mediated toxicity and immune-mediated cytotoxicity to the rapid turnover of HIV-1–infected cells, and to understand the relative contributions of mitotic (proviral) and infectious (virion) spread of retroviruses within the host. This understanding may in turn directly influence drug treatment and vaccine strategies for retroviral infections.

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VIEWPOINT

Population Biology of Multihost Pathogens

Mark E. J. Woolhouse,* Louise H. Taylor, Daniel T. Haydon

The majority of pathogens, including many of medical and veterinary importance, can infect more than one species of host. Population biology has yet to explain why perceived evolutionary advantages of pathogen specialization are, in practice, outweighed by those of generalization. Factors that predispose pathogens to generalism include high levels of genetic diversity and abundant opportunities for cross-species transmission, and the taxonomic distributions of generalists and specialists appear to reflect these factors. Generalism also has consequences for the evolution of virulence and for pathogen epidemiology, making both much less predictable. The evolutionary advantages and disadvantages of generalism are so finely balanced that even closely related pathogens can have very different host range sizes.

Most pathogens are capable of infecting more than one host species. This includes the 60% of human pathogen species that are zoonotic (*1*), causing diseases of major public health concern such as influenza, sleeping sickness, Lyme disease, food poisoning, and variant CJD. It also includes more than 80% of pathogens of domestic animals (*2*), notably those causing 57 of the 70 livestock diseases of greatest international importance (*3*), such as rinderpest, foot-and-mouth disease, and heartwater. Pathogens such as influenza A virus, rabies virus, and *Blastocystis hominis* can infect hosts not only of different species but from different orders or classes (*2*). Yet, despite their ubiquity and importance, multihost pathogens have been largely neglected by population biologists in favor of the simpler paradigm of a single-host species.

Many, though not all, pathogens that can infect multiple hosts can also be transmitted by multiple hosts, and these can be regarded as ecological generalists rather than specialists. The advantages of generalism are poorly understood: it has been suggested that evolution should favor specialism, either because of the existence of functional trade-offs that limit the fitness of generalists in any one habitat or because evolution may proceed faster within narrower niches (*4*); these arguments apply especially to pathogens because they are under selection pressure to coevolve with their hosts (*5*). Yet paradoxically, only a minority of pathogens are specialists in the sense that they exploit a single host species.

So what processes lead to pathogens having multiple hosts, and why do multihost pathogens seem so pervasive? The evolution of generalism requires that pathogens have both the capability to exploit potential alternative host species and the opportunity to transmit to them. The subsequent maintenance of generalism depends on the consequences of an increased host range for pathogen population biology, especially such features as pathogenicity and epidemiology.

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Capability to Infect Multiple Hosts

Pathogens are usually, though not always, less infectious to a different host species. This is referred to as the species barrier (*6*), and there are two main strategies for overcoming it. Some pathogens have an inherent ability to infect multiple host species; for example, *Trypanosoma brucei rhodesiense* has a number of variant surface glycoprotein genes that encode for receptors with different affinities to specific mammalian transferrins (*7*). More commonly, pathogens produce many different genetic variants, some of which become associated with different host species, e.g., rabies (*8*). Gene products involved in host specificity have been identified for some pathogens, such as human immunodeficiency virus (HIV), mouse hepatitis virus, and *Citrobacter rodentium* (*9*).

Genetic change associated with host switching constitutes host adaptation. This may involve a small number of nucleotide substitutions or more major genetic changes such as reassortment, e.g., influenza A (*10*), or the acquisition of genetic elements (sometimes associated with virulence as well as host specificity), e.g., *Salmonella typhimurium* (*11*). Host adaptation can be so rapid that pathogen lineages adapt to different host tissues (*12*) or to vector versus host cells (*13*).

Species barriers are routinely crossed by some pathogens (such as rabies virus, which is regarded as a true multihost pathogen), but much more rarely by others [such as simian immunodeficiency virus, which is thought to have been transmitted to humans from other primates only very rarely and to have diverged rapidly into new single-host pathogens, HIV-1 and HIV-2 (*14*)]. Another example of pathogen

speciation associated with host shift is feline panleukopenia virus in cats evolving into canine parvovirus in dogs (*15*).

The extent of host adaptation is therefore linked to and limited by the genetic variability of the pathogen. In practice, pathogen populations are characterized by very high genetic diversity, which facilitates evasion of (i) within-host immune responses, (ii) herd immunity in the host population, and (iii) localized evolution of host resistance (*16*). A variety of mechanisms have evolved to generate this diversity, potentially affecting genes involved in all aspects of the pathogen-host interaction (*17*). In addition, most pathogens produce vast numbers of transmission stages (*18*). The implication is that a huge array of different pathogen genotypes will be available at any one time. Because a novel host may become infected even if exposed to a very small number of compatible pathogens (*19*), the frequent evolution of generalism is a likely outcome.

This interpretation of host adaptation and the species barrier leads to testable predictions. For example, pathogens with higher mutation rates should produce more genetic variants and are therefore more likely to be generalists. RNA viruses have a mutation rate per genome replication estimated to be 300 times higher than DNA viruses (*20*). Consistent with this, among pathogens infecting humans, RNA viruses are more likely to be zoonotic than DNA viruses (67% compared to 36%, respectively, for those transmitted by direct contact, which is the usual route for DNA viruses).

Opportunity to Infect Multiple Hosts

Pathogens may have differing opportunities to infect multiple hosts according to their route of transmission. Pathogens exit hosts, are transmitted between hosts, and enter new hosts by many different routes, which can be categorized as direct contact (physical contact or close proximity), indirect contact (including contamination of food, contact with environmental reservoirs, and contact with free-living infectious stages, including those emerging from intermediate hosts), and vector-borne (via biting arthropods, including mechanical transmission).

Some transmission routes (e.g., direct transmission by sexual contact or in utero) provide extremely limited opportunity for infecting other species, whereas others (e.g., indirect transmission involving widespread contamination of the environment) provide many such opportunities. For vector-borne pathogens, the vector itself determines whether there are opportunities for interspecific transmission. Many biting arthropods are generalist feeders, but some specialize on a single host species (*21*). As expected, most of the few vector-borne human pathogens that are not zoonotic [12 species (*1*)] are transmitted entirely or predominantly by anthropophilic vectors, e.g., *Plasmodium falciparum* (transmitted by anopheline mosquitoes), *Wuchereria bancrofti* (mainly by *Culex* mosquito species), and *Borrelia recurrentis* and *Bartonella quintana* (both by the louse *Pediculus humanus*). However, even for generalist vectors, a combination of host preferences, host distribution, and vector dispersal pattern can limit opportunities for interspecific transmission (*22*).

Different transmission routes are also associated with different reproductive costs and benefits of generalism or specialism. This particularly applies to pathogens transmitted by generalist vectors. For these pathogens, the presence of an incompatible host species can have a high reproductive cost, because transmission opportunities for vector-borne pathogens are limited—a blood meal taken by a vector on one host means a blood meal not taken on another (Fig. 1A). In contrast, for pathogens transmitted by direct or indirect contact, the presence of a second host species need not have such an impact, because of the overproduction of infective stages, although there are exceptions: e.g., pathogens such as *Gnathostoma spinigerum* that are transmitted by predation.

These arguments imply that transmission biology influences both opportunities for generalism and costs of specialism. Consistent with this, among human pathogens, the trend is that those transmitted by direct contact are less likely to be zoonotic than those transmitted by indirect contact, and those transmitted by vectors are most likely to be

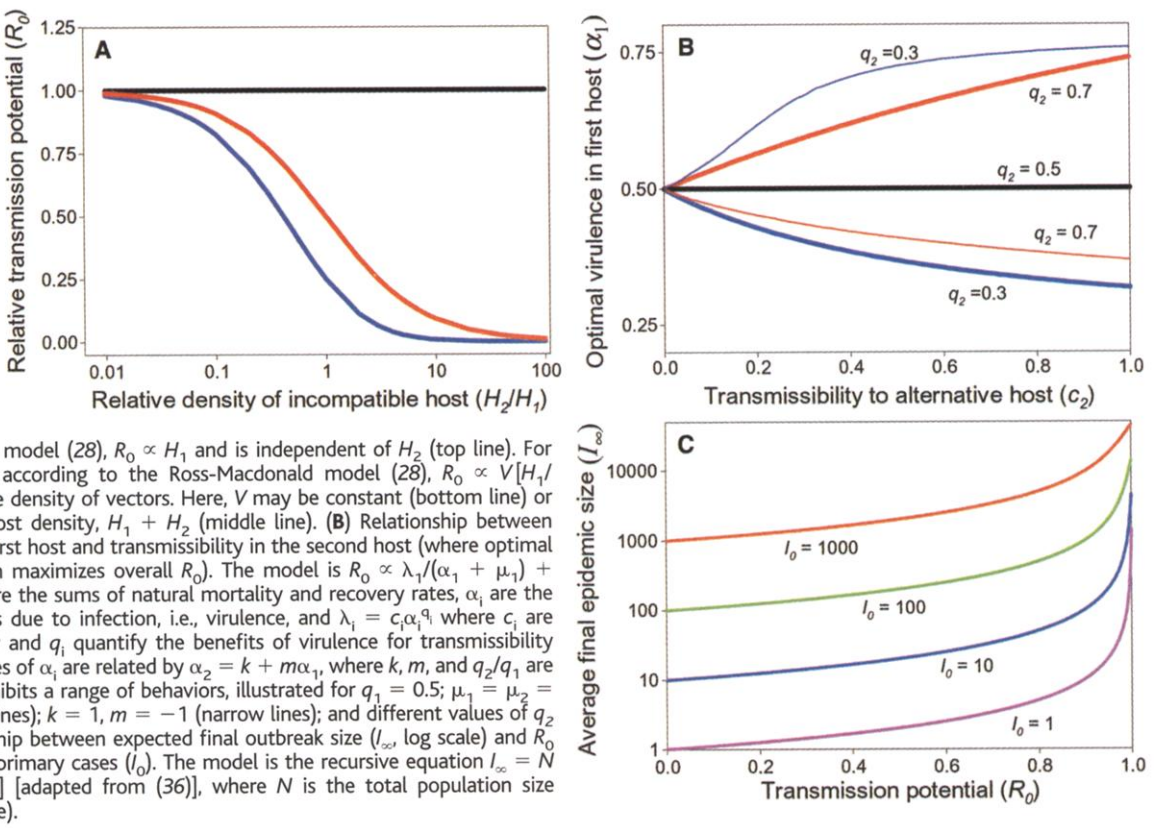

Fig. 1. Theoretical aspects of multihost pathogen biology. (**A**) Effects of a noncompatible host population on transmission potential. The density of a second, incompatible, host relative to the first, compatible, host (H_2/H_1 with H_1 constant, log scale) is related to the overall transmission potential (relative R_0). For pathogens transmitted by direct or indirect contact, according to the standard "SIR" model (*28*), $R_0 \propto H_1$ and is independent of H_2 (top line). For vector-borne pathogens, according to the Ross-Macdonald model (*28*), $R_0 \propto V[H_1/(H_1+H_2)]^2$, where V is the density of vectors. Here, V may be constant (bottom line) or proportional to overall host density, $H_1 + H_2$ (middle line). (**B**) Relationship between optimal virulence in the first host and transmissibility in the second host (where optimal refers to the value which maximizes overall R_0). The model is $R_0 \propto \lambda_1/(\alpha_1 + \mu_1) + \lambda_2/(\alpha_2 + \mu_2)$ where μ_i are the sums of natural mortality and recovery rates, α_i are the additional mortality rates due to infection, i.e., virulence, and $\lambda_i = c_i\alpha_i^{q_i}$ where c_i are indices of transmissibility and q_i quantify the benefits of virulence for transmissibility (where $0 \le q_i \le 1$). Values of α_i are related by $\alpha_2 = k + m\alpha_1$, where k, m, and q_2/q_1 are constants. The model exhibits a range of behaviors, illustrated for $q_1 = 0.5$; $\mu_1 = \mu_2 = 0.5$; $k = 0$, $m = 1$ (bold lines); $k = 1$, $m = -1$ (narrow lines); and different values of q_2 (as shown). (**C**) Relationship between expected final outbreak size (I_∞, log scale) and R_0 for different numbers of primary cases (I_0). The model is the recursive equation $I_\infty = N - (N - I_0)\exp[-R_0 I_\infty/N]$ [adapted from (*36*)], where N is the total population size (assumed to be very large).

zoonotic (Fig. 2A). These patterns will at least partly reflect phylogeny (*23*), although different transmission routes are thought to have evolved independently many times (*24*).

Consequences of Infecting Multiple Hosts

An important, but largely unconsidered, consequence of generalism is its effect on pathogenicity. Evidence from theoretical, laboratory, and field studies indicates that single-host pathogens evolve to an optimum level of virulence (*25*) determined by the trade off between virulence and transmissibility (*26*). For multihost pathogens, however, the situation is much more complicated. Depending on how transmission and virulence are related within and between host species, the pathogen can be more or less virulent in a second host than the first, and introduction of a second host can lead to an increase or a decrease in virulence in the first host (Fig. 1B). Moreover, if the second host contributes little to pathogen fitness, then there is no selective constraint on pathogen virulence in that host, which may explain why some zoonotic pathogens in which humans are "dead end" hosts, such as *Echinococcus multilocularis* or hantaviruses, are unusually virulent (*27*). Another complication is that some pathogens have only recently acquired the opportunity or ability to infect novel host species (e.g., *Escherichia coli* O157 in humans) and so may not yet have evolved optimal levels of virulence in that host. Overall, theory suggests no simple rule as to whether multihost pathogens will be more or less virulent than single-host pathogens, and there are examples of human pathogens showing all possible combinations of high or low virulence, long-standing or recent associations with humans, and generalism or specialism.

Another consequence of generalism is its effect on pathogen epidemiology. Single-host pathogens must, by definition, be able to persist in their host species. This requires that the transmission potential (R_0) exceeds one and that the host population exceeds a critical size (*28*); thus, endangered species are rarely threatened by specialist pathogens. In contrast, multihost pathogens can affect hosts in which they do not persist independently, e.g., *Escherichia coli* O157 in humans or measles in nonhuman primates. Such pathogens must have reservoir host(s) in which they do persist (*29*), but occur outside that reservoir as localized outbreaks (*30*). Outbreak sizes are expected to be overdispersed, i.e., most outbreaks will be small but a few very large (Fig. 1C). This is because expected average outbreak size is nonlinearly related both to the number of primary cases (between-species transmission) and to the basic reproduction number (R_0) within the local population (within-species transmission), so that small variations in either can lead to large variations in outbreak size (*31*). This prediction is supported by data for a variety of infectious diseases (e.g., Fig. 2B). In general, the mean and variance of outbreak sizes obey Taylor's Power Law (*32*) with exponent greater than 2 (Fig. 2C), indicative of overdispersed distributions with longer tails. Outbreaks outside a major reservoir, characteristic of many multihost pathogens, can therefore be of variable and unpredictable timing and magnitude. The epidemiological and evolutionary processes that determine whether a pathogen occurs in an alternative host as sporadic infections (e.g., rabies in humans), minor outbreaks (e.g., Ebola), or major epidemics (e.g., influenza A) remain poorly understood, but are of crucial importance, notably in the context of emerging diseases.

These and other consequences of generalism have implications for macroevolutionary patterns of hosts use. Single-species pathogens are under strong selection pressure to, and appear predisposed to, cross the species barrier and exploit additional host populations, thereby becoming multihost pathogens. However, crossing the species barrier can itself lead to further pathogen specialization and subsequent speciation, and the ease with which they achieve this may explain why there are so many kinds of pathogens (*33*). Moreover, it is likely that generalist pathogens will be less prone to extinction, because their fate is not tied to that of a single host species (*34*). Thus, there are evolutionary advantages and disadvantages of generalism and specialism, and observed host range will be determined by a delicate balance between powerful selective pressures in both directions (*5*). The result is that pathogens may shift rapidly from one strategy to the other at different phases of their evolutionary history and that even closely related pathogens may have very different host range sizes (*35*).

Population biologists have been very successful in developing a formal understanding of the dynamics and evolution of single-host pathogens (*27, 28*). Understanding the more complex population biology of multihost pathogens will be one of the major challenges to biomedical science in the 21st century.

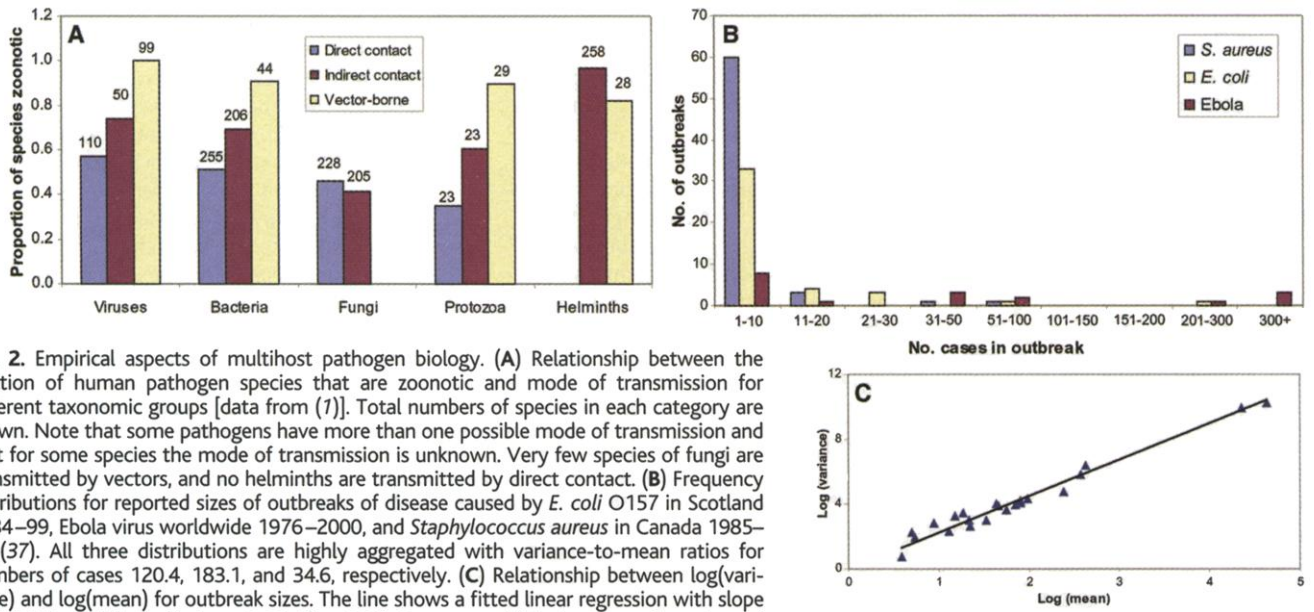

Fig. 2. Empirical aspects of multihost pathogen biology. (**A**) Relationship between the fraction of human pathogen species that are zoonotic and mode of transmission for different taxonomic groups [data from (*1*)]. Total numbers of species in each category are shown. Note that some pathogens have more than one possible mode of transmission and that for some species the mode of transmission is unknown. Very few species of fungi are transmitted by vectors, and no helminths are transmitted by direct contact. (**B**) Frequency distributions for reported sizes of outbreaks of disease caused by *E. coli* O157 in Scotland 1984–99, Ebola virus worldwide 1976–2000, and *Staphylococcus aureus* in Canada 1985–86 (*37*). All three distributions are highly aggregated with variance-to-mean ratios for numbers of cases 120.4, 183.1, and 34.6, respectively. (**C**) Relationship between log(variance) and log(mean) for outbreak sizes. The line shows a fitted linear regression with slope 2.25 (95% confidence limits ± 0.08, $R^2 = 0.97$). Data are published reports of numbers of clinical cases during outbreaks of *Clostridium botulinum*, *S. aureus*, *Bacillus cereus*, *Campylobacter* spp. (2 data points), human echovirus, *Salmonella* spp. (3 data points), *Clostridium perfringens*, *E. coli* O157 (2 data points), *Shigella* spp., small round structured virus, *Listeria* spp., Ebola virus, *Cryptosporidium* spp. (2 data points), *Trichinella spiralis*, measles virus, human polio virus, and *Vibrio cholerae* (*38*).

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38. Details available from the authors on request.

39. We gratefully acknowledge colleagues at the Centre for Tropical Veterinary Medicine for valuable discussions, and the Wellcome Trust for financial support.

VIEWPOINT

Why We Don't Get Sick: The Within-Host Population Dynamics of Bacterial Infections

Bruce R. Levin and Rustom Antia

To pathogenic microparasites (viruses, bacteria, protozoa, or fungi), we and other mammals (living organisms at large) are little more than soft, thin-walled flasks of culture media. Almost every time we eat, brush our teeth, scrape our skin, have sex, get bitten by insects, and inhale, we are confronted with populations of microbes that are capable of colonizing the mucosa lining our orifices and alimentary tract and proliferating in fluids and cells within us. Nevertheless, we rarely get sick, much less succumb to these infections. The massive numbers of bacteria and other micro- and not-so-micro organisms that abound and replicate in our alimentary tract and cover our skin and the mucosa lining our orifices normally maintain their communities in seemingly peaceful coexistence with the somatic cells that define us. Why don't these microbes invade and proliferate in the culture media within the soft, thin-walled flask that envelops us? Why don't they cause disease and lead to our rapid demise?

For several microparasites, and for bacteria and viruses in particular, we have a good part of the answers to the question of why we don't get sick. There is a plethora of detailed, but almost exclusively qualitative, information about the genetics, molecular biology, development, biochemistry, cell biology, and physiology of the nonspecific and specific immune defenses that protect mammals from bacterial infections (*1*) and the virulence factors bacteria use to evade these defenses, sequester iron and other nutrients essential for their replication, and cause disease (*2*, *3*). Although these details are fundamental to understanding the mechanisms of pathogenesis, by themselves they are not sufficient. Knowing why we don't get sick and, by default, knowing why we do, ultimately comes down to a quantitative understanding of the processes responsible for the rise, dissemination, fall, and evolution of the populations of infecting microparasites and those of the somatic cells of the mammalian defenses.

There have been several quantitative studies of the within-host population dynamics of microparasite infections using mathematical models. The majority of these have been for viruses such as human immunodeficiency virus (HIV) and its interaction with the specific immune system (*4*–*6*). There have also been few studies of the within-host population dynamics of other microparasites such as protozoa (*7*, *8*) and bacteria (*9*, *10*). Although there are certainly exceptions, for example,

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