



Population Biology, Evolution, and Infectious Disease: Convergence and Synthesis

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Traditionally, the interest of population and evolutionary biologists in infectious diseases has been almost exclusively in their role as agents of natural selection in higher organisms. Recently, this interest has expanded to include the genetic structure and evolution of microparasite populations, the mechanisms of pathogenesis and the immune response, and the population biology, ecology, and evolutionary consequences of medical and public health interventions. This article describes recent work in these areas, emphasizing the ways in which quantitative, population-biological approaches have been contributing to the understanding of infectious disease and the design and evaluation of interventions for their treatment and prevention.

Ever since Darwin, population and evolutionary biologists have been interested in infectious disease (Fig. 1). For most of the history of this enterprise, however, infectious diseases have been seen as primarily agents of natural selection in “higher” organisms, rather than as subjects of study in their own right. In the last two decades, this situation has changed. An increasing number of population and evolutionary biologists have turned to infectious diseases and the microorganisms responsible as the subjects of their research. In many areas, the infectious disease problems being addressed by population and evolutionary biologists have converged with (or complement) those studied by microbiologists, immunologists, epidemiologists, and clinicians. Here, we consider three of these areas: molecular epidemiology, the mechanisms of pathogenesis, and intervention. In place of a literature review of these areas, we offer a critical perspective that is less comprehensive but more personal.

Molecular Epidemiology

As measured by the number of practitioners and international meetings (1), the most developed area of this convergence is molecular epidemiology. The practical goals of molecular epidemiology are to identify the microparasites (viruses, bacteria, fungi, and protozoa) responsible for infectious diseases and determine their physical sources, their biological (phylogenetic) relationships, and their routes of transmission and those of the genes (and accessory elements) responsible for their virulence, vaccine-relevant antigens, and

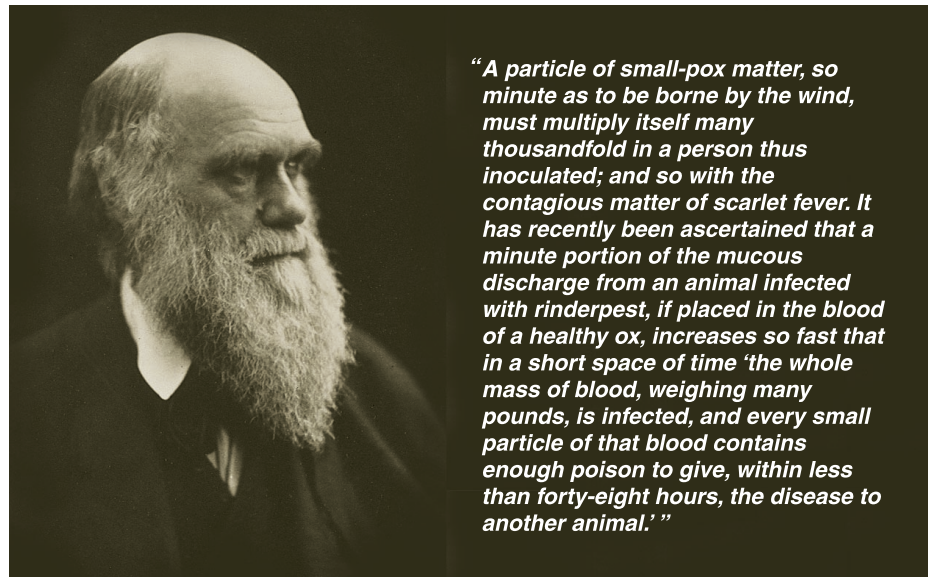
drug resistance.

Early in the development of the “germ theory,” it became clear that there was considerable variation in the incidence and severity of infections with microbes classified as members of the same “species.” As a means of understanding the microbiological basis of this variation and classifying the organisms within species more finely, a variety of typing schemes were developed using serological and other phenotypic markers. The widespread application of these methods led to the observation that specific arrays of

disease symptoms could be attributed to particular serotypes or phage types within species such as *Escherichia coli* and *Salmonella*. This discovery supported the notion that bacterial lineages maintain their genetic integrity over long time intervals and over great distances—that is, their genomes are not rapidly broken down or reshuffled by recurrent mutation and recombination. This view of the genetic structure of bacterial populations became known as the “clone concept” (2).

As the data accumulated, however, it became clear that bacterial populations and species are not merely arrays of genetically separate lineages. The degree of clonality varies among different species: Some, like *E. coli* and *Salmonella*, are highly clonal, whereas the populations of other species like *Neisseria gonorrhoeae* and *Bacillus subtilis* are effectively panmictic (3). Moreover, it also became apparent that even the most clonal bacteria, like *E. coli*, are chimeras bearing chromosomal genes (4) and portions of genes of different ancestries (5).

Among viruses, extensive attention has



“A particle of small-pox matter, so minute as to be borne by the wind, must multiply itself many thousandfold in a person thus inoculated; and so with the contagious matter of scarlet fever. It has recently been ascertained that a minute portion of the mucous discharge from an animal infected with rinderpest, if placed in the blood of a healthy ox, increases so fast that in a short space of time the whole mass of blood, weighing many pounds, is infected, and every small particle of that blood contains enough poison to give, within less than forty-eight hours, the disease to another animal.”

Fig. 1. This quotation from Darwin’s *Variation in Animals and Plants Under Domestication* illustrates not only how well developed the contagion school was before Pasteur and Koch’s demonstration of bacteria as the etiologic agents of disease, but also how infectious disease has played a secondary role in evolutionary biology. Here Darwin was using germs to bolster his argument that the “gemmules” he postulates in his “provisional hypothesis of pangenesis” as the carriers of the information of inheritance and development could be small enough to fit in the sperm of higher organisms. Darwin’s other references to infectious disease (and vices) in *The Descent of Man* are as agents of natural selection in higher organisms, the role they have played for most of the history of population and evolutionary biology.

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been devoted to the molecular epidemiology of the human immunodeficiency virus (HIV). These studies have revealed identifiable lineages of recent common ancestry, but they have also shown that some clinical isolates are chimeras of two or more ancestral lines (6). Clonal population structures have also been suggested for eukaryotic microparasites, like *Trypanosoma cruzii* (7), in which it is unknown whether recombination occurs during the life cycle. Most surprisingly, some studies have indicated a degree of clonal population structure (with important caveats) for eukaryotes for which recombination occurs as part of the reproductive cycle, such as the malarial parasite *Plasmodium falciparum* (8). Thus, in contrast to the naïve expectation, it appears that some organisms for which recombination is not a normal part of the life cycle are nearly panmictic, whereas some microparasites with well-characterized mechanisms for recombination maintain a nearly clonal population genetic structure.

A perusal of the literature on the genetic epidemiology of microparasites would yield the impression that the clone concept (the "clone controversy," as some prefer to see it) is central to the enterprise. Is it? From a practical perspective, understanding the genetic structure of microparasite populations is important for two main reasons. First, for epidemiological and forensic investigations, a clonal population structure makes it possible to trace the sources of different isolates of a pathogen. However, microparasites that on larger spatial and temporal scales are effectively panmictic have clonal population structures when isolated from outbreaks (3). Consequently, a detailed knowledge of the overall genetic structure of a pathogen population may be unnecessary for short-term epidemiological tracking. Rather, the challenge is to use typing characters that change at rates that are informative for the particular question at hand (9). Thus, a relatively fast-changing genetic marker, the restriction pattern of insertion sequences, has been useful for tracking the transmission of tuberculosis in San Francisco (10) but would be unhelpful for looking at trends in the global population of *Mycobacterium tuberculosis* over many decades. Similarly, broad categories such as serogroup and serotype are useful in global surveys of disease patterns for some bacterial infections but might provide inadequate discrimination for investigating local outbreaks.

Second, knowledge of the genetic structure is important to understand (and, ideally, predict) the responses of pathogen populations to selective pressures imposed by host immunity, both natural and vaccine-induced, and is important for the effective management of antimicrobial drugs. These areas are discussed further below.

Within-Host Population Dynamics of Pathogen Proliferation

If the course of a microparasite infection in a vertebrate host were described without jargon, the process would be readily recognized as one of population dynamics and evolution. A microbe proliferates in a habitat (host tissue), in which it is normally limited by physical and chemical barriers or by predators and competitors (phagocytic and other cells of the host immune system, and other microorganisms). These microbial invaders often have phenotypes that enhance their survival in this novel habitat (virulence factors, including the ability to attach to and invade cells and to resist the host's constitutive chemical and cellular defenses). Evolution occurs in both the parasite population and the host's immune system. Parasite-mediated selection favors the proliferation of predators (such as B and T cells) that specifically target the microparasite. Selection in the microparasite population favors mutants (antigenic variants) that are able to evade these targeted predators or avoid predation and competition by invading different microhabitats (cells and tissues) where the (immunological) predation pressure is less intense. Either the microparasite population will be controlled or cleared by the response of the cell community (host), with only modest disturbance (morbidity), or the defenses will fail and the cell community will be destroyed (mortality). Figure 2 is a schematic diagram of these interactions.

This perspective on pathogenesis and the immune response as ecological, population-dynamical, and evolutionary processes has been well recognized for some time (11). However, it has had little impact on contemporary research on the mechanisms of pathogenesis. Much of this research is qualitative rather than quantitative, and it can be described as a quest to characterize (genetically, biochemically, and physiologically) the interaction between infectious pathogens and the host's immune defenses. Although this research provides an indispensable basis for understanding pathogenesis and the host's response to infection, it tells only a part of the story. A complete account of the course of an infectious disease must include a quantitative description of the major forces that determine the abundance, diversity, and distribution of a pathogen population within an infected host and the immune defenses involved in its control.

During the past decade, population and evolutionary biologists have begun to develop a quantitative theory of the within-host population dynamics of infections (12). Among the most fruitful of these investigations are those that have involved direct collaborations between population biologists, immunologists, and virologists working on HIV. Simple mathematical models describing the nonlinear interaction between populations of HIV and of CD4⁺ T cells were instrumental in uncovering the rapid viral replication that underlies an apparently slow disease.

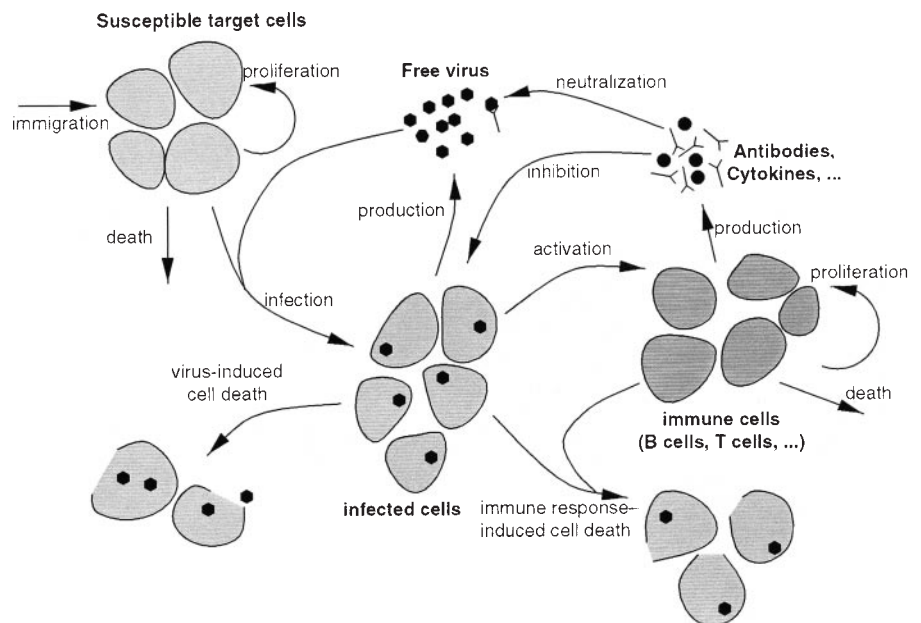


Fig. 2. Schematic illustration of the population dynamics of a virus infection. The replication of a virus in an infected host can be likened to a natural ecosystem with resources, predators, and prey. By infecting a cell the virus preys on its resource, the susceptible target cells, while itself being subjected to predation by the host's immune response. Classical virological and immunological research is mostly concerned with uncovering the direct interactions between the virus and different cell types of its host. In contrast, population-dynamical research aims to disentangle the complicated and often counterintuitive dynamical behavior resulting from the web of nonlinear interactions.

Mathematical analysis of clinical data showed that more than 10^{10} virus particles are produced and cleared every day and that about one-third of the actively virus-producing cells are replaced every day (13). Before these analyses, the low viral load during the asymptomatic phase of the infection was commonly attributed to slow virus replication. The population-dynamical analysis, however, showed that the low virus load reflects a dynamic equilibrium between very high rates of production and clearance.

Analogous studies of the dynamics of hepatitis B and C virus and simian immunodeficiency virus (SIV) are now beginning to provide a comparative perspective (14). In addition to contributing to our understanding of viral pathogenesis, the population-dynamical approach led to predictions about the minimum duration of treatment for the elimination of a viral infection, provided the rationale for the current recommendation to treat HIV early during the asymptomatic phase, and helped explain the differences in the rates at which drug resistance appears in the treatment of different infections (13, 14).

The Ecology of the Immune Response

An "ecological" perspective may also be helpful in studying the dynamic nature of the immune response to infectious pathogens in vivo. For example, a population-dynamical analysis of cross-sectional data of T cell counts in humans after radiotherapy provided the first estimates for the proliferation, death, and interconversion rates of naïve and memory T cells in vivo (15). A more direct estimate of these rates in macaques was recently obtained by collecting longitudinal data for the uptake and washout of a marker that labels dividing cells (16). Mathematical modeling and analysis not only enabled the estimation of proliferation and death rates of CD4⁺ and CD8⁺ T cells in normal macaques, but also enabled the quantification of how these rates change in the presence of SIV infection.

Quantifying the dynamics of immune responses not only provides valuable information for the study of infectious disease but also sheds light on many central issues in immunology and identifies critical questions for further experimental analysis. The macaque study, for example, suggests that the death rate exceeds the proliferation rate of T cells in the blood (16). If so, what source makes up for the difference? Could immigration of T cells from the thymus play numerically a more important role than commonly believed? What regulates the cell populations in the periphery? Many experimental and theoretical studies have addressed these questions separately, but only a few combine both approaches (17). However, it is clear that a combination of

both is necessary to develop a comprehensive quantitative understanding of the immune response to infectious pathogens.

Vaccination

Population-biological models have already played a major role in the design and targeting of vaccination programs. They have been used, for example, to calculate the critical fraction of a population that must be vaccinated to eliminate a particular pathogen; to design clinical trials of vaccines; to target vaccination programs (or other interventions) to achieve maximal reductions in disease; to anticipate possible "perverse" effects of vaccination (for example, increases in congenital rubella syndrome as vaccination increases the average age of rubella infection); and to predict potential outbreaks of a disease in time to take preventive measures (18, 19). These successful, practical applications rest on more basic insights provided by the models into the mechanisms underlying observed spatial and temporal patterns in disease incidence (19, 20). In both basic and applied settings, the success of these models stems from their extensive use of epidemiological data to adapt the models to individual diseases and to estimate key parameters of disease transmission.

The successful vaccines of the past were directed at organisms with little antigenic variation, whereas many of the current efforts at vaccine development target microparasites with considerable antigenic diversity, such as HIV, *Plasmodium* spp., and *Streptococcus pneumoniae*. This diversity raises a number of new population-biological and evolutionary questions that are beginning to be addressed. How will populations of antigenically diverse microparasites evolve in response to mass vaccination, which may only target a subset of the antigenic variants, and how will this evolution affect the vaccine's benefits in reducing total disease (21, 22)? How must calculations of key epidemiological parameters like the basic reproductive rate of a microparasite be changed when considering antigenically diverse organisms, and how can clinical trials be designed to provide maximal information about the evolutionary effects of the vaccine (22, 23)?

Antimicrobial Resistance

Resistance to antimicrobial drugs is now a serious clinical problem in a wide range of infections (24, 25). New drugs are unlikely to appear soon enough and in sufficient numbers to solve many of these resistance problems. Hence, there is a growing need to understand the factors that lead to the evolution of the spread of resistance, and to design strategies to maximize the effectiveness of existing drugs while minimizing the spread of resistance to them.

The prevalence of resistance of a particular organism to a given drug shows a strong positive correlation with the extent of use of the drug (25, 26). However, the pattern becomes more complex in the broader context of the patterns of antimicrobial use and resistance. For some drugs used to treat some infections, resistance has been an obvious problem since treatment was first introduced (27); in other cases, resistance has emerged relatively recently (or not at all), despite several decades of use (28). A variety of pharmacological, genetic, ecological, and social factors are responsible for these varying patterns of resistance. Mathematical models of the population dynamics of sensitive and resistant organisms are beginning to provide explanations for these patterns of resistance, as well as testable predictions for the impact of changes in antimicrobial use on the extent of resistance in individuals and populations (29–36).

These models predict that the frequency of drug resistance and the rate of change of that frequency depend primarily on a few measurable properties of the pathogen and the drug in question, the most important of which are (i) the duration of infectiousness of infected individuals, (ii) the incidence of drug treatment, (iii) the extent to which treatment of a sensitive infection reduces the transmission of that infection, (iv) the degree to which resistance reduces the competitive fitness of the microparasite in the absence of treatment, and (v) the probability that a drug-sensitive infection becomes resistant upon treatment (29–34).

The effects of these factors are apparent in the contrasting predictions of two recent mathematical models of antiviral resistance. A model of acyclovir treatment of genital herpes (32) predicted that a sustained increase in antiviral treatment would probably result in a very slow increase in resistance, taking several decades to increase to 5 to 10%. The reasons for this slow increase include the long infectious period of genital herpes, the substantial fitness burden imposed on resistant viruses in the absence of treatment, and the fact that treatment of an individual with a drug-sensitive infection rarely causes a permanent switch to drug resistance. By contrast, a model of influenza A infections predicted that resistance would rapidly reach substantial frequencies, in the tens of percents, in a community where anti-influenza drugs were used to treat large numbers of infected individuals. The reasons for this rapid rise include the short duration of infectiousness and the fact that treatment of drug-sensitive cases commonly results in "acquired" resistance in the treated patients as well as the transmission of resistant viruses (33).

A key question now is how drug use can be altered to reduce the spread of resistance while maintaining the quality of treatment for

individual patients. Several studies, both empirical and theoretical, have addressed the question of how the extent of resistance will change after reductions in the extent of antimicrobial use (29, 35). At present, there is still a considerable distance between the theory and empirical work, largely because epidemiological studies rarely measure most of the basic parameters of the models, as listed above. Nonetheless, models have already produced results that should be useful, or at least provocative, to empirical researchers and public health practitioners. For instance, models suggest that cycling of antibiotics, which is often recommended as a tool for reducing resistance, may in fact speed the ascent of resistance in the population (34). The model of antiviral treatment of influenza A described above (33) suggests that the use of anti-influenza drugs for prophylaxis, rather than treatment, would prolong the efficacy of these drugs considerably.

Finally, population-biological models have been used to study the evolutionary response of bacterial and viral populations within a treated patient (36). These models help to define the relative importance of non-compliance with drug regimens, heterogeneity in drug concentrations, pathogen population size and diversity, and other factors that are implicated in the emergence of drug resistance in a treated individual. The models offer quantitative support for the long-standing idea that, to overcome the problems of acquired resistance, as Paul Ehrlich said long ago, it is best to "hit hard and hit early," and to combine drugs (37). Moreover, if integrated into realistic models of within-host dynamics of infections and their control by host defenses, these models may aid in the design of treatment protocols that maximize the efficacy of treatment while minimizing the side effects to the treated host and the dissemination of drug resistance into the community. Particularly in the current, early stages of these modeling efforts, carefully designed trials are necessary to test the effectiveness of policies suggested by the models.

Conclusions and Outlook

In this article, we have focused on the ways in which population and evolutionary biology have been (and can be) contributing to microbiology and medicine. We have not considered the fascinating opportunities that microbiology offers to study evolution and population biology in real time and experimentally (38). Furthermore, we have omitted two topics that actually belong in the broader context discussed here: emerging infectious diseases and the evolution of virulence. There are two reasons for this omission. First, these areas have already been extensively reviewed (39–41). Second, and more important, it is our conviction that the research questions and approaches we have de-

scribed are fundamental to making real progress in understanding the factors responsible for the emergence or reemergence of old and new diseases and the evolution and maintenance of virulence (42, 43).

The work described above represents some of the early steps toward a convergence of population biology and infectious disease. The examples discussed here have shown that this convergence has led to new fundamental insights, but they also highlight the need to further intensify the collaborative efforts of infectious disease biologists and clinicians with population biologists to advance our quantitative understanding of infectious diseases and to apply this knowledge to their control and treatment.

References and Notes

- In June 1998, the III International Workshop on Molecular Epidemiology and Evolutionary Genetics of Infectious Diseases was held in Rio de Janeiro. Fewer than 10% of the 200 or so participants were trained in population and evolutionary biology. A number of smaller recent meetings were specifically devoted to the population biology and evolution of disease, for example, Evolution in Health and Disease, 6 to 11 April 1997, Institut Kurt Bösch, Sion, Switzerland; Virulence Management, December 1997, IIASA, Laxenburg, Austria. [Proceedings of the Sion meeting are now available: S. Stearns, *Evolution in Health and Disease* (Oxford Univ. Press, Oxford, 1999).]
- F. Ørskov et al., *Med. Microbiol. Immunol.* **162**, 73 (1976); F. Ørskov and I. Ørskov, *J. Infect. Dis.* **148**, 346 (1983). Although it might be said that the clonal structure of bacterial populations was independently discovered by population biologists [R. K. Selander and B. R. Levin, *Science* **210**, 545 (1980)], that independence can also be attributed to the ignorance of the medical microbiology literature at that time.
- J. Maynard Smith, N. H. Smith, M. O'Rourke, B. G. Spratt, *Proc. Natl. Acad. Sci. U.S.A.* **90**, 4384 (1993).
- R. F. DuBose et al., *ibid.* **85**, 7036 (1988); D. E. Dykhuizen and L. Green, *J. Bacteriol.* **173**, 7257 (1991); J. G. Lawrence and H. Ochman, *Proc. Natl. Acad. Sci. U.S.A.* **95**, 9413 (1998).
- L. D. Bowler et al., *J. Bacteriol.* **176**, 333 (1994).
- D. L. Robertson et al., *Nature* **374**, 124 (1995); J. Louwagie et al., *AIDS* **7**, 769 (1993); F. E. McCutchan et al., *ibid.* **10**, S13 (1996).
- S. Revollo et al., *Exp. Parasitol.* **89**, 30 (1998).
- R. E. Paul et al., *Science* **269**, 1709 (1995); S. M. Rich, R. R. Hudson, F. J. Ayala, *Proc. Natl. Acad. Sci. U.S.A.* **94**, 13040 (1997); M. Tibayrenc, *Int. J. Parasitol.* **28**, 85 (1998).
- M. C. J. Maiden et al., *Proc. Natl. Acad. Sci. U.S.A.* **95**, 3140 (1998).
- C. Casper et al., *Am. J. Public Health* **86**, 551 (1996).
- F. M. Burnet and D. O. White, *Natural History of Infectious Diseases* (Cambridge Univ. Press, Cambridge, 1972); F. M. Burnet, *The Clonal Selection Theory of Acquired Immunity* (Cambridge Univ. Press, Cambridge, 1959); G. I. Bell, *Nature* **228**, 739 (1970).
- Z. Agur et al., *Proc. Natl. Acad. Sci. U.S.A.* **86**, 9626 (1989); M. A. Nowak et al., *Science* **254**, 963 (1991); A. R. McLean and M. A. Nowak, *J. Theor. Biol.* **155**, 69 (1992); A. S. Perelson et al., *Math. Biosci.* **114**, 81 (1993); R. Antia et al., *Am. Nat.* **144**, 457 (1994); R. Antia et al., *Proc. Natl. Acad. Sci. U.S.A.* **93**, 985 (1996).
- X. Wei et al., *Nature* **373**, 117 (1995); D. D. Ho et al., *ibid.*, p. 123; A. S. Perelson et al., *ibid.* **387**, 188 (1997).
- M. A. Nowak et al., *Proc. Natl. Acad. Sci. U.S.A.* **93**, 4398 (1996); M. A. Nowak et al., *J. Virol.* **71**, 7518 (1997); A. U. Neumann et al., *Science* **282**, 103 (1998).
- C. A. Michie et al., *Nature* **360**, 264 (1992); A. R. McLean and C. A. Michie, *Proc. Natl. Acad. Sci. U.S.A.* **92**, 3707 (1995).
- H. Mohri et al., *Science* **279**, 1223 (1998).

- A. R. McLean et al., *Proc. Natl. Acad. Sci. U.S.A.* **94**, 5792 (1997); M. K. Slika, et al., *Immunity* **8**, 363 (1998).
- R. M. Anderson and R. M. May, *J. Hyg.* **90**, 259 (1983); A. R. McLean, D. J. Nokes, R. M. Anderson, *Int. J. Epidemiol.* **20**, 1107 (1991); I. M. Longini Jr. et al., *Stat. Med.* **17**, 1121 (1998); R. M. Anderson and B. T. Grenfell, *J. Hyg.* **96**, 305 (1986).
- R. M. Anderson and R. M. May, *Infectious Diseases of Humans: Dynamics and Control* (Oxford Univ. Press, Oxford, 1991).
- B. M. Bolker and B. T. Grenfell, *Proc. Natl. Acad. Sci. U.S.A.* **93**, 12648 (1996).
- S. Gupta, N. M. Ferguson, R. M. Anderson, *Proc. R. Soc. London Ser. B* **264**, 1435 (1997).
- M. Lipsitch, *Proc. Natl. Acad. Sci. U.S.A.* **95**, 6571 (1997).
- S. Gupta et al., *Science* **263**, 961 (1994).
- H. C. Neu, *ibid.* **257**, 1064 (1992).
- Antibiotic Resistance: Origins, Evolution, Selection and Spread. Ciba Foundation Symposium 207* (Wiley, Chichester, UK, 1997).
- K. G. Kristinsson, *Microb. Drug Resist.* **3**, 117 (1997); F. Baquero et al., *J. Antimicrob. Chemother.* **28** (suppl. C), 31 (1991).
- G. Canetti, *Am. Rev. Respir. Dis.* **92**, 687 (1965); D. D. Richman, *Rev. Infect. Dis.* **12** (suppl. 5), S507 (1990).
- D. L. Horn et al., *Clin. Infect. Dis.* **26**, 1341 (1998); R. C. Moellering Jr., *Am. J. Med.* **104** (5A), 35 (1998).
- B. R. Levin et al., *Clin. Infect. Dis.* **24**, S9 (1997); F. M. Stewart et al., *Theor. Popul. Biol.* **53**, 152 (1997); D. J. Austin, M. Kakehashi, R. M. Anderson, *Proc. R. Soc. London Ser. B* **264**, 1629 (1997).
- B. R. Levin and R. M. Anderson, in *Evolution in Health and Disease*, S. Stearns, Ed. (Oxford Univ. Press, Oxford, 1998), pp. 125–137.
- E. Massad, S. Lundberg, H. M. Yang, *Int. J. Biomed. Comp.* **33**, 65 (1993).
- S. M. Blower, T. C. Porco, G. Darby, *Nature Med.* **4**, 673 (1998).
- N. I. Stilianakis, A. S. Perelson, F. G. Hayden, *J. Infect. Dis.* **177**, 863 (1998).
- S. Bonhoeffer, M. Lipsitch, B. R. Levin, *Proc. Natl. Acad. Sci. U.S.A.* **94**, 12106 (1997).
- J. J. Rahal et al., *J. Am. Med. Assoc.* **280**, 1233 (1998); H. Seppala et al., *N. Engl. J. Med.* **337**, 441 (1997).
- M. Lipsitch and B. R. Levin, *Antimicrob. Agents Chemother.* **41**, 363 (1997); in (24), pp. 112–127; *Int. J. Tubercul. Lung Dis.* **2**, 187 (1998); D. J. Austin, N. J. White, R. M. Anderson, *J. Theor. Biol.* **194**, 313 (1998); A. R. McLean and M. A. Nowak, *AIDS* **6**, 711 (1992); S. Bonhoeffer and M. A. Nowak, *Proc. R. Soc. London Ser. B* **264**, 631 (1997); S. Bonhoeffer, J. M. Coffin, M. A. Nowak, *J. Virol.* **71**, 3275 (1997); S. Bonhoeffer et al., *Proc. Natl. Acad. Sci. U.S.A.* **94**, 6971 (1997).
- P. Ehrlich, *Lancet* **ii**, 445 (1913).
- R. E. Lenski et al., *Am. Nat.* **91**, 1315 (1991); T. Palzkill and D. Botstein, *Proteins* **14**, 29 (1992); S. J. Schrag and V. Perrot, *Nature* **381**, 120 (1996); B. R. Levin, *Proc. R. Soc. London Ser. B* **264**, 1287 (1997); J. Björkman, D. Hughes, D. I. Andersson, *Proc. Natl. Acad. Sci. U.S.A.* **95**, 3949 (1998).
- J. Lederberg, R. E. Shope, S. C. Oaks Jr., Eds., *Emerging Infections: Microbial Threats to Health in the United States* (National Academy Press, Washington, DC, 1992); S. S. Morse, *Emerging Viruses* (Oxford Univ. Press, New York, 1993).
- J. J. Bull, *Evolution* **48**, 1423 (1994).
- P. W. Ewald, *The Evolution of Infectious Disease* (Oxford Univ. Press, New York, 1994); S. A. Frank, *Q. Rev. Biol.* **71**, 37 (1996); B. R. Levin, *Emerg. Infect. Dis.* **2**, 93 (1996).
- S. J. Schrag and P. Wiener, *Trends Ecol. Evol.* **10**, 319 (1995).
- B. R. Levin and C. Svanborg Eden, *Parasitology* **100**, S103 (1990); B. R. Levin and J. J. Bull, *Trends Microbiol.* **2**, 76 (1994); M. Lipsitch and E. R. Moxon, *ibid.* **5**, 31 (1997); L. R. Gooding, *Cell* **71**, 5 (1992).
- Supported by NIH, the National Institute of General Medical Sciences (NIGMS) and National Institute of Allergy and Infectious Diseases (B.R.L.), NIGMS (M.L.), the Swedish National Science Foundation, NFR (B.R.L.), and the Wellcome Trust and Gand et Bernadel (S.B.).