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Introduction

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Toward the end of the 1960s, by dint of science and collective efforts, humankind had managed to eradicate smallpox and to land on the moon. Accordingly, some of the best-informed experts felt that the time had come to close the book on infectious diseases, and that the colonization of interplanetary space was about to begin. Today, these predictions seem as quaint as the notion – also quite widespread at the time – that the Age of Aquarius was about to begin.

The subsequent decades have taught us to be less sanguine about the future. In 2001 we do not send out manned spacecraft to meet with extraterrestrials, but instead are shutting down obsolete space accommodation. And far from closing the book on infectious diseases, we find that books on infectious diseases still have to be written. Few experts believe, nowadays, that we are witnessing the beginning of the end of our age-old battle against germs. In 1999, for instance, the World Health Organization (WHO) launched an ambitious program, "Roll Back Malaria" – a battle cry that seems tellingly defensive. In the 1960s, optimists still entertained hopes that malaria could be wiped out altogether. And why not? It had worked for smallpox, after all.

Aside from the disappointments with malaria and other infectious diseases – alarming outbreaks of cholera or foot-and-mouth epidemics, for instance – we had to learn to come to terms with other baffling setbacks. New scourges such as acquired immunodeficiency syndrome (AIDS, which is killing humans by the millions), the prions pandemonium, or the humiliating effectiveness of bacteria in their arms races against pharmaceutical companies are but a few examples.

Not that scientific progress has come to a halt: far from it. But it has led us to a point at which we can see, much more clearly than before, a long and bumpy stretch of road extending before us, probably with many twists and turns hidden from view. Cartographers of yore would have inscribed the warning "there be monsters here". In this book we have tried to be a bit more specific, with the help of some of the most expert scouts in the field. However, infectious diseases are among the relatively uncharted realms in evolutionary biology, offering plenty of drama and scope for adventure – witness, for instance, the efforts to reconstruct the genome of the virus responsible for the 1918 Great Influenza Epidemic: monsters be here indeed!

A generation ago, medical doctors and biologists were brought up on what is nowadays called the "conventional wisdom". It holds that pathogens should evolve toward becoming ever more benign to their hosts, since it is selectively

Box 1.1 Notions of virulence

Virulence describes the detrimental effect of parasitic exploitation on the host (just as resistance characterizes the detrimental effect of host defense on the parasite). Virulence therefore arises from processes through which parasites exploit their host to further their own multiplication and transmission. This general definition is respected throughout the present book.

To unravel alternative, more specific notions of virulence, it is useful to distinguish diseases according to how the process of damage to the hosts unfolds:

- *Killing the host*. For relatively harmful diseases, the exploitation of hosts often results in their death. In such cases, a large part of the parasite's tendency to inflict harm can usually be summarized in terms of the parasite-induced additional mortality rate of the hosts. Many chapters in this book focus on this case and therefore equate virulence with parasite-induced mortality.
- *Impairing other life-history characters*. Other negative consequences of parasite exploitation gain in relative importance if infection only rarely leads to death. Such alternative detrimental impacts of the parasites – ranging from a decrease in host fecundity through a change in its competitive abilities to a mere plunge in its mobility or well-being – are important aspects of parasite virulence in their own right and can impact on its evolution. While changes in mortality and fecundity affect host fitness directly, to understand the contributions of other side-effects of host exploitation to both parasite and host fitness may require an in-depth consideration of relatively subtle mechanisms.
- *Gaining entrance*. Especially in the plant world, the potential of a pathogen to inflict damage often strongly depends on whether or not there is a match between resistance genes in the host and genes in the parasite to overcome that resistance. Often little variation is found in the damage inflicted on hosts by different parasite strains once they have gained entrance to the host. The relative capacity of parasites to enter the host then becomes the key determinant of any detrimental effects. Plant pathologists thus tend to use the term virulence to refer to those capacities. In this book, the term "matching virulence" is used for this; in contrast to this, and when the need arises, the term "aggressive virulence" is used for the detrimental effects of the parasite's exploitation strategy.
- *Local spreading*. When hosts are structured into local populations, the harm that pathogens can bring to these depends on their transmission within the local populations – which, in turn, depends both on the local transmission rate and on the damage inflicted on individual hosts. "Virulent" parasites may then be defined as those that quickly and relentlessly spread throughout a local population. Such a use of the word virulence correlates it with traits that affect the transmissibility of the pathogen.

In an agricultural setting, these last two aspects of virulence tend to be present together (with a farm's crop as the local population), which explains the different terminological tradition in the phytopathological literature compared to, for example, the medical literature. While the last three aspects of virulence listed above may all be attractive for defining virulence for particular systems, the goal of conceptual clarity compelled us, throughout the book, to use them only with further qualification.

advantageous for parasites to have efficient vehicles at hand for their transmission. Thus, the virulence of a pathogen (Box 1.1) was envisaged as an adaptive trait: all pathogens would eventually become avirulent if given enough time to evolve. This Panglossian view has not always been that conventional: indeed, it helped, in its day, to spread the idea that virulence is subject to evolution, very rapid evolution, in fact – and this was quite a revolutionary insight at one time. Of course, it was but a first step. Evolutionary biologists have since learned that constraints within the relationship between transmissibility and virulence can seriously upset the trend toward harmlessness (Box 1.2), and that competition between several strains of a pathogen within one host demand an altogether more complex analysis than the former optimization arguments offered. These insights have prompted the idea that it may be feasible to interfere with or even redirect the evolution of virulence to achieve some desired practical goals – such as low virulence in the parasites of crops, cattle, or humans, and high virulence in the parasites that control weeds and pests. This Darwinian approach gave rise to a new research program on virulence management (Box 1.3) and provides the basis for this book.

Many of the arguments on the adaptive dynamics of virulence have become so involved that they are easier to analyze mathematically rather than verbally. We have nevertheless tried in this book to keep the mathematical techniques down to earth, and to display the modeling techniques in "stand-alone" boxes which, in combination, offer a concise and coherent introduction to the theoretical approaches used in the book (see the overview on page xvi).

Our emphasis is on the connection of this theory with empirical data and experimental set-ups. It turns out, in fact, that the data prove quite hard to interpret without a clear understanding of the actual meaning of basic notions such as virulence and fitness. To a first approximation, fitness is reproductive success and virulence is the additional mortality caused by the pathogen (see Box 1.1). However, in many instances, such as for populations that are not well mixed but distributed in clumps, this first approximation is not adequate. Case studies from infectious diseases in humans, chestnut blight, senescence in fungi, rinderpest, and, of course, the celebrated myxoma virus in rabbits, all show how difficult it is to disentangle rival concepts and to assess different modeling approaches.

Like all good Darwinians, we look toward theory to guide us through the plethora of facts. So in this book the initial chapters set the stage by discussing the impact of alternative transmission modes and ecological feedbacks on the evolution of virulence (Part A). We then proceed systematically to analyze, first, the implications of host population structure for the evolution of virulence (Part B), second, the competition of pathogens within a host (Part C), and, finally, pathogen–host coevolution (Part D) and multilevel selection (Part E). We firmly believe that only when armed with these tools is there a reasonable chance of understanding the long-term effects of vaccines and drugs (Part F) and of successfully addressing the options and problems of virulence management (Part G).

Box 1.2 A simple example of virulence evolution and management

Here we illustrate how evolutionary theory can be used to suggest measures that will help manage the virulence of a pathogen. We start with some conventional assumptions about the disease under consideration.

Single-species assumptions

- Pathogens only survive in living hosts.
- Pathogens can enter disease-free hosts only through contact between these and infected hosts.
- Once in a host, pathogens multiply rapidly, so that the first infection determines the final impact.
- Within the hosts, pathogens compete only with their own offspring.
- The per-host disease-free death rate is constant.

Interaction assumptions

- The rate at which susceptible hosts become infected is proportional to the product of the density of infected and that of susceptible hosts (law of mass action). The proportionality constant, termed per-host disease transmission rate, increases with pathogen replication.
- Pathogen replication occurs at the expense of the host's resources, and this damage to the host, termed virulence, increases the per-host disease-induced death rate.
- The trade-off between the per-host transmission rate and the per-host disease-induced death rate conforms to a law of diminishing returns.

For pathogens to transmit they require living hosts, so pathogen fitness depends on the average survival time of the hosts. Thus too high a virulence is not expected to pay off. As a representative measure of pathogen fitness, we use the number of new infections produced per host over the period it survives and is infectious, known as the pathogen's basic reproduction ratio R_0 (see Box 2.2). As shown in Box 9.1, the pathogen strain with highest R_0 outcompetes all others.

The disease-induced death rate that maximizes R_0 can be found graphically, the rationale for which is given in Box 5.1. In the figure at the end of this box, the fixed disease-free death rate is plotted to the left of the origin, while the evolutionarily variable disease-induced death rate, or virulence, is plotted to the right. The thick trade-off curve describes the effect of virulence on the disease transmission rate. Figure (a) shows how, by drawing a tangent line from the point on the left to the trade-off curve on the right, the optimal level of virulence is found just below the tangent point. In this simple example, pathogens are therefore expected to evolve toward intermediate levels of virulence.

continued

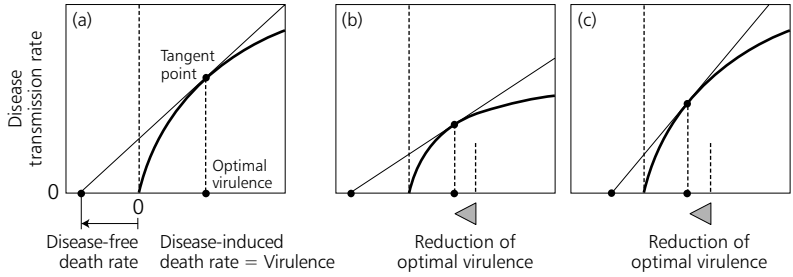
Box 1.2 *continued*

This graphic construction immediately suggests two possible routes to managing virulence:

- Either we change the trade-off curve such that the tangent point shifts to the left, Figure (b);
- Or we decrease the disease-free host death rate and keep the trade-off curve in place, Figure (c).

Both options are expected to result in the evolution of reduced virulence levels. Moreover, the second option generates the interesting hypothesis that investment in host health – so as to promote the life span of the hosts *in the absence of the disease* – creates an environment in which pathogens evolve to become more benign.

Of course the model as discussed above is overly simplistic. The remainder of this book investigates the various intricacies that should be considered to capture a wider range of circumstances.



Whenever public health officials, veterinary epidemiologists, advisory plant pathologists, conservation biologists, or biocontrol workers want to devise strategies to manage the course of infectious diseases, they must bear in mind that they are merely adding one level of strategic action on top of other, age-old layers of strategic interactions. These have been devised through the programming by natural selection of both the pathogens and hosts – organisms that differ widely in scale, generation time, and life history, and that use individual variability and polymorphisms to fuel their arms races. If public health decisions are not based on a sound knowledge of these underlying tugs of war, they risk being counterproductive. Many human interferences, far from managing disease, have helped disease to manage us.

No doubt the next generations will know vastly more than we do now, but we hope that this book will offer no reason for them to deem us naively oversimplistic, as the 1960s appear to us now. To take Einstein's dictum to heart, we and all the contributors to this book have tried to present matters as simply as possible, but not simpler, and have endeavored to approach the complexity of our subject with the appropriate respect.

Box 1.3 A research program on virulence management

As a backbone for further research efforts, we outline a systematic sequence of steps to test hypotheses about virulence evolution and to probe options for virulence management:

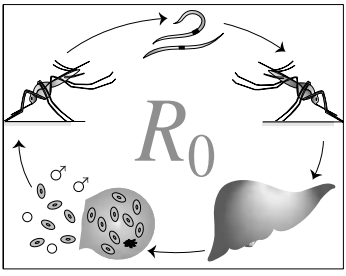
1. Specify how the hosts are affected by the parasite's exploitation (effects of virulence).
2. Assess which of these effects influences parasite transmission (identification of trade-offs).
3. Spell out the ecological setting (e.g., which of the participants interact with each other, and how mixing takes place). Derive suitable representative measures for fitness given the ecological setting (e.g., R_0).
4. Analyze the adaptive dynamics of the ecological and evolutionary feedback processes.
5. Extract model predictions on how selection affects virulence and, in particular, how controllable epidemiologic parameters can be changed to select for reduced virulence.
6. Test these predictions theoretically (e.g., robustness of the model) and empirically.
7. Search for alternative explanations (e.g., multiple instead of single infection) and, if necessary, carry out tests to distinguish between the alternative mechanisms.

The chapters in the book follow this agenda and describe results for particular ecological settings. Given the diversity of relevant scenarios and the empirical uncertainty regarding some of their key components, it is evident that much research remains to be done in pursuit of this program.

Acknowledgments Development of this book took place at the International Institute of Applied Systems Analysis (IIASA), Laxenburg, Austria, where IIASA's former director Gordon J. MacDonald and current director Arne Jernelöv have provided critical support. To achieve as much continuity across the subject areas as possible we organized two workshops in which the authors were brought together to discuss their contributions. The success of a book of this kind depends very much on the cooperation of the authors in dealing with the many points the editors are bound to raise, and we thank our authors for their patience. The book has benefited greatly from the support of the Publications Department at IIASA; we are especially grateful to Anka James, Martina Jöstl, Eryl Maedel, John Ormiston, and Lieselotte Roggenland for the work they have put into preparing the manuscript. Any mistakes that remain are our responsibility.

Part A

Setting the Stage



Introduction to Part A

Investigating options for virulence management is a multidisciplinary endeavor. To identify the most promising avenues, contributions from epidemiology, ecology, microbiology, genetics, and theoretical biology have to be integrated into a common perspective. That goal is an inspiration and challenge for this book as a whole.

Before diving into this complexity, some readers might appreciate a gentle start. Part A therefore introduces the essential ideas and concepts in this book and addresses the following questions:

- Is it realistic to expect measures of virulence management to succeed in practice?
- What are the epidemiological and ecological complexities that virulence management strategies ultimately may have to deal with?
- Which methods are suitable for assessing outcomes of virulence evolution and for predicting consequences of managerial interference?
- Which problems and dilemmas are bound to arise in the context of virulence management efforts?

Chapter 2 provides first suggestions of management options that can successfully influence the virulence of pathogens. Ewald and De Leo emphasize the critical importance of the mode of pathogen transmission for virulence evolution. They propose that, if pathogens can be transmitted from host to host along several routes, public health managers should be concerned primarily with those routes that are least dependent on the host's health. Taking waterborne transmission as an example, a model of diarrheal disease is presented. Maximization of the basic reproduction ratio shows that, when waterborne transmission prevails, evolutionarily stable levels of virulence tend to be high. Narrowing this transmission channel will therefore often select for less virulent pathogens.

Whereas Chapter 2 offers an optimistic view on the feasibility of virulence management for systems in which interventions are relatively easy and data are available, Chapter 3 concentrates on the opposite end of the scale. In their review of wildlife diseases, De Leo, Dobson, and Goodman flag some of the problems that arise from the distinction between micro- and macroparasites, from genetic diversity, and from coevolution. They make the important point that much of theory on the evolution of virulence has been developed for microparasites, even though macroparasites can have a major impact on host dynamics and community structure. The authors also stress that both micro- and macroparasites exert strong selection pressures on the host and that frequency-dependent selection plays an important role in the evolution of virulence. Moreover, they highlight that human

populations expand and thereby come into contact with wildlife and their parasites: this creates the danger of parasites jumping over to humans, which in turn may lead to newly emerging diseases.

Chapter 4 explains why the traditional approach of predicting evolutionary outcomes by maximizing the basic reproduction ratio of a disease is not always appropriate. Since pathogens tend to affect their host environment in radical ways, selection pressures usually depend on the types of pathogens and hosts that are established in an infected population. In this chapter, Dieckmann outlines the theory of adaptive dynamics as a versatile toolbox for investigating the evolution and coevolution of pathogen–host interactions under conditions of frequency-dependent selection. Examples illustrate how classic methods and the new models presented here result in different predictions about the evolution of infectious diseases.

Decisions on virulence management strategies are fraught with dilemmas, as illustrated by the investigation of a model for the coevolution of virulence and recovery ability in Chapter 5. Van Baalen explains why there can be conflicts of interest between the individual host and the host population as a whole. Since selection tends to favor virulent parasites or those that can overcome host defenses, increased investment in the defense of individual hosts does not necessarily minimize the parasite load for the population as a whole. If more aggressive parasites are favored, hosts play "defense games" against each other, and thereby potentially trigger selection for a further increase of virulence. In the long run, hosts either pay heavily to defend themselves against a rare but extremely virulent parasite or they tolerate the parasite if it stays relatively benign. Human health care managers may thus be confronted with the ethical dilemma of creating either common-but-mild or rare-but-serious diseases.

The four chapters of Part A set the stage for this book by indicating the range of basic issues that have to be considered in the evaluation of strategies of virulence management: transmission routes (direct versus indirect; vertical versus horizontal), distinction between micro- and macroparasites, genetic diversity in host resistance and parasite virulence, frequency-dependent and reciprocal selection, multiplicity of evolutionarily stable virulence levels, and ethical dilemmas in medical epidemiology. Of course, many more aspects must be considered to assess and improve the match between models and epidemiological reality. That is what the remainder of this book is about.

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Alternative Transmission Modes and the Evolution of Virulence

Paul W. Ewald and Giulio De Leo

2.1 Introduction: Historical Background

For most of the 20th century, medical scientists writing about the evolution of infectious diseases generally concluded that parasites are expected to evolve toward states of benign coexistence with their hosts (reviewed in Ewald 1994a). According to this line of reasoning, parasites that harm their hosts are harming their own long-term chances of survival, and are therefore at a disadvantage over evolutionary time. Theory developed since the 1980s emphasizes that this traditional viewpoint is based on faulty assumptions about the level at which natural selection acts. Specifically, natural selection is a process by which organismal variants that contribute more of their genetic instructions into future generations become increasingly represented in the gene pool of future generations. When applied to parasite virulence, the appropriate focus is therefore on the short-term competitive processes among parasite variants rather than on the characteristics that would allow a particular parasite species to persist most stably over the long term. According to this reasoning, by the time any variants reap such long-term benefits, they would already have been displaced by the variants that held the short-term advantage. Any increases in long-term survival of the parasite species associated with benignity are therefore of little if any relevance to the evolution of virulence if benign strains lose the short-term competition.

A large body of theory and empirical evidence now supports the idea that natural selection can favor evolution of parasitism toward virtually any position along a spectrum that ranges from commensalism to lethality (Fine 1975; Anderson and May 1981, 1982; Levin and Pimentel 1981; Levin *et al.* 1982; Ewald 1983, 1994a; Frank 1996c). Central to this theoretical framework is the trade-off concept, which proposes that the level of virulence to which a pathogen evolves is determined by a trade-off between the benefits and costs associated with increased host exploitation. In this case, benefits and costs are measured in units of evolutionary fitness, which quantify, at the genetic level, the passing on of particular genetic instructions relative to alternative instructions. At the organismal level, evolutionary fitness results from the differential survival and reproduction rates of organisms, in accordance with the definition of natural selection presented above. The fitness benefits associated with increased host exploitation are generated by the increased conversion of host resources into pathogen production and propagation. In models of virulence, fitness benefits are typically portrayed as a result of competition