Chapter 41 Social Behavior, Demography, and Rodent-Borne Pathogens

Richard S. Ostfeld and James N. Mills

Population and community ecologists tend to focus on the obvious. Unlike many other branches of biology, the focal entities (populations of whole organisms) typically are macroscopic and the key processes (or their consequences) often can be observed directly, without highly specialized equipment. In the case of rodents, interactions between the focal population and its resources, predators, and competitors tend to be relatively easily observable and the consequences discernable with simple, nontechnical tools (e.g., live traps, field enclosure/exclosure designs, vegetation sampling). As a consequence, much is known about the two-way interactions between rodents and their food resources, predators, and competitors. In contrast, beyond lists of species involved, the interactions between rodents and their pathogens and parasites are not well understood. Perhaps this relative neglect exists because these pathogens and parasites tend to be microscopic, are often hard to detect and monitor without specialized laboratory procedures, and have until recently been left out of the ecological/behavioral mainstream.

Clearly, though, such neglect is not justified on the basis of the strength of the interspecific interactions. Pathogens and parasites of rodents are likely at least as important in influencing population dynamics as are macroscopic predators, resources, and competitors, and they are much more numerous, both in terms of species and individuals. Similarly, demographic and behavioral traits of rodents probably are at least as important to the dynamics of their pathogens as to those of predators, resources, and competitors. Unlike most predators, biotic resources, and competitors, pathogens are often highly specialized on, and therefore tightly coupled to, their hosts. This chapter focuses on what we know and need to know about social and demographic factors that influence the *maintenance* and *transmission* of pathogens (broadly defined to include viruses, *Rickettsia*, and bacteria, as well as eukaryotic parasites) in rodent populations and between rodents and tangential hosts, particularly humans.

Prior Impediments to an Understanding of Rodent-Pathogen Interactions

Rodent-pathogen interactions are bidirectional. Early studies of these interactions focused on pathogens and disease as factors regulating rodent populations (Elton 1931; Elton et al. 1935; Chitty 1954b). As advocated in the scientific philosophy of Dennis Chitty (1996) and perpetuated by his academic descendents (e.g., Lambin et al. 2002), these studies tended to limit their inquiries to the question of whether disease is both necessary and sufficient to cause cycles in host population density. They (Elton 1942; Chitty 1996) have concluded that, despite being pervasive in rodents, disease has not been demonstrated as both necessary and sufficient to cause cycles. Therefore, like many other factors deemed not necessary and sufficient, disease should be dropped from consideration as a factor influencing population dynamics. This position appears to have been an influential one in that relatively little research has been conducted regarding the role of disease in rodent population dy-

namics other than a few well-studied cases, such as plague (etiological agent, *Yersinia pestis*) decimating populations of prairie dogs (*Cynomys* spp.; Cully et al. 1997).

In contrast, epidemiologists have long been interested in rodent-borne zoonoses, including plague, tularemia, leptospirosis, leishmaniasis, trypanosomiasis, and various viral hemorrhagic fevers. But, the focus has been largely on determining the primary reservoirs of zoonotic pathogens. Documenting the important reservoir species is helpful but inadequate for assessing how rodent population dynamics influence changes in risk of human exposure to zoonoses. Until recently, little effort has been devoted to understanding the determinants of transmission rates within rodent populations or from rodents to people.

Detection of Pathogens within Rodent Populations

Rodent pathogens and parasites of epidemiological importance include viruses, bacteria, and protists, all of which are microscopic. Three major types of methods have been used to assess their presence, and in some cases to quantify abundance. First, the presence of pathogens can be detected directly by one of several means. Preparations of tissues invaded by the pathogen can be examined microscopically, sometimes using immunohistochemical staining, to visualize the microbes. Pathogens can sometimes be isolated from host tissue by growth in culture for later identification. An increasingly popular method is the use of polymerase chain reaction (PCR) to detect nucleic acid (usually DNA, occasionally RNA) specific to pathogens, which often can be recovered from host tissues without death or injury to the host. Typically, both isolation and PCR are qualitative methods (pathogens present or absent), although quantitative PCR methods have been developed. Finally, specific antigen may be detected in blood or tissue using immunologic assays that employ antibody that binds specifically with the pathogen when present. A second kind of immunological assay employs antigen to a specific pathogen to detect recent or remote infection. Typically, host blood is drawn from free-ranging or laboratory-held animals, and specific antibody is assayed from serum. In the case of antibody detection via serology, results can be considered qualitative (hosts are categorized as infected or not), or semiquantitative, based on antibody titers. Seroprevalence is the proportion of a population with detectable antibody to a pathogen; seroconversion describes the change in antibody status of an individual host, usually from negative to positive or from low titer to higher titer (usually a four-fold or greater rise in antibody titer), and indicates recent infection. An important difference between antibody assays and direct detection of pathogens is that the presence of antibody does not necessarily indicate current infection, but demonstrates that the host was infected at some unknown time in the past. Detection of different immunoglobulin fractions may reveal more specific information about infection. The presence of IgG antibody only indicates that the host has been infected in the past (weeks, months, or years previously). However, the current status of the host could be infected, previously infected but recovered, or even immune to further infection. The presence of IgM antibody indicates a very recent infection, and the pathogen may still be present in host blood or tissues. In the special cases of hantaviruses and arenaviruses, infected hosts typically develop a chronic infection that involves persistent shedding of virus into the environment (in urine, feces, and saliva) for extended periods, perhaps the lifetime of the rodent. In this case, hosts with IgG antibody are often assumed to be currently infected and infectious.

A third method for detecting infection in rodent hosts, termed xenodiagnosis, is limited to vector-borne pathogens. For these types of pathogens, naïve (uninfected) arthropod vectors are allowed to take a blood meal from a host and the vector is then subjected to an assay (e.g., PCR, microscopy, and others) for the pathogen. If the vector tests positive, the host must have been infected; however, if the vector tests negative, the host might still have been infected but did not transmit the pathogen to the vector.

Factors Influencing Pathogen Transmission and Maintenance within Rodent Populations

Background

Pathogens disperse from one individual host to another via several different modes, including direct transmission, blood-feeding arthropod vectors, consumption of pathogens in water or food, or sexual contact. The direct transmission category typically includes both the deposition of pathogens via bites and scratches, and deposition into urine and feces of pathogens that enter other individuals through mucous membranes (e.g., inhalation) or the digestive system (i.e., consumption). Most pathogens probably use only one mode as the exclusive means of dispersing from host to host, although some use more than one method. An example is the bacterium (*Francisella tularensis*) that causes tularemia, which can be transmitted by tick vectors or by consumption of contaminated materials (Reintjes et al. 2002).

To understand disease dynamics within populations, it is useful to categorize individuals by their status with respect

to the pathogen, that is, whether they are infected (*I*) or uninfected and susceptible (*S*). In some cases, when infection is followed by immunity, a third category is added to represent uninfected and recovered (not susceptible) individuals (*R;* Kermack and McKendrick 1927; Anderson and May 1978; May and Anderson 1978). For an infection that is transmitted directly between individuals, the spread of disease is thought to depend largely on the rate of contact between (*S*) and (*I*) individuals. If the population has no spatial structuring and (*S*) and (*I*) individuals show no bias in their probability of associating with other individuals, their rate of contact should be a function of the combined density of (*S*) and (*I*). Under these conditions, disease spread is expected to be density dependent.

The assumption that pathogen transmission rates are density dependent arises from epidemiological models of the basic reproductive rate of a pathogen, R_0, which is usually defined as the average number of new (secondary) infections generated by a single infectious host entering a naïve (susceptible) host population. R_0 is a positive function of the population abundance of the host species (*S*), the rate of transmission between individual hosts (*T*), and the length of time infected individuals remain infectious (*L;* e.g., Anderson and May 1978), or

$$R_0 = (S \times T \times L)$$

Greater population abundance provides more opportunities for transmission; the transmission rate defines the proportion of those opportunities that are realized; and length of time hosts are infectious defines how long those opportunities will persist. If $R_0 > 1$, then the disease spreads; if $R_0 < 1$, then the disease declines to extinction.

In reality, the basic reproductive rate of an infection under ideal conditions is probably overemphasized in epidemiology, as is the threshold value described previously. Rodent ecologists are well aware that populations tend to fluctuate through time, sometimes dramatically. Therefore, the idealized reproductive rate of an infection might rarely be reached or be transient. This is particularly important for diseases with R_0 values that are near unity; small fluctuations in host density can cause R_0 to oscillate around the critical threshold separating disease spread from disease extinction. Perhaps more important to predicting disease spread than R_0 is R_E, or the effective reproductive ratio, which can be defined as the number of secondary cases produced in a host population that is not entirely naïve, that is, one consisting of a mixture of susceptible, infected, and recovered individuals. If the pathogen reduces survival or fecundity of the host, and therefore population growth rate, then the pathogen should tend to stabilize host density (Anderson and May 1978; May and Anderson 1978). As a consequence, R_E, which increases with increasing host density, should also be stabilized. Therefore, these types of epidemiological models predict more or less constant rates of infection and the coexistence of pathogen and host. Measuring the rate of disease spread across a continuous range of host population densities, particularly in taxa such as rodents, would be useful for predicting both the impact of host population dynamics on pathogens and the effects of pathogens on host population dynamics. Such studies are rare (see the following discussion).

In contrast, some pathogens are not transmitted directly among individuals that interact randomly in the absence of spatial structuring. These pathogens include those associated with vector-borne diseases and those that are transmitted during sexual or aggressive encounters. For the latter types of transmission, disease spread is more likely to depend on the *proportion* of individuals that are infected than on their absolute abundance or density; therefore, in these situations disease spread is thought to be frequency dependent (May and Anderson 1978; Getz and Pickering 1983). For vector-borne diseases, frequency dependence arises because an individual arthropod vector is limited in the number of hosts it can bite, and therefore, the number of bites per vector (a surrogate for disease transmission) will be largely independent of host density. Instead, vector bites resulting in pathogen transmission will be more closely tied to the probability that any given bite results in acquisition or transmission of a pathogen, and this value should vary with the frequency of infected individuals in the population. Similarly, because the number of sexual or aggressive encounters (but see the following for possible exceptions) should tend to be independent of population density, pathogen transmission will more likely vary with the probability that the fixed number of sexual or aggressive encounters per individual involve an infectious individual.

Pathogens with frequency-dependent transmission do not incorporate the stabilizing effect of density-dependent processes, but instead are expected to cause highly unstable dynamics of both pathogen and host (Getz and Pickering 1983). When transmission rates increase with the proportion (frequency) of individuals infected, a positive feedback loop ensues, such that low frequencies foster the extinction of the pathogen and high frequencies lead to increasingly rapid spread. Frequency dependence therefore results in the existence of a threshold proportion infected, below which the infection rapidly ceases and above which the infection, if lethal, causes the demise of hosts and consequently of the pathogen. Declining host density does not, in this case, rescue the host from extinction. New epidemics would be expected to arise following recolonization events or dispersal events that establish new populations temporarily free of infection.

Clearly, the consequences of density-dependent versus frequency-dependent transmission for both hosts and pathogens are profound. Rodents host many arthropod vectors and their associated pathogens, and rodent populations are often highly spatially and behaviorally structured. Because both of these features are associated with frequency dependence, one might expect pathogens with frequency-dependent transmission to predominate. Moreover, rodents are notorious for their dispersal and colonizing abilities, which would be able to promote the global persistence of pathogens with exclusively frequency-dependent transmission. Unfortunately, tests that attempt to measure density and frequency dependence and distinguish between them are rare, although interest in this issue appears to be increasing.

Population density

The primary means of assessing whether transmission rates or infection prevalence within rodent populations increase with density is to monitor rates of seroprevalence or seroconversion in natural populations over sufficiently long periods that some ability to detect a trend exists. Although such correlative studies can be criticized as not addressing cause-and-effect relationships, the potential for significant correlations to be spurious seems low. Clear mechanisms exist that would explain how increasing host density can increase disease prevalence, but mechanisms that would account for high disease prevalence causing high density (i.e., the reverse causal direction) do not seem plausible. Nevertheless, we suspect that experimental manipulations of host density would contribute importantly to the assessment of density dependence in rodent-disease interactions.

Correlative studies of the relationship between rodent population density and prevalence of infection have demonstrated positive associations for several types of pathogens and rodent hosts (table 41.1). In some cases, unusually high prevalence has been detected in low-density rodent populations, but only after a recent decline from high density (Smith et al. 1993; Niklasson et al. 1995; Abbott et al. 1999). These would seem to represent cases of delayed density dependence rather than a lack of density dependence. The only studies we are aware of that reject density-dependent and support frequency-dependent transmission of rodent pathogens involve cowpox virus in bank voles (*Clethrionomys glareolus*) and wood mice (*Apodemus sylvaticus;* Begon et al. 1999, 2003; Hazel et al. 2000). However, the relative lack of published studies that support frequency dependence might simply reflect a lack of exploration rather than rarity of frequency-dependent transmission.

Finally, we suspect that the *pattern* of population dynamics might be as important to the maintenance and transmission of pathogens in rodents as is density per se. Populations that fluctuate strongly are characterized by prolonged periods of new recruitment, which would represent a rapid influx of new, susceptible individuals—a situation that should promote epizootics. Moreover, we would expect crashes in rodent populations to pose a strong risk of extinction to pathogens, which might then require immigration events by infected rodent hosts for reinvasion (see below). Consequently, we expect that disease dynamics might be linked to features such as population growth rates and the length and severity of crashes, possibilities that so far have not received attention (fig. 41.1).

Demographic biases

Embedded within an apparent trend for infection prevalence to increase with increasing population density of rodents is the frequent overrepresentation of some demographic categories in the infected fraction (fig. 41.1). For hantaviruses and some arenaviruses, males and older indi-

Table 41.1 Studies finding a link between rodent population density and some measure of transmission or maintenance of pathogens in rodent host populations

Disease	Disease measure	Type of pathogen	Rodent host	Source
Hemorrhagic fever with renal syndrome	Antibody prevalence in host population	Puumala hantavirus	Bank vole (*Clethrionomys glareolus*)	Escutenaire et al. 1997; Niklasson et al. 1995; Olsson et al.2002
Hantavirus pulmonary syndrome	Antibody prevalence in host population	Sin Nombre hantavirus	Deer mouse (*Peromyscus maniculatus*)	Kuenzi et al. 1999; Mills et al. 1999a; Biggs et al. 2000
	Abundance of infected mice	Sin Nombre hantavirus	Deer mouse (*Peromyscus maniculatus*)	Yates et al. 2002
Argentine hemorrhagic fever	Abundance of infected mice	Junin arenavirus	Drylands vesper mouse (*Calomys musculinus*)	Mills et al. 1992
Lyme disease	Population density of infected ticks	spirochete bacterium	White-footed mouse (*Peromyscus leucopus*)	Ostfeld et al. 2001

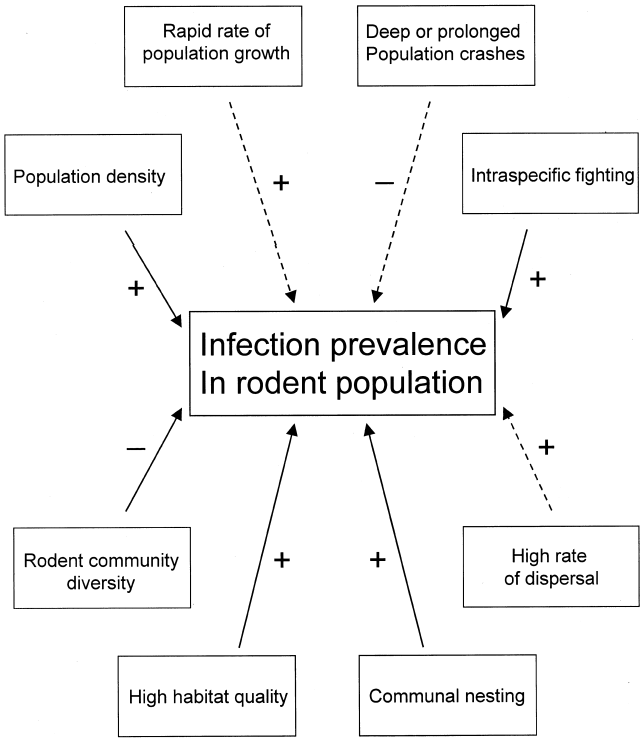

Figure 41.1 Selected factors known or suspected to affect intraspecific rates of transmission or prevalence of infection with a zoonotic pathogen. Plus signs near arrows indicate a positive effect on infection prevalence, and minus signs indicate a negative effect. Dashed arrows indicate relationships suspected to occur but without strong empirical support, whereas solid arrows represent established relationships.

viduals are more likely to be infected than are females and younger individuals (Childs et al. 1987; Glass et al. 1988; Niklasson et al. 1995; Mills et al. 1997; Mills and Childs 1998; Douglass et al. 2001; Yahnke et al. 2001). This pattern indicates that transmission of these agents within host populations is predominantly horizontal (from adult to adult) and by a specific mechanism that favors males. On the other hand, there seems to be no age or sex bias in multimammate rats (*Mastomys* spp.) infected with Lassa arenavirus (Demby et al. 2001), suggesting vertical transmission of virus from dam to pups. Lymphocytic choriomeningitis virus, another Old World arenavirus, may also be transmitted vertically, probably in utero, in populations of its host, the house mouse (*Mus musculus;* Mims 1966).

The degree of male bias in antibody prevalence varies among the various hantavirus-host pairings. For example, the ratio of antibody prevalence in males to antibody prevalence in females ranges from 1:1 for Norway rats (*Rattus norvegicus*), reservoir of Seoul virus, to 2:1 for deer mice, host of Sin Nombre virus, and 7:1 for brush mice (*Peromyscus boylii*), host of Limestone Canyon virus (Glass et al. 1988; Mills et al. 1997). These differences presumably result from differences in mechanisms of transmission (e.g., fighting versus venereal versus communal nesting), or differences in the relative frequency of such behaviors between genders in different species.

Habitat biases

Studies of rodent populations that incorporate specific habitat types are beginning to reveal sometimes dramatic differences among subpopulations in seroprevalence. For instance, working in the Paraguayan Chaco, Yahnke et al. (2001) found that hantavirus antibody prevalence in populations of small vesper mice (*Calomys laucha*) inhabiting croplands was higher than those inhabiting either pastures or native thorn scrub. Similar among-habitat variation in prevalence of infection with Junin arenavirus has been found in drylands vesper mice (*Calomys musculinus;* Mills et al. 1992, 1994). Kuenzi et al. (2001) found higher prevalence of antibody to Sin Nombre virus in deer mice from peridomestic habitats in Montana than in nearby sylvan habitats, and Mills et al. (1997) found substantial variation in prevalence of antibody to hantaviruses among natural habitat types. Correlation of antibody prevalence with habitat on the scale of a single trapping grid has also been described (Abbott et al. 1999; Mills, Ksiazek et al. 1999). Prevalence of antibody to Limestone Canyon virus in brush mice was associated with islands of apparently preferred microhabitat. Nevertheless, these pockets of virus activity became blurred during periods of high population density, indicating an interaction between habitat selection and population density. The mechanisms that underlie the observed patterns of spatial variation are not well understood, although local population density of rodent hosts and abiotic conditions conducive to survival of pathogens in the environment have been implicated.

Social behavior

Social behavior—fighting—has repeatedly been implicated as increasing the probability of pathogen transmission between individuals (fig. 41.1). However, the evidence to support the association between fighting and exposure is indirect; individuals with wounds or scars are more likely to be seropositive for hantaviruses (Glass et al. 1988; Douglass et al. 2001) and some arenaviruses (Mills and Childs 1998). In addition, demographic categories (i.e., older males) most likely to fight tend to demonstrate the highest antibody prevalence. Lower prevalence in females than conspecific males suggests that sexual transmission of zoonotic pathogens is relatively unimportant for hantaviruses and at least one arenavirus that has been well studied (Junin virus; Mills et al. 1994). The possibility exists that greater seroprevalence in males results from a biased sexual transmission

from females to males, compared to male-to-female transmission. To our knowledge, this possibility has not been assessed. With the possible exceptions of the arenaviruses, Machupo virus (Johnson 1985), Lassa virus, and lymphocytic choriomeningitis virus (Childs and Peters 1993), no evidence exists to suggest that parent-offspring social interactions represent a common pathway for pathogen transmission. In fact, in some host-virus systems, vertical transfer of maternal antibody during gestation and lactation appears to protect dependent young against hantavirus infection for at least 3 months postpartum (Bernshtein et al. 1999). In other systems (e.g., Lassa virus; Demby et al. 2001) such antibody may not be protective.

A study in Colorado (Calisher et al. 1999) showed that there were two seasonal peaks in seroconversions in a population of deer mice infected with Sin Nombre virus. A peak in seroconversions during the breeding season affected mostly males, while a second over-winter peak affected males and females equally, suggesting different mechanisms of virus transmission during the two periods. Transmission during the breeding season may result from agonistic encounters (primarily between males), while winter transmission may occur during communal nesting (Mills, Yates et al. 1999).

Preliminary evidence suggests that the male bias in antibody prevalence does not occur for vesper mice (*Calomys* sp.) infected with Machupo arenavirus (D. Carroll and J. Mills, unpublished data). There is some laboratory evidence that Machupo virus may be maintained by venereal transmission in its rodent host, and that chronically infected females are rendered effectively sterile. A model has been proposed whereby Machupo virus causes cyclic epizootics and subsequent crashes in host populations; this rodent cycle, in turn, controls the incidence of Bolivian hemorrhagic fever in humans (Johnson 1985). Field studies are needed to test this hypothesis.

Another behavioral phenomenon, dispersal, is likely to be profoundly important to the dynamics of disease in rodents, but is poorly studied in this context (fig. 41.1). Given the unstable dynamics expected under frequency-dependent transmission, dispersal between populations or demes, or dispersal events leading to colonization, would be critical in maintaining both host and pathogen populations. Dispersal following population crashes of prairie dogs (*Cynomys* spp.) afflicted with plague is thought to be important in reestablishing extinct or nearly extinct populations of prairie dogs (Anderson and Williams 1997; Roach et al. 2001). In many cases, hantaviruses appear to become locally extinct when rodent populations decrease to very low densities (Kuenzi et al. 1999; Calisher et al. 2005). Under such situations, the virus may be locally absent for a few months to a few years, but always seems to reappear, presumably via reintroduction by dispersing individuals from adjacent populations. The persistence of pathogens during unfavorable conditions is currently an area of active investigation. It has been hypothesized that higher host densities (and consequently hantavirus transmission) are maintained in refugia of ideal habitat, and that less favorable habitats are repopulated via dispersal by infected individuals from these refugia during periods of more favorable environmental conditions.

Establishment and defense of territories is another behavior that may be associated with the transmission of pathogens. Males defending territories may be more likely to be involved in aggressive encounters than are females or males without territories. Several studies have shown a positive correlation between hantavirus antibody prevalence and longevity on trapping sites (when corrected for age; Mills et al. 1998; L. Ruedas and others, unpublished data), and long-lived residents have been hypothesized to be important in the trans-seasonal maintenance of hantaviruses (Abbott et al. 1999; Calisher et al. 2001).

Community composition and diversity

Evidence is mounting that pathogen transmission within host populations is inhibited by high species diversity within the rodent community (fig. 41.1). Lyme disease is a zoonosis caused by the bacterium *Borrelia burgdorferi,* which is transmitted by *Ixodes* ticks. The presence of a high diversity of small mammals results in reduced abundance of *Borrelia*-infected ticks (Ostfeld and Keesing 2000a, 2000c), which in turn reduces the inoculation rate of both competent disease reservoirs (e.g., the white-footed mouse, *Peromyscus leucopus*) and incompetent reservoirs (Schauber and Ostfeld 2002). In this case, high diversity of small mammals and other vertebrates, most of which are incompetent at transmitting infection to feeding ticks, dilutes the impact of white-footed mice and reduces pathogen transmission rates (LoGiudice et al. 2003; Ostfeld and LoGiudice 2003).

A similar pattern appears to exist for directly transmitted viral and bacterial diseases, including hantaviruses, arenaviruses, and possibly *Bartonella*. Yahnke et al. (2001) found that the percent of vesper mice seropositive for Laguna Negra hantavirus decreased with increasing community diversity of small mammals. Mills (in press) found a similar pattern with hantaviruses in the US Southwest. A reanalysis of data in Kosoy et al. (1997) similarly demonstrated a pattern of reduced prevalence of antibody to the bacterium *Bartonella* in rodent communities of high species diversity (Ostfeld and Keesing 2000c). Mills (2005) suggests that the primary mechanism by which high species diversity reduces the transmission of these pathogens within their principal host is the increase in interspecific encoun-

ters at the expense of intraspecific ones. Because interactions between the principal host and heterospecifics typically result in a "dead-end" infection (the pathogen is not passed on to other hosts), the presence of high species diversity results in "wasted" encounters (from the perspective of the pathogen). An additional mechanism, proposed for Lyme disease by Schmidt and Ostfeld (2001), is the potential for the absolute density of the primary host species to be reduced in communities of high diversity, owing to stronger regulation by competitors and predators. A recent review of effects of predators on rodent-borne pathogen transmission found support for the hypothesis that predators can suppress disease transmission in rodent reservoirs, although some exceptions exist (Ostfeld and Holt 2004).

Factors Influencing Pathogen Transmission from Rodents to Humans

Background

Zoonotic pathogens often use the same mode of transmission between individuals within rodent populations as they do in cross-species transmission, including from rodents to humans. Some of the most epidemiologically important rodent-borne pathogens are most frequently transmitted either via inhalation of viral aerosols or virus-contaminated dust (e.g., the hantaviruses and arenaviruses) or via the bites of haematophagous arthropods (e.g., Lyme disease, ehrlichiosis, leishmaniasis, Rocky Mountain spotted fever). For both these modes, the force of transmission potentially could vary positively with: (1) the population density (or size) of the rodent reservoir; (2) the frequency of infection (infection prevalence or seroprevalence) in the rodent reservoir; and (3) the density of infected individuals in the reservoir population (fig. 41.2).

Although prevalence of infection within reservoir populations often has been used as a determinant of disease risk to humans (Mills and Childs 1998), we suspect that prevalence by itself is unlikely to be informative in human risk assessment. Consider two populations of a rodent reservoir species, one consisting of 100 individuals ha^{-1} with 25% prevalence of infection and the other at ten individuals ha^{-1} with 50% prevalence. We suggest that twenty-five infected individuals ha^{-1} would pose a higher risk to nearby humans than five infected individuals ha^{-1}, despite the lower prevalence in the former. Instead, we expect that total population density of rodent reservoirs, or the density of infectious individuals, will better predict disease risk to people.

Rodent population density and dynamics

Studies from several different parts of Europe have recently demonstrated temporal correlations between superannual

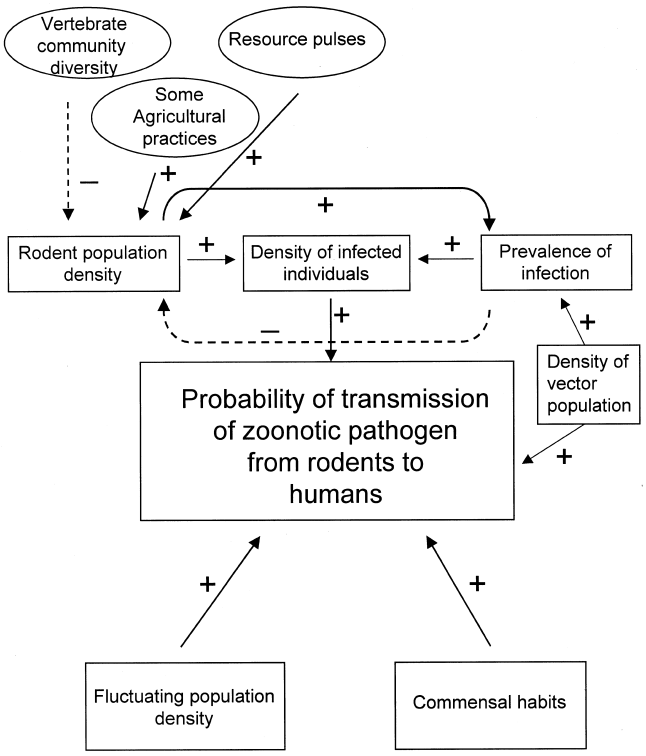

Figure 41.2 Selected factors known or suspected to affect the probability of transmission of a zoonotic pathogen from rodent hosts to humans. Plus signs near arrows indicate a positive effect on infection prevalence, and minus signs indicate a negative effect. Dashed arrows indicate relationships suspected to occur but without strong empirical support, whereas solid arrows represent established relationships.

peaks in fluctuating populations of bank voles and outbreaks of nephropathia epidemica in humans caused by Puumala hantavirus (Niklasson et al. 1995; Escutenaire et al. 1997; Brummer-Korvenkontio et al. 1999). Population outbreaks of deer mice in the US Southwest are sometimes, but not always, associated with epidemics of hantavirus pulmonary syndrome (Yates et al. 2002; Brown and Earnest 2002). An abrupt increase in the population density of corn mice was followed by a similar increase in cases of Argentine hemorrhagic fever in central Argentina (Mills et al. 1992). For Lyme disease in the northeastern US, annual risk of human exposure, as measured by the density of infected nymphal ticks, is a positive linear function of the prior year's population density of white-footed mice (Ostfeld et al. 2001). Risk of human exposure to Lyme disease also has been shown to increase with decreasing size of forest fragments, ostensibly as a result of the loss of vertebrate diversity and/or increases in abundance of white-footed mice (Allan et al. 2003).

In stark contrast to these examples of positive associations between density of rodent reservoirs and human disease risk or incidence, the culling of Norway rats (*Rattus norvegicus*) could result in the initiation or exacerbation of human outbreaks of Bubonic plague. Using a metapopula-

tion model, Keeling and Gilligan (2000) found that strong reductions in abundance of rats, which serve as the zoonotic reservoir for *Yersinia pestis* and as the primary host for the flea vectors, can cause fleas to switch from rats to humans. The consequence of rat population crashes, counterintuitively, can therefore be increased rates of contacts between fleas and people and therefore human epidemics; this scenario is thought to have played a role in the Bubonic plague epidemics of Europe in the previous millennium (Keeling and Gilligan 2000).

Ultimate causes

The emerging pattern of increased risk or incidence of human disease with increased density of rodent reservoirs begs the question of what controls rodent abundance. Several chapters in this volume address this question. For herbivorous rodents such as voles, evidence is mounting that top-down effects of predators, often combined with bottom-up impacts of food supply, play a major role (Berryman 2002). However, for the most epidemiologically important rodent-borne diseases, the rodent hosts tend to be granivorous or omnivorous. In this category we include the sigmodontine rodents that serve as reservoirs for New World hantaviruses, arenaviruses, and bacteria (*Borrelia, Anaplasma* [= *Ehrlichia*]), the murine reservoirs for *Borrelia* and Old World hemorrhagic fever viruses, and the murine and gerbilline reservoirs for the agents of visceral and cutaneous leishmaniasis in Africa, Asia, and southern Europe. For these granivorous rodents, it appears that bottom-up effects of food supply predominate in determining abundance (fig. 41.2).

In some arid parts of South America and North America, El Niño events produce heavy rains followed by dramatically increased primary production. El Niño-induced seed production by annual plants, and masting in oak- or beech-dominated forests, constitute resource pulses that drive population increases in many rodent species (Ostfeld and Keesing 2000b). Epidemics of hantavirus pulmonary syndrome (HPS) have been associated with El Niño years in both North and South America (Yates et al. 2002; Toro et al. 1998). Similarly, high densities of ticks infected with Lyme disease bacteria have been detected following heavy mast years (Ostfeld et al. 2001).

El Niño events and oak/beech masting are natural events (although some evidence suggests that El Niño years will become more frequent and more intense with human-caused global warming [Herbert and Dixon 2003]). Human-induced changes to the environment also can induce local increases in rodent reservoir populations, or decreases in species diversity, both of which can increase disease incidence in people. Clearing of forests or agricultural practices in Central and South America have been associated with localized irruptions of rodent hosts or more generalized changes in rodent community composition and associated risk of transmission of arenaviruses (Enría et al. 1999) and hantaviruses (Ruedas et al. 2004, Carroll et al. 2005). Habitat fragmentation in the northeastern US is associated with increased risk of Lyme disease in humans (Allan et al. 2003). Irrigation for local agriculture promotes populations of both fat sand rat (*Psammomys obesus*) reservoirs and sandfly (*Phlebotomus papatasi*) vectors of the etiologic agent of cutaneous leishmaniasis in Israel (Wasserberg et al. 2003).

Behavior

A behavioral trait with critical consequences for human disease is dispersal by rodents from sylvan to peridomestic environments (fig. 41.2). The presence of deer mice in or around human dwellings is a clear risk factor for HPS in the southwestern US (Zeitz et al. 1995) and probably elsewhere. Unfortunately, little is known about the factors that affect either rodent dispersal to human dwellings or those that regulate rodent populations in a commensal setting. Commensal populations of deer mice appear to have less stable composition (i.e., greater turnover of individuals) than do nearby sylvan populations (Douglass et al. 2003), but the generality of this difference is not known. We suggest that the behavioral and demographic causes and consequences of rodent commensalism are critical areas for future research involving behaviorists and epidemiologists.

Concluding Thoughts

To illustrate the patterns we have described, we relied heavily on examples from a few reasonably well-studied systems, such as the rodent-borne hemorrhagic fever viruses and Lyme disease. Clearly, many more studies are needed before we can conclude that the patterns observed in these systems can be generalized. One reason for the dearth of studies on the ecology of host-pathogen interactions may be that few investigators are schooled in ecology *and* microbiology *and* immunology/infectious diseases. Furthermore, some questions (e.g., the possibility of venereal transmission and the protectiveness of maternal antibody) must be addressed using laboratory studies. Nevertheless, because laboratory results do not always reflect what happens in nature, conclusions from laboratory studies should be tested in the field (Mills and Childs 1998; Wolff 2003c). Additionally, ecologists and epidemiologists have historically conducted their studies with little interdisciplinary consultation, and have published them in their own separate literature. These facts underscore the need for multidisciplinary studies involving ecologists, microbiologists, and public health researchers.

Ecologists generally prefer to work in pristine, sylvan ecosystems. However, diseases in rodent populations are probably most prevalent in perturbed ecosystems where biodiversity, community composition, and population dynamics have been altered. Studies are also quite rare in peridomestic habitats. These are precisely the environments where most transmission of zoonotic pathogens to humans takes place. Not only are disturbed and peridomestic habitats some of the most interesting to study in terms of host-pathogen dynamics, but the potential rewards in terms of understanding and prevention of zoonotic diseases in humans can be great.

Many of the reservoirs for serious human pathogens are highly opportunistic taxa (*Mastomys, Mus, Rattus, Calomys, Peromyscus, Sigmodon, Zygodontomys, Apodemus*). It is unclear whether this relationship is artefactual—zoonotic diseases carried by nonopportunistic species may remain unknown to us because we rarely encounter them—or if the ability to reproduce quickly and reach high population densities in temporarily ideal habitats is conducive to the evolution and maintenance of pathogens. If the apparent association between deadly zoonotic pathogens and opportunistic rodent taxa is real, then anthropogenic environmental changes (e.g., habitat fragmentation, conversion to agriculture, climate change) might be expected to increase the burden of human disease in the future.

Summary

As a group, rodents are probably the predominant natural reservoirs for pathogens that cause disease in humans. Nevertheless, beyond documenting the associations between specific rodents and their pathogens, little is known about how behavioral and population dynamics of rodents influence transmission either between individuals within rodent populations or between rodents and humans or other mammals. In this chapter, we provided an overview of how pathogens are detected within rodent hosts and what factors contribute to pathogen transmission. High population density, old age structure, fighting, and occupation of commensal or other disturbed (e.g., agricultural) habitats are associated with high rates of pathogen transmission. Although disperal has a high potential to influence pathogen transmission and disease dynamics, the role of host dispersal is poorly studied. Pathogen transmission and maintenance tend to be maximized in low rodent-diversity communities and in habitats where predators have been reduced or removed. Neither the generality of nor the precise mechanisms that underlie these apparent patterns are well understood, and therefore linkages between rodent demographic and behavioral dynamics and disease dynamics comprise a major research frontier. Lastly, we note an apparent pattern whereby rodent species of great importance to human disease tend to be widespread, opportunistic, and resilient species that are favored by anthropogenic environmental change. Whether this pattern is simply an artifact of heavy research focus on these species, or represents a true correlation between rodent population and life-history traits and disease dynamics, is unknown. If the pattern is real, the implication is that further anthropogenic environmental changes will result in further health risks to humans via their impacts on rodents.

Conclusions