuitive. For example, changes in human behavior and the administration of drugs and vaccines clearly generate an immediate reduction in transmission. Models of virulence evolution show that reducing transmission *per se* and the concomitant reduction in multiple-strain infected hosts might also select for lower virulence.

Although the application of evolutionary virulence models to the design of public health policy is still in its infancy, evolutionary epidemiology clearly has the potential to improve the choices available to policy makers. One success story has been in using predictive models of the evolution of epidemic influenza strains to improve vaccine selection by the Centers for Disease Control in America [53]. Further interaction and collaboration between modelers and public health officials is crucial, particularly as public health policy can have unforeseen evolutionary

repercussions. Predictions from virulence models about spatial structuring and host heterogeneity can also be applied to the design of agricultural practices and conservation reserves to help prevent the dissemination of virulent parasites.

Many avenues of theoretical and empirical research remain to be explored (Box 2). Further elucidation of the epidemiological and evolutionary processes acting on virulence is needed before many public health policies can be accurately evaluated. It is particularly important to address the ecological interactions between parasites and their hosts when considering the long-term consequences of public health policy, in addition to the immediate epidemiological impact.

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