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Epilogue

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Far from conquering infectious diseases through good sanitation, vaccines, and antimicrobial agents, populations of humans – as well as those of other animals and plants – continue to be harassed by an onslaught of pathogens. Complex processes of host–pathogen adaptation are responsible for the perennial persistence of this threat.

To develop sustainable control strategies, it is important to ask which new selective pressures on virulence will thus be created, and how resistance against control measures can be slowed, prevented, or even reversed. On the one hand, population growth, increased mobility, and climate change create new opportunities for diseases, while on the other hand adaptations allow disease agents to overcome the current transmission barriers.

Can epidemiological changes be steered in the desired directions and can they be prevented from veering off course in detrimental ways? That is what this book is about. Its aims are

- To show how evolutionary epidemiology as a science can profit from modeling techniques that take both population dynamics and natural selection into account;
- To explore the design of strategies for virulence management based on models of the evolutionary dynamics of pathogen–host systems;
- To highlight important unresolved research questions that need to be addressed before evolutionary predictions and management options are to be trusted; and
- To foster the dialogue between theorists and empiricists in the field of evolutionary epidemiology.

What are the general predictions regarding the evolution of virulence traits, as they have emerged throughout this book? An overarching principle appears to be the following: the more control the pathogen has over the host, the smaller the likelihood that the pathogen will become virulent. The basis for this prediction is that whenever exploitation by a pathogen cannot be interfered with by other pathogens or environmental causes, the well-being of the host is in the evolutionary interest of the parasite. However, under unclear conditions of "ownership", restrained exploitation is less likely. This can best be viewed as an instance of the Tragedy of the Commons. Whenever the resource (the host) is not safely monopolized, consideration of long-term benefits loses importance. The following points can be viewed as special cases of this principle.

- Under conditions of guaranteed transmission, selection favors the strains that replicate faster. This highlights why it is important to analyze alternative transmission modes, be they actual or potential.
- Under vertical (horizontal) transmission, low (high) virulence is favored. A vertically transmitted pathogen is generally much more closely tied to the host than an invader can ever be. There are relatively few theoretical analyses on this aspect, but it is likely to play an essential role in long-term evolution.
- The larger the multiplicity of infections, the higher the virulence. This is the result of arguments based on game theory (rather than optimization arguments) and the core of the Tragedy of the Commons: the more players, the less interest each has in safeguarding the common resource.
- Compared with well-mixed systems, in socially or spatially structured systems less virulent parasites are favored.

From these considerations, important options for virulence management emerge. We list them succinctly, with cross-references to the corresponding chapters for the essential caveats.

- Evolutionary optimality principles should be used with caution when managing virulence evolution under frequency-dependent selection (Chapter 4).
- In the presence of multiple infections, the evolutionary stability of biological control strategies must be assessed in the light of multiple levels of selection (Chapters 9 to 12, 22, and 32).
- Routes of pathogen transmission that function independently of host health, or that even intensify for sick hosts, should be at the very focus of management measures (Chapters 2 and 28).
- Altering transmission networks so that virulent pathogens are exposed to the detrimental consequences of their aggressive exploitation strategy selects for decreased virulence (Chapter 7).
- In animal husbandry and crop management, enhancing the relatedness of infected hosts is expected to select for decreased virulence (Chapters 7 and 11).
- Influencing the likelihood of horizontal versus vertical transmission can select for decreased virulence (Chapters 20 and 21).
- Models based on subdividing the host organism into compartments may help us to prevent the disease from escaping standard control measures (Chapter 30).
- By preventing hosts from acquiring multiple infections, decreased virulence can be selected for (Chapters 9 to 11).
- In the presence of multiple infections, long-term benefits arise from sanitation and vaccination that would otherwise be absent (Chapter 11).
- Tolerating relatively benign parasites, rather than trying to eliminate them, may often be advisable from an evolutionary perspective (Chapter 5).
- Strengthening the "conspiracy" between plants and arthropod predators in tritrophic interactions can improve the prospects for controlling the herbivores sandwiched in between (Chapter 22).

- In the context of biological control efforts, it must be kept in mind that pathogens genetically engineered to have a high virulence may be at a selective disadvantage (Chapters 6 and 32).
- Management-induced supply of novel genetic material from source to sink populations provides the genetic variation needed for local responses in the sink, but can also swamp the local adaptation of pathogens and hosts (Chapter 8).
- Uncontrolled spillover of pathogens from reservoir populations to endangered populations must be minimized, since the former pathogens tend to be more virulent than those in the latter populations (Chapter 29).
- By fostering host evolution and mate choice, it is possible to diminish disease losses in breeding programs for endangered species and livestock production (Chapters 15 and 18).
- To keep virulence at bay in systems with gene-for-gene interactions between parasites and their hosts, fostering the genetic diversity of hosts is essential (Chapter 17).
- If gene-for-gene interactions prevail, breeding schemes can be devised to select for hosts that have simultaneous resistance against multiple pathogen strains (Chapter 31).
- If more than one antibiotic is available to treat a bacterial infection, they should be administered, in a population-wide campaign, to individual hosts through combination therapy (Chapter 23).
- The suppression of a competitively superior pathogen strain by a vaccine that confers little cross-immunity may set off outbreaks of earlier, competitively inferior strains (Chapter 24).
- When nonvaccine serotypes outcompete vaccine serotypes, serotype replacement may augment the effectiveness of a vaccination program in a community (Chapter 26).

It hardly needs to be emphasized that many theoretical and empirical questions remain still unanswered. As with all good engineering, the development of techniques for virulence management requires a process of stepwise scaling up from small-scale predictions and controlled experiments toward applications of realistic complexity. In this context, our impression is that the following problems need to be addressed most urgently.

- A deeper understanding of the genetic basis of virulence traits is needed to better predict virulence evolution in the short term.
- More information is needed on the evolution of mutation rates.
- More experimental clues to the mechanisms of intraspecific competition of pathogens within hosts are needed.
- Actual patterns of competitive and cooperative interactions between different pathogenic strains need to be better understood.
- The existence of alternative transmission routes and their evolutionary implications should be explored in greater depth, both empirically and theoretically.
- Evolutionary implications of spatial structure are as yet imperfectly understood.

- The role of ecological networks in shaping pathogen–host interactions is still largely unexplored, especially if the hosts harbor several pathogen species and parasites can use multiple hosts.
- The richness of patterns in pathogen–host coevolution driven by reciprocal selection warrants further analysis.

If readers feel that this leaves them with more unanswered questions than they had before, the editors will be perfectly satisfied. The main goal of this book is to set a research program for evolutionary virulence management firmly on the road.