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Review

Fluctuating Rodent Populations and Risk to Humans from Rodent-Borne Zoonoses

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ABSTRACT

The fluctuations in abundance of a wildlife reservoir are an attractive explanation for temporal variation in primary human cases of a zoonosis. This is because high abundance may lead to more contact between humans and animals, but also to outbreaks of disease within the reservoir population. We propose a mathematical framework that sets out the consequences of correlation between reservoir abundance and reservoir prevalence for how numbers of human cases are related to reservoir abundance. The fluctuations of rodent populations are well studied and often dramatic. A review of field studies of rodent reservoirs for plague, hantaviruses, and other zoonoses shows that, at a seasonal time scale, a positive correlation between host abundance and host prevalence is rarely observed. More commonly, there is an inverse relationship or negative correlation such that a seasonal increase in rodent abundance is not accompanied by a corresponding increase in the abundance of infectious animals. Seasonal changes in rodent abundance are hence unlikely to fully explain seasonal variation in primary human cases. The few longer field studies (>5 years) show a positive but delayed relationship between reservoir abundance and reservoir prevalence. Key Words: Force of infection—Hantavirus—Plague. Vector-Borne Zoonotic Dis. 5, 305–314.

INTRODUCTION

MANY HUMAN INFECTIONS are zoonoses. For some of these, the source of infection is a wildlife reservoir. Examples are hantavirus disease in Eurasia and the Americas, and bubonic plague in Asia, Africa, and the Americas. One feature of this group of zoonoses is that the control measures that are possible when wildlife carry the disease are quite different than those that are possible when domestic pets or livestock are the source of infection. Another is that the abundances of wildlife populations tend to naturally fluctuate. Nowhere is this more obvious than for rodent populations whose dramatic fluctuations continue to attract the attention of ecologists (Stenseth et al. 2004, Lambin and Graham 2003).

Many authors have linked fluctuations in abundance of a rodent reservoir population with variability in numbers of new human cases or outbreaks of disease (Rose et al. 2003, Olsson et al. 2003, Heyman et al. 2001, Mills and Childs 1998). And a growing number of studies have found that high rainfall can be linked to high numbers of human cases of rodent-borne zoonoses (Enscore et al. 2002, Franke et al. 2002). This has led some to propose a trophic cascade hypothesis whereby high amounts of precipitation lead to increased

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primary production, leading to increased rodent abundance and then to increased risk of epizootics and human cases (Gage and Kosoy 2005). Support for this hypothesis is not always found (Brown et al. 2002).

Rodent populations fluctuate in abundance over both seasonal and multiannual time scales. Almost all rodent populations have an annual cycle, an aspect of their dynamics that follows from a breeding and a non-breeding season combined with a relatively short lifespan. In temperate areas, females typically begin producing litters early spring, and this can continue into the fall. For species with a short generation time, such that the females of the first and later litters also produce litters within the same breeding season, exponential-like population growth is possible and this can lead to very large fluctuations in abundance within a single year (Singleton et al. 2001). Dramatic fluctuations can also occur over longer time scales. The best known example of this is the Norwegian lemming (*Lemmus lemmus*), populations of which fluctuate over several orders of magnitude within time scales of 3–4 years (Stenseth 1999). In fact many rodent populations in the northern hemisphere exhibit regular multiannual cycles in abundance including populations of *Clethrionomys glareolus* in Scandinavia—the host for Puumala virus, an etiological agent of hantavirus disease in humans (Klingstrom et al. 2002). Amongst cyclic populations the regularity of the multiannual cycle varies, as does the length of the cycle. Other rodent populations, such as the multimammate mouse (*Mastomys natalensis*), which is a host for plague (*Yersinia pestis*) throughout Africa, fluctuate dramatically and irregularly (Leirs et al. 1996).

Here we take stock of what we know about the consequences of population fluctuations for the risk of human infection from a wildlife reservoir. We focus on rodent-borne zoonoses with a review of the available field studies on rodent reservoirs. However, the arguments apply equally well to any zoonoses for which the source of primary human cases is a fluctuating wildlife population. The review is preceeded by a brief mathematical exploration of the impact of different dynamics of infection within the rodent host population on the relation between rodent abundance and human cases. Our conclusions are of considerable interest to public health officials that manage rodent-borne diseases and who may respond to high rodent abundance believing there is an association with human cases.

FORCE OF INFECTION ON HUMANS

The force of infection on humans for a rodent-borne zoonosis is a per capita rate acting on the susceptible part of the population and that is realised as whole numbers of new primary human cases. It is determined by three components; the rate of contacts (of the appropriate type) between humans and rodents, how often such contact is with an infectious animal and how often such contact actually results in transmission of the infection. Using the notation of Begon et al. (2002), this may be written as $\lambda = cpv$, where λ is the force of infection, c is the number of contacts over some time period (having dimension time^{-1}), p is the prevalence of the infection in the rodent population (a probability and hence dimensionless), and v is the probability that transmission actually occurs given contact has occurred (again with no dimension). If contacts between humans and rodents increases with abundance of rodents (whether numbers or density) then $c = kN$ and the force of infection on humans becomes

$$\lambda = kNpv = \beta Np \qquad (1)$$

where N is the abundance of rodents and the parameter $\beta = kv$ is called the transmission coefficient (Begon et al. 2002). The dimensions of β depend on the dimensions of N, that is, whether abundance is measured as density or numbers of animals.

Put simply, equation (1) states that the rate at which new cases of a zoonosis appears is proportional to the abundance of infectious animals. This is intuitively appealing, even if the route of transmission from the rodent host to humans is indirect. Equation (1) presents the abundance of infectious animals as the product of population abundance and prevalence. In wild populations both of these variables typically vary but not necessarily independently.

The context of equation (1) is the transmission term that traditionally appears in mathe-

matical models for the spread of an infection. In the case of describing transmission from a wildlife reservoir to a human population, it is the rate at which primary human cases appear. If H_S denotes the number of humans that are susceptible and at risk, then an equation for the number of new primary cases (C) over some time interval is,

$$C \approx H_S\lambda = H_S\beta Np^1 \qquad (2)$$

where it is assumed that only a small fraction of the susceptible human population becomes infected and λ is much less than 1. Numbers of new human cases can vary between seasons, between years and over various spatial scales. The data on human cases of nephropathia epidemica in Sweden and Finland provide an excellent example of all three types of variation (Rose et al. 2003, Niklasson et al. 1995)—the seasonal and interannual variation is shown in Figure 1. Equation (2) makes explicit the possible sources of variation that might explain such data: the number of infectious animals (the product Np), the transmission coefficient (β) and the number of humans that are susceptible and at risk (H_S). Any explanation for an observed pattern in numbers of new human cases must logically relate to variation in at least one of these factors.

Equation (2) seeks to represent a very large set of complex interactions between humans and wildlife. In reality there will be parts of the human population that due to their profession or economic status are more exposed to contacts with rodents than others, and so the force of infection will vary between groups of people. Also changes in human behaviour in response to either health education or an increased awareness of the risk factors could well be the main determinant of future numbers of human cases, and so the dynamics of the wildlife reservoir become somewhat irrelevant. However, equation (2) remains an effective framework in which hypotheses that suggest changes in the rodent population are responsible for fluctuations in primary human cases can be clarified and tested.

The equation for the force of infection emphasises the role of the product Np, representing the number or density of infectious animals. For this reason the relationship between abundance and prevalence in the reservoir population is our focus from this point on. There is a range of relations between abundance and prevalence that are expected from theory on host-pathogen dynamics or that have been empirically observed. Published field studies of rodent reservoirs where abundance of the host and prevalence of infection has been estimated concurrently are listed in Table 1. The majority are longitudinal studies that run for 2–3 years. We did not include studies on zoonoses such as *Echinoccocus multilocularis* or *Toxoplasma gondii*, where rodents are intermediate hosts and the final host is a predator such as the fox or cat respectively. For these zoonoses, the relation between rodent abundance and prevalence of infection among the rodent population will depend in a complex way on both the dynamics and behaviour of the predator population (for a review of the links between abundance and prevalence in host-parasite systems where rodents are a necessary intermediate host, see Fichet-Calvet et al. 2003).

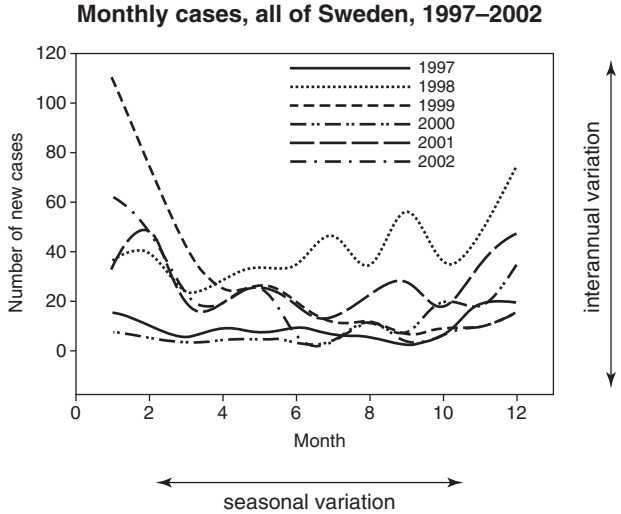

FIG. 1. Seasonal and annual variation in numbers of new cases of Puumala Hantavirus disease in humans. Data is from all of Sweden, 1997–2002, provided by The Swedish Institute for Infectious Disease Control (see also http://www.smittskyddsinstitutet.se).

[1]For calculating the number of human cases over some time period for which it can be assumed that the force of infection is constant then $C = H_S(1) - H_S(0)$ where $H_S(t)$ is the solution to $\frac{dH_S}{dt} = -\lambda H_S$ and hence $C = H_S(0)(1 - e^{-\lambda})$. When $\lambda << 1$, then $e^{-\lambda} \approx 1 - \lambda$.

Table 1. Review of Field Studies Monitoring Reservoir Abundance (N) and Prevalence (p) Concurrently

Pathogen	*Reference*	*Host species*	*Duration (years)*	*Number of sites*	*JDE*	p *versus* N
Sin Nombre virus	Boone et al. 1998	*Peromyscus maniculatus*	1	4	No	No correlation
	Boone et al. 1998	*Peromyscus maniculatus*		114	Unclear	+ (threshold)
	Douglass et al. 2001	*Peromyscus maniculatus*	6	6 (10 grids)	Yes	−
	Calisher et al. 1999	*Peromyscus maniculatus*	2	2	Unclear	+
Limestone	Abbott et al. 1999	*Peromyscus boylii*	3	1	Unclear	−
	Kuenzi et al. 1999	*Peromyscus boylii*	2.5	1	Unclear	+
Puumala virus	Niklasson et al. 1995	*Clethrionomys glareolus*	8	1	Yes	+
	Olsson et al. 2002	*Clethrionomys glareolus*	5	6	Yes	+
	Verhagen et al. 1986	*Clethrionomys glareolus*	2	1	Yes	Not studied
	Escutenaire et al. 2000	*Clethrionomys glareolus*	3	4	Yes	+
	Heyman et al. 2002	*Clethrionomys glareolus*		15	Unclear	Not studied
	Sauvage et al. 2002	*Clethrionomys glareolus*	3	2	Yes	Not studied
	Brummerkorvenkontio et al. 1982	*Clethrionomys glareolus*	3	1	Unclear	Not studied
	Ahlm et al. 1997	*Clethrionomys glareolus*		8	Unclear	+
	Bernshtein et al. 1999	*Clethrionomys glareolus*	5	2	Unclear	Not studied
Unspecified hantavirus	Cantoni et al. 2001	*Oligoryzomys longicaudatus; Abrothix longipillis; Loxodontomys micropus*	2	2	Unclear	No correlation
Yersinia pestis	Golvan and Rioux, 1961	*Meriones vinogradovi/persicus*	3	9	Unclear	+
	Davis et al. 2004	*Rhombomys opimus*	41	2	Unclear	+ (threshold)
Lassa virus	McCormick et al 1987	*Mastomys spp*		14	Unclear	Not studied
	Demby et al. 2001	*Mastomys spp*		26	Yes	Not studied
Junin virus	Mills et al. 1992	*Calomys musculinus*	2.5	7	No	Not studied
Cowpox virus	Begon et al. 2003	*Clethrionomys glareolus*	2	15	Unclear	−
Borrelia crocidurae	Godeluck et al. 1994	*Arvicanthis niloticus*	2	1	No	No correlation
	Godeluck et al. 1994	*Mastomys huberti*	3	1	Yes	No correlation
Leishmania major	Fichet-Calvet et al. 2003	*Psammomys obesus*	2	1	Yes	No correlation

The column labeled JDE (juvenile dilution effect) indicates whether the author(s) found support for this effect in their data. The final column indicates the relationship between abundance and prevalence: +, positive correlation between prevalence and abundance; −, negative correlation.

RELATIONSHIPS BETWEEN ABUNDANCE AND PREVALENCE

That prevalence should increase with abundance is a common expectation in the literature surrounding wildlife diseases in general and rodent-borne zoonoses in particular (Hudson et al. 2002, Grenfell and Dobson 1995, Mills et al. 1999, Olsson 2003, Escutenaire et al. 2000).

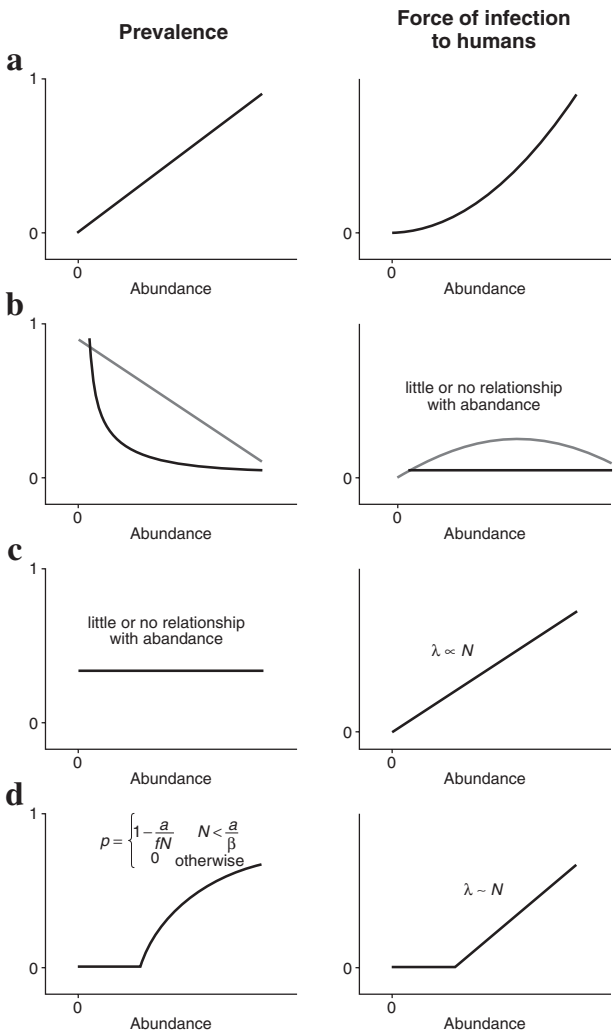

FIG. 2. Relationships between abundance and the force of infection on humans for a range of expected and empirically observed relationships between prevalence of disease in a host population and host abundance. (**a**) Positive correlation. (**b**) An inverse or negative correlation. (**c**) No discernible relationship. (**d**) A threshold relationship. Since prevalence is restrained to lie between 0 and 1, then linear relationships between abundance and prevalence are only possible for some interval of abundance. Similarly, an inverse relationship between prevalence and abundance can only hold when abundance is greater than some lower limit.

This is largely because a positive correlation between prevalence and abundance is consistent with density-dependent horizontal transmission (Mills et al. 1999).

An important implication of a positive correlation between prevalence and abundance (Fig. 2a) is that fluctuations in abundance will lead to a corresponding and amplified variation in the force of infection. This may be seen mathematically by substituting $p = p_1 N$ into equation (1), where p_1 is a constant and this relationship only holds for some limited range of N since prevalence is constrained to be between 0 and 1 and there must necessarily be a saturation effect as N increases. Equation (1) becomes the following:

$$\lambda = \beta^* N^2 \tag{3}$$

where now $\beta^* = kvp_1$. The force of infection is now proportional to the square of abundance. This means that a twofold increase in abundance of the rodent host population leads to a fourfold increase in the force of infection. In this case, ecological studies of rodent reservoirs that monitor changes in abundance are more obviously valuable to health officials. It implies that a positive association between rodent abundance and numbers of primary cases should be obvious. This is because any variation in rodent abundance will be reflected and amplified in the numbers of human cases.

A decreasing prevalence of infection with increasing abundance at first seems unlikely but it is often observed at a seasonal time scale. Longitudinal monitoring of hantavirus infection in populations of *Peromyscus boylii* indicated lowest prevalence at high densities and highest prevalence at low densities (Abbott et al. 1999). The mechanism appears to be that the likelihood of infection increases with age (Mills et al. 1999, Escutenaire et al. 2000, Olsson et al. 2002) such that a large influx of juvenile mice will result in a population having an overall low prevalence. This is sometimes referred to as the juvenile dilution effect (Mills et al. 1999).

A negative correlation between prevalence and abundance (Fig. 2b) may be represented mathematically as:

$$p = p_0 - kN \tag{4}$$

where as for a positive correlation such a linear relationship can only be appropriate for some range of values for N (since $0 < p < 1$). An alternative relationship, suggested by some authors (Mills et al. 1999), is that prevalence is inversely related to abundance ($p \propto 1/N$, $N > 0$). Either of these make a dramatic contrast with a positive correlation between abundance and prevalence since if $\lambda \propto Np$ and $p \propto 1/N$ then $\lambda \propto N \times 1/N = 1$. This leads to a disassociation between the force of infection on humans and abundance of the rodent reservoir. In this case, variation in primary cases will not be related to variation in rodent abundance.

It should be emphasized here that finding a negative correlation between abundance and prevalence does not preclude finding a positive correlation between abundance and abundance of infectious animals (Douglass et al. 2001). This may be the case if abundance varies over the interval in which $Np = p_0N - kN^2$ (substituting equation [4]) is increasing with N (this interval is $[0, p_0/2k]$).

A plot of prevalence and abundance may reveal a lack of relationship between the two (Fig. 2c), as might be expected for example for sexually transmitted infections where transmission is frequency-dependent rather than density-dependent. The force of infection on humans is then the product of two independent variables with the implication that the force of infection on humans depends linearly on the abundance of rodents. However, a lack of relationship between prevalence and current abundance does not preclude a relationship with past abundance. The combination of a fluctuating rodent population and a delay between high prevalence of infection and high abundance produces a complex expression for the force of infection on humans; with

$$p = kN_{t-\tau} \tag{5}$$

equation (1) becomes

$$\lambda \propto N_t \mathrm{N}_{t-\tau} \tag{6}$$

where equation (5) indicates a positive relationship between prevalence and past abundance with a delay τ. The relationships between current abundance and prevalence (and between current abundance and the force of infection on humans) depend on the length of the delay τ relative to the time scale over which fluctuations in abundance occur. When the delay (τ) is long then an inverse relationship between abundance and prevalence can be produced (as can be demonstrated with simulations, see Fig. 3). When the delay is relatively short then simulation of equation (6) in a population with regular fluctuations produces a somewhat noisy but positive correlation (results not shown).

Thresholds for abundance (Fig. 2d), below which an infectious disease cannot invade or cannot persist in a host population, are another common expectation for wildlife disease (Hudson et al. 2002, Grenfell and Dobson 1995).

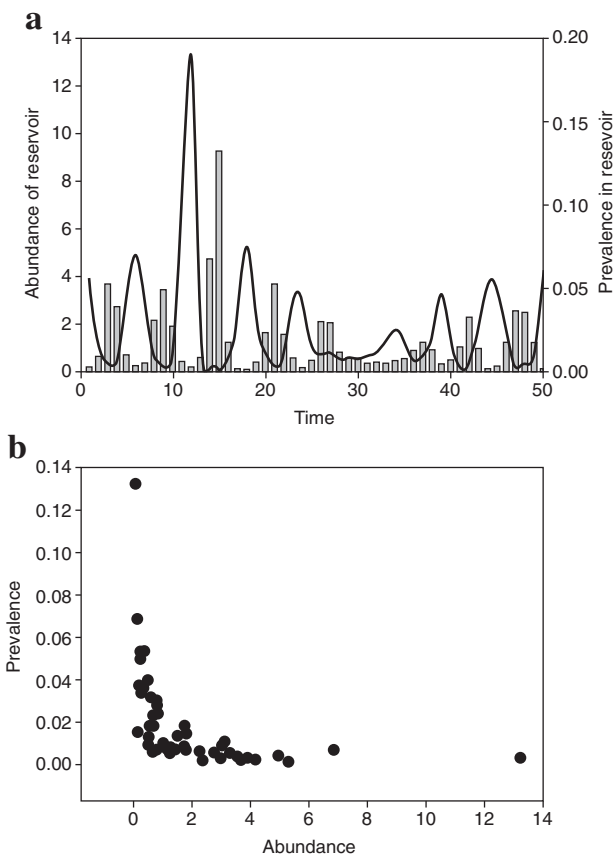

FIG. 3. (**a**) Simulated timeseries of a delayed relationship between prevalence (vertical bars) and abundance (line) in a cyclic reservoir produces. (**b**) An inverse relationship between concurrent abundance (N_t) and prevalence in reservoir (p_t). The simulated dynamics were generated with $p_t \propto N_{t-3}$ and $\ln(N_t) = 0.9\ \ln(N_{t-1}) - 0.9\ \ln(N_{t-2}) + \varepsilon_t$, where $\varepsilon_t \sim U(-1,1)$.

Some of the best empirical evidence that abundance thresholds operate in nature come from rodent reservoirs; an abundance threshold for plague (*Y. pestis*) was quantified using time series data from central Asia (Davis et al. 2004), and data from deer mice trapped at 114 sites and tested for antibody to hantavirus show that infection was less likely at sites where rodent densities were below a critical density (Boone et al. 1998). In terms of predicting the presence of a zoonoses in a (potential) reservoir population, and therefore a risk of human infection, knowledge of either an invasion threshold or a persistence threshold is invaluable (Davis et al. 2004, Daszak et al. 2000). This remains true when the threshold relationship is with past abundance and fluctuations generate an inverse relationship between prevalence and current density. In this case, the dynamics generate three broad levels of risk: (i) no risk of human infection when the infection is absent from the rodent population, (ii) an intermediate level when infection is present and the fluctuations of the host are regular, and (iii) a high level of risk in situations in which the infection is present *and* the anticipated decline phase of the host population is delayed.

FIELD STUDIES

The majority of the field studies of rodent reservoirs listed in Table 1 present longitudinal data on prevalence of infection in a small number of rodent populations. In these studies, seasonal and interannual variation in abundance generate the possibility of testing for a relation between prevalence and abundance. A few of the studies in Table 1 measure prevalence of an infection at a large number of sites where abundance of the host varies across space, and again there is the possibility to test for a relation between abundance and prevalence.

The expectation of a positive correlation between abundance and prevalence has been borne out by field studies, but neither frequently nor consistently. For Puumala virus infection in *C. glareolus*, an association between high seroprevalence and a rapid increase in rodent numbers was reported (Escutenaire et al. 2000). Other authors also found a link between prevalence and population phase, concluding that the chance of infection in bank voles was greatest during the peak of the population cycle (Olsson et al. 2002). The juvenile dilution effect, or at least the finding of a negative correlation between abundance and prevalence, is a reasonably common feature of the reviewed field studies.

The few studies that cover a greater time period, or sample a large number of sites, conclude that there is a positive (and in two of the three studies delayed) relationship between abundance and prevalence (Niklasson et al. 1995, Davis et al. 2004, Boone et al. 1998). Given the small number of these studies the conclusions drawn must necessarily be tentative. However it is worth noting that the three studies relate to three different zoonoses—Sin Nombre virus, Puumala virus, and plague.

DISCUSSION

The relationship between abundance and prevalence can be complex and may be scale dependent. For the same zoonosis and the same reservoir population, different relationships could well arise at different temporal and spatial scales. For example, it is possible that at a seasonal time scale there is an inverse relationship while at a multiannual scale there is a positive correlation. With time series data of considerable length (>5 years), these different temporal scales can be separated and patterns are more likely to emerge.

A negative correlation between abundance and prevalence at a seasonal time scale implies that seasonal fluctuations in abundance of a rodent reservoir do not explain seasonal peaks in human cases, it is more likely that seasonal shifts in rodent and/or human behavior are responsible. The seasonal peak in winter in Figure 1, for example, is thought to arise from changes in bank vole behavior; voles enter human dwellings seeking shelter from the harsh colder weather and the contact rate between humans and voles increases (Olsson et al. 2003). Interannual variation is more difficult to ex-

plain by shifts in human or rodent behavior, and is more likely to be due to reservoir dynamics.

For some zoonoses, the infectiousness of an individual may depend on the time elapsed since becoming infected. This is thought to be the case for hantaviruses such as Puumala virus (Yanagihara et al. 1985), where even though there is chronic shedding of virus, newly infected animals are particularly infectious. This implies that the probability that transmission ocurrs given there is contact between a human and an infectious rodent will depend on how recent the infection is. And this in turn implies the force of infection on humans may in fact be highest when there is an influx of susceptible animals and there is a high level of transmission among rodents such that there are many newly infected individuals.

The rodent populations that humans are most likely to come into contact with are peridomestic populations. For example, hantavirus pulmonary syndrome in the United States has been demonstrated to be associated with entering or cleaning buildings that had been infested with deer mice (Armstrong et al. 1995). In the peridomestic setting, populations of rodents may be more stable and at higher densities than those in the sylvan setting and hence provide a stable environment for an infection. Kuenzi et al. (2001) found that Sin Nombre Virus antibody prevalence was generally higher in peridomestic populations of deer mice than in sylvan populations. If it is peridomestic populations that are responsible for transmitting the infection to humans, then it is the flucuations in these populations that are of most interest to health officials concerned with preventing human cases.

The relations in Figure 2 must be treated with caution when considering the benefit of rodent removal programs that reduce either the density or the size of the reservoir population. Reducing abundance should have an immediate effect on the force of infection on humans by reducing contacts between humans and animals. But also, as suggested by Figure 2a,d, when abundance and prevalence are correlated, rodent removal will reduce transmission between rodents so that prevalence begins to decrease. However, this will not be an immediate effect; how quickly it is realized (as a population with few infectious animals) depends on the dynamics of the infection.

It is also possible that rodent removal programs acheive the precise opposite of what was intended; Douglass et al. (2003) found that removing deer mice from buildings not only increased the abundance of deer mice but created a turnover in the rodent population such that infected mice entered some of the buildings that were previously free of infected mice. Similarly, with plague, use of rodenticides without use of insecticides can sharply increase the risk of transmission to humans by increasing the numbers of fleas searching for a host.

When transmission from rodents to humans requires contact with an arthropod vector, rather than direct contact, then the relevance of equations (1) and (2) is more difficult to sustain. This is because the abundance of arthropod vectors, or even more importantly the abundance of those searching for a new host, may be largely independent of the abundance of rodents. In this case, it is more appropriate to relate the force of infection to the abundance of infectious arthropod vectors that fail to find their preferred host (Keeling and Gilligan 2000). Some arthropod vectors, such as the ticks responsible for tick-borne encephalitis, do not have a preferred host, and in this case, the force of infection should simply be dependent on their abundance. Interestingly, the dynamics of a host-specific infection among generalist arthropod vectors feeding on a range of hosts can generate correlations between biodiversity and zoonotic risk to humans, for example, in the case of Lyme disease (Ostfeld and Keesing 2000).

CONCLUSION

We have described two ways that an inverse relationship between current abundance and prevalence might occur: (i) when changes in abundance are dominated by pulses of young entering the population, and (ii) when there is a delayed relationship between abundance and prevalence and cycles in abundance are regular. In either case, the value of abundance as a predictor of risk is unclear. This is not true for a reservoir population that fluctuates irregularly and in

which there is a positive delayed relationship between prevalence and abundance. Monitoring abundance in this case does provide useful predictive knowledge, since when a reservoir population remains at high densities for prolonged periods, the risk of infection will be relatively high. A positive correlation between current/past abundance and prevalence is a feature of the more extensive field studies reviewed, particularly when the authors considered interannual or spatial variation. Such relationships imply that increases in the rodent population will be amplified in the force of infection on humans, and hence encourage the use of surveillance as a tool for managing rodent-borne disease.

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