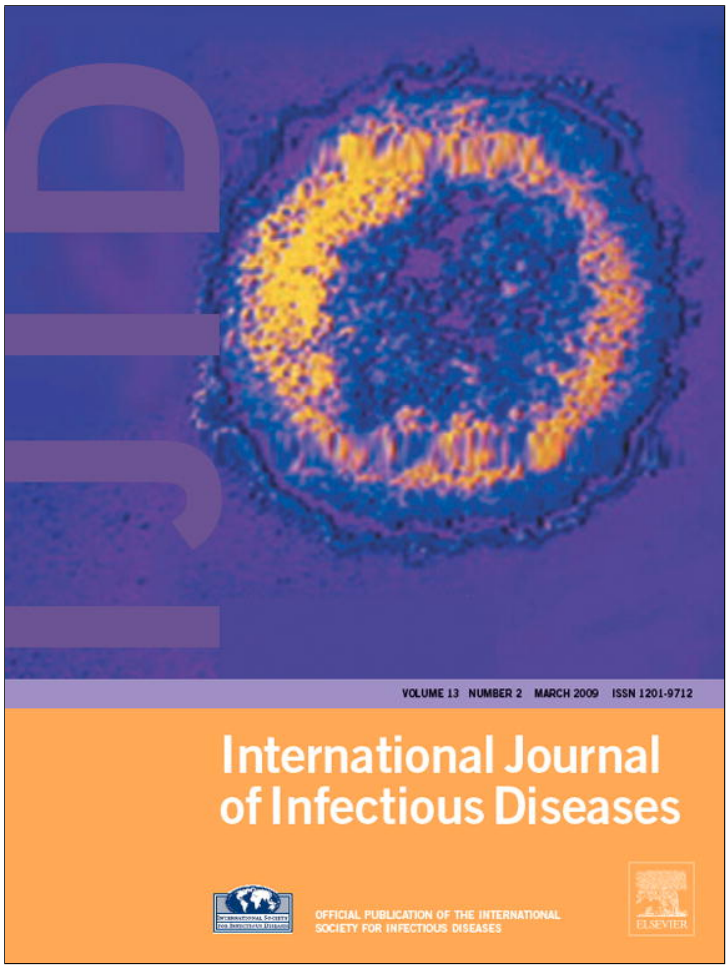

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PERSPECTIVE

Life histories of pathogen populations

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Summary The populations of pathogens in individual hosts have many of the characteristics of multicellular organisms, or individuals. These populations go through a life cycle within a host and they reproduce by founding daughter populations in new hosts. Natural selection shapes the life history characteristics of pathogen populations—life expectancy, trade-offs in the allocation of resources between growth, survival, and fecundity, and aging—in ways that maximize the reproductive fitness of the pathogens. In turn, these life history characteristics shape the natural histories of infectious diseases. Transmissibility and virulence may be thought of as properties of pathogen populations rather than as properties of the constituent microorganisms within these populations. The poor correlation of virulence with pathogen fitness is a major obstacle to the development of a theory of virulence. Consideration of the life histories of pathogen populations complements the traditional epidemiological focus on host populations and provides a valuable perspective for understanding human infectious diseases.

Introduction

Before the rise of bacterial genetics, bacteriologists were interested in such aggregate properties as colony growth and morphology, and thought of bacterial cultures as organisms. Later, when attention shifted to bacterial cells, colonies were considered simply collections of cells.[1] But the older focus on bacterial colonies as organisms was not misdirected. Populations of bacteria (and other pathogens, or parasites) in individual hosts have many of the characteristics of multicellular organisms, or individuals.[2] These populations have spatiotemporal boundaries, they are isolated from pathogen populations in other hosts, they progress through a life cycle, and they reproduce—specifically, by founding daughter populations in new hosts. Moreover, the microorganisms in these populations exhibit a variety of social or cooperative behaviors that give the populations some degree of internal integration. Bacteria exchange genetic information, they cooperate to construct biofilms and to evade host defenses, and they secrete, share, and respond to a variety of molecules, including quorum sensors, toxins, and siderophores.[2—5] Likewise, populations of viral genomes in infected cells may cooperate in the production and utilization of viral RNAs and proteins.[6] Pathogenic microorganisms, like social insects, can survive and transmit genes (either their own or those of genetically similar organisms) only as members of populations with these individual-like characteristics.[7]

If pathogen populations are thought of as individuals, the natural histories of infectious diseases can be understood in terms of the life history characteristics of these

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populations—life expectancy, allocation of resources between growth, survival, and fecundity, and aging.[8] These life history characteristics are shaped by natural selection in ways that maximize the reproductive fitness of the pathogens. Analysis of the life histories of pathogen populations complements the traditional epidemiological focus on host populations.

Models of pathogen transmission

Standard models of pathogen transmission focus on the basic reproductive ratio of the parasite (R_0), the average number of secondary infections produced by the introduction of one infectious individual into a population of susceptible hosts.[9] Hosts progress at specified rates from susceptible (S) to infectious (I) and then to recovered (R) states (SIR models). For directly transmitted pathogens, R_0 can be expressed in terms of the size (or density) of the host population (N), a parasite transmission rate (β, the probability of transmission per susceptible host per unit time), and the duration of infectivity (D):

$$R_0 = N \cdot \beta \cdot D$$

The duration of infectivity is determined by the background and disease-induced host mortality rates, and the rate at which hosts recover from infections. If $R_0 > 1$, the pathogen will spread in the host population, producing an epidemic. As it spreads, however, its reproduction decreases, because fewer and fewer hosts remain susceptible. The net reproductive ratio, R, is given by:

$$R = R_0 \cdot \left(\frac{S}{N}\right)$$

where (S/N) is the fraction of susceptible hosts in the population. At endemic equilibrium, a constant percentage of the host population remains susceptible; under these conditions, $R = 1$, and $(S/N) = 1/R_0$. In an endemic situation, R_0 is a measure of the reproductive fitness of the parasite; natural selection will be expected to maximize R_0 and thereby maximize the percentage of hosts that is colonized by the parasite. Although the value of R_0 determines whether or not a pathogen will spread in a host population, it does not by itself provide information about the rate at which this spread will occur, because the basic reproductive ratio expresses the spread of a parasite per generation, not per unit time, and only rarely is the generation time of the pathogen population (the average age at which these populations give rise to new infections) specified.

These standard epidemiological models consider pathogen transmission in terms of properties of the host population. Pathogen transmission can also be understood in terms of the life histories of pathogen populations. The growth of pathogen populations—the increase in the number of hosts who are infected by the parasite—can be analyzed in terms of age-specific schedules of pathogen survival and reproduction. If $l(x)$ is the probability that a pathogen population will survive to age x and $m(x)$ is the average number of daughter populations produced by a population of age x, then r, the intrinsic growth rate of the pathogen in the host population (the rate of increase of infected hosts), is given by the Euler–Lotka equation:[10]

$$\sum e^{-rx} l(x) m(x) = 1$$

where the summation is carried out over the entire period of infectiousness. Roughly,

$$r \approx \frac{(\ln R)}{t}$$

where R is the net reproductive ratio of the parasite population and t is the generation time.[11]

r is another measure of reproductive fitness. Natural selection will be expected to maximize r, subject to ecological constraints,[12] and so will maximize the survival of pathogen populations through their infectious period and their fecundity, the number of daughter populations they produce. Under endemic conditions, when $r = 0$, selection for early reproduction will reflect selection for reproduction before the pathogens are cleared from the host. Pathogens that spread in epidemics ($r > 0$) will also undergo selection for shorter latent periods, or earlier reproduction, independent of the rate of pathogen clearance.[13] There may also be selection for traits that enable the pathogen to survive between epidemics (production of latent infections, for example), since these traits also contribute to fitness.

Several authors have considered aspects of the life histories of infectious diseases within the framework of SIR models. Day has discussed the timing of disease life-history events and the evolution of virulence in terms of the evolutionary theory of aging.[14] Disease life-history traits can affect the interactions between multiple strains of a pathogen[15] as well as the emergence of novel pathogens.[16] Analysis of the life histories of pathogen populations is the counterpart of the analysis of the life histories of diseases in the host population: these two perspectives highlight different aspects of host–pathogen interactions.[14,17–19]

Life histories and life expectancies

The life histories of pathogen populations include a latent or pre-infectious period, an infectious or reproductive period, and, for some, a post-reproductive period. Life histories are shaped by the rates at which organisms suffer extrinsic, or environmentally induced, mortality; successful pathogens must evolve life history strategies that enable them to reproduce before they die. Pathogens grow in the environment provided by their hosts and they die because of the immune defenses or the death of their hosts. Pathogens can be divided into three broad groups, based on their interactions with the host's immune system. Some pathogens—rhinoviruses and other respiratory viruses, for example—are killed by the innate immune mechanisms that are activated immediately upon contact with a parasite. Many respiratory viruses cause infections with latent and infectious periods of only a few days each; although infected hosts may develop immunity to the strain of virus with which they were infected, the viruses are probably cleared by innate immune mechanisms before adaptive immunity develops.

Many viral and bacterial pathogens are not killed by innate immune defenses but are susceptible to the adaptive immune responses of the host, which take days to become manifest and weeks or months to become fully developed.[20] These pathogens produce acute infections with time-limited latent and infectious periods; typically, they are cleared from the host within two to four weeks.[9] The infectious periods of

many of these pathogens appear to be normally distributed with relatively small variances, suggesting that they are under strong selection—selection on the pathogen for an early onset of infectiousness and selection on the host for an early termination of the infection.[21]

A third class of pathogens has evolved mechanisms to evade or resist host defenses and so cause long-lasting infections that may persist for the life of the host. These organisms may have long infectious periods—*Treponema pallidum* and *Plasmodium falciparum*, for example, may be transmissible for months or years, and *Mycobacterium tuberculosis* is commonly transmitted from reactivated infections decades after the initial infection.

Growth, survival, and fecundity

Pathogens acquire nutrients and other resources from their hosts. Natural selection will optimize the allocation of these resources between replication (growth of the population in an individual host), survival of the population, and reproduction (transmission and formation of daughter colonies in new hosts). Although replication and reproduction will frequently co-vary, as an increase in the pathogen population will often be accompanied by an increase in the formation of propagules, there may be trade-offs in the utilization of resources for growth, survival, and fecundity. Reproduction, or transmissibility, will be affected by the fraction of the parasite population that is released in, or converted to, propagules. Pathogens that are cleared by innate host defenses typically cause only localized infections of epithelial tissues and devote their resources almost entirely to reproduction; the parasites are restricted to the sites at which propagules are formed and, presumably, a relatively large fraction of the parasite population is released in propagules. In contrast, pathogens that escape these innate defenses often cause systemic disease and thus allocate more resources to survival and replication in their hosts.

Some parasites have evolved mechanisms to vary their allocation of resources between survival and fecundity.[12] This trade-off is clearly seen with malaria—parasites balance the production of merozoites, which maintain the parasite population, with the production of gametocytes, which are necessary for parasite transmission, and presumably do so in ways that optimize their reproductive fitness.[22]

Aging

Many parasites produce infectious propagules and continue to reproduce from the onset of infectivity until they are cleared from the host or the host dies. As immune defenses develop, however, fewer and fewer populations survive to older and older age classes, and the surviving populations become smaller; after infectivity has peaked, these surviving populations make smaller and smaller contributions to the gene pool of subsequent generations. As the expected future reproduction of these populations decreases, the force of natural selection acting to prevent their death also decreases.[12,17,23] As a result, pathogen populations, like most multicellular eukaryotic organisms, may undergo aging or senescence.[17] One manifestation of aging is a decline in infectiousness. Pathogens such as *T. pallidum*, which have evolved mechanisms of immune evasion, may survive and replicate within infected hosts after infectivity has waned and the pathogen's reproductive period has ended.

Superinfection, cooperation, and cheating

Many pathogens can cause superinfections, in which a host is infected simultaneously by multiple strains of the same parasite. Parasites would be expected to resist superinfection and to minimize the sharing of host resources with unrelated strains. On the other hand, superinfection may be an important feature of the life histories of pathogens because it allows genetic or sexual recombination between pathogen strains.[24] Perhaps for this reason pathogens may not prevent superinfection completely and so may be forced to cooperate with superinfecting strains.

Pathogens may incur a cost in producing the factors that enhance survival, replication, or reproduction. To the extent that these processes entail cooperative behavior (sharing bacterial or viral products, for example), there will be selection for 'cheaters', parasites that reap the benefit of cooperation without paying the cost. Successful parasite lineages must have evolved mechanisms to 'purify' the population by removing or decreasing the frequency of these and other parasite variants whose replication decreases the fitness of the population.[25] One such mechanism is the founding of new populations from a relatively small number of parasites. Although only a single parasite may be sufficient to initiate a new infection, infectious propagules typically contain many organisms. Because parasites cannot completely exclude cheaters or superinfecting strains from propagules, they are not as fully integrated individuals as are multicellular organisms that go through an obligatory single-cell stage in their life cycle.[26]

Diversity of life histories

The host populations that pathogens colonize are characterized by diversity. Hosts are heterogeneous with respect to genetics, age, immune status, nutrition, health, and behavior. Many pathogens exhibit a diversity of life histories in different hosts; they may cause acute infections of some hosts and persistent infections of others, or they may cause mild or localized infections in some hosts and severe or systemic infections in others. This diversity in the life histories of parasites is due in large part to the heterogeneity of the hosts they infect;[27] genetic factors appear to be especially important determinants of the susceptibility of humans to parasites.[28] Natural selection will act most strongly, and will therefore shape the properties of parasite populations, in those classes of hosts (that is, those environments) in which they have the greatest expected reproductive success.[17,29] Pathogens that cause the so-called childhood infections are presumably adapted for maximal transmission between children. The severe diseases caused by the measles and varicella-zoster viruses in susceptible adults are probably the unfortunate byproducts of natural selection acting on these viruses in children.

Virulence

Virulence may be defined as the pathogen-induced host mortality rate or as the decrease in host fitness produced by a pathogen (but see Poulin and Combes[30] and Weiss[31]). Early models of parasite virulence assumed that virulence would co-vary with transmissibility; utilization of host resources for replication would lead both to debilitation of the host and to the formation of infectious propagules. Replication of parasites within a host, however, is only one cause of virulence. Virulence may also be caused by pathogen-produced toxins, by the growth of pathogens in critical organs, by secondary infections, and by the immune response of the host;[27,32] for all of these reasons, virulence is only indirectly related to pathogen fitness. Moreover, the virulence of a pathogen may differ greatly in different hosts. Finally, although host infertility also decreases host fitness, it has different consequences for the pathogen than does death of the host, as parasites may continue to be transmitted from infertile hosts. All of these factors have complicated the development of comprehensive theories for the evolution of virulence.[33]

Conclusions

The transmissibility and virulence of pathogens may be thought of as properties of the pathogen populations rather than as properties of their constituent microorganisms. Analysis of the life histories of pathogen populations complements the traditional focus on the properties of host populations; together, these two perspectives provide a fuller understanding of the natural histories of infectious diseases.

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References

1. Summers WC. From culture as organism to organism as cell: historical origins of bacterial genetics. *J Hist Biol* 1991;**24**:171—90.
2. Shapiro JA. Thinking about bacterial populations as multicellular organisms. *Annu Rev Microbiol* 1998;**52**:81—104.
3. Griffin AS, West SA, Buckling A. Cooperation and competition in pathogenic bacteria. *Nature* 2004;**430**:1024—7.
4. West SA, Griffin AS, Gardner A, Diggle SP. Social evolution theory for microorganisms. *Nat Rev Microbiol* 2006;**4**:597—607.
5. Williams P, Winzer K, Chan WC, Cámara M. Look who's talking: communication and quorum sensing in the bacterial world. *Philos Trans R Soc Lond B Biol Sci* 2007;**362**:1119—34.
6. Brown SP, Hochberg ME, Grenfell BT. Does multiple infection select for raised virulence? *Trends Microbiol* 2002;**10**:401—5.
7. Maynard Smith J, Szathmáry E. *The major transitions in evolution*. Oxford: W.H. Freeman; 1995.
8. Stearns SC. *The evolution of life histories*. Oxford: Oxford University Press; 1992.
9. Anderson RM, May RM. *Infectious diseases of humans: dynamics and control*. Oxford: Oxford University Press; 1991.
10. Fisher RA. *The genetical theory of natural selection*. 2nd rev. ed New York: Dover; 1958.
11. May RM. Estimating *r*: a pedagogical note. *Am Nat* 1976;**110**:496—9.
12. Hamilton WD. The moulding of senescence by natural selection. *J Theor Biol* 1966;**12**:12—45.
13. Lewontin RC. Selection for colonizing ability. In: Baker HG, Stebbins GL, editors. *The genetics of colonizing species*. New York: Academic Press; 1965. p. 77—94.
14. Day T. Virulence evolution and the timing of disease life-history events. *Trends Ecol Evol* 2003;**18**:113—8.
15. Restif O, Grenfell BT. Integrating life history and cross-immunity into the evolutionary dynamics of pathogens. *Proc R Soc B* 2006;**273**:409—16.
16. André JB, Day T. The effect of disease life history on the evolutionary emergence of novel pathogens. *Proc R Soc B* 2005;**272**:1949—56.
17. Frank SA. Models of parasite virulence. *Q Rev Biol* 1996;**71**:37—78.
18. Hesterbeek JA. A brief history of R_0 and a recipe for its calculation. *Acta Biotheor* 2002;**50**:189—204.
19. Levin BR, Bull JJ, Stewart FM. The intrinsic rate of increase of HIV/AIDS: epidemiological and evolutionary implications. *Math Biosci* 1996;**132**:69—96.
20. Janeway Jr CA, Travers P, Walport M, Shlomchik MJ. *Immunobiology: the immune system in health and disease*. 6th ed. New York: Garland Science; 2005.
21. Bailey NT. On estimating the latent and infectious periods of measles: I. Families with two susceptibles only. *Biometrika* 1956;**43**:15—22.
22. Buckling AG, Taylor LH, Carlton JM, Read AF. Adaptive changes in Plasmodium transmission strategies following chloroquine chemotherapy. *Proc R Soc B* 1997;**264**:553—9.
23. Rose MR. *Evolutionary biology of aging*. New York: Oxford University Press; 1991.
24. Michod RE, Bernstein H, Nedelcu AM. Adaptive value of sex in microbial pathogens. *Infect Genet Evol* 2008;**8**:267—85.
25. Kreft JU, Bonhoeffer S. The evolution of groups of cooperating bacteria and the growth rate versus yield trade-off. *Microbiology* 2005;**151**(Pt 3):637—41.
26. Buss LW. *The evolution of individuality*. Princeton, NJ: Princeton University Press; 1987.
27. Ebert D, Bull JJ. Challenging the trade-off model for the evolution of virulence: is virulence management feasible? *Trends Microbiol* 2003;**11**:15—20.
28. Cooke GS, Hill AV. Genetics of susceptibility to human infectious disease. *Nat Rev Genet* 2001;**2**:967—77.
29. Holt RD. Demographic constraints in evolution: towards unifying the evolutionary theories of senescence and niche conservatism. *Evolutionary Ecol* 1996;**10**:1—11.
30. Poulin R, Combes C. The concept of virulence: interpretations and implications. *Parasitol Today* 1999;**15**:474—5.
31. Weiss RA. Virulence and pathogenesis. *Trends Microbiol* 2002;**10**:314—7.
32. Day T, Graham AL, Read AF. Evolution of parasite virulence when host responses cause disease. *Proc R Soc B* 2007;**274**:2685—92.
33. Frank SA, Schmid-Hempel P. Mechanisms of pathogenesis and the evolution of parasite virulence. *J Evol Biol* 2008;**21**:396—404.