

Are predators good for your health? Evaluating evidence for top-down regulation of zoonotic disease reservoirs

Richard S Ostfeld¹ and Robert D Holt²

Zoonotic diseases, caused by pathogens transmitted to people from vertebrate reservoirs, take an enormous toll on human health worldwide. Many of these disease agents are harbored in rodent populations, and humans are victims of “accidental” transmission. Here we explore the idea that predatory vertebrates indirectly protect human health by reducing population size of rodent reservoirs of human disease. Research frontiers include the importance of rodent population density to the incidence of human disease, as opposed to behavior or age structure effects; the roles of different types of predators in determining both population dynamics and rodent density per se; and the effects of human-caused environmental change on predators and their rodent prey. A better understanding of these basic ecological issues will inform both environmental and health policy.

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The explosive outbreak and intercontinental spread of Severe Acute Respiratory Syndrome (SARS) shows how vulnerable we are to disease agents that typically reside, unnoticed, in animal populations. In a sense, the SARS outbreak is nothing new – pathogens have been jumping from wildlife or livestock populations to humans since antiquity, often with devastating results. Recent analyses estimate that about 60% of all infectious disease agents affecting humans are zoonotic in origin, meaning that the pathogen typically resides in non-human vertebrate reservoirs; about three-quarters of emerging infectious diseases of humans are zoonotic (Taylor *et al.* 2001). Transmission to humans can come from swallowing or inhaling waste products from the animal reservoir, from eating them or being bitten, or from ectoparasites such as

mosquitoes, fleas, or ticks that deliver pathogens to human hosts. In some cases, notably SARS and AIDS, once the pathogen has jumped to our species, humans become a self-sufficient arena of transmission – but these are exceptions to the more typical zoonotic pattern, in which humans can only acquire an infection from non-human reservoirs.

The vast majority of zoonotic reservoir species are mammals, and most are rodents (Mills and Childs 1998). Monkeypox, hantavirus pulmonary syndrome (HPS), Lassa fever, Argentine and Bolivian hemorrhagic fevers, Lyme disease, granulocytic ehrlichiosis, leishmaniasis, bubonic plague, scrub typhus, tick-borne encephalitis, Crimean-Congo hemorrhagic fever – for these diseases and many more, we are the unwitting victims of pathogens that cycle, often cryptically, within rodent populations. Most of these diseases are characterized in humans by unpredictable outbreaks followed by lulls. For example, HPS was first discovered when an epidemic struck the US Southwest in 1993 (Yates *et al.* 2002).

Other zoonoses appear to be a more constant threat, but with some years worse than others. For instance, Lyme disease strikes, on average, about 15 000 people in the US each year, but annual case loads vary by up to 40% (Ostfeld 1997; Wilson 1998). What causes outbreaks and bad disease years? Have zoonotic diseases become more common or severe in recent years, and if so, why? Are human-caused alterations of the environment playing a role in generating patterns of disease risk or incidence?

In a nutshell:

- Disease agents transmitted from rodents to people afflict human populations worldwide
- It is commonly assumed that more rodents means greater disease risk, and that predators should protect our health if they help reduce rodent numbers
- The incidence of rodent-borne disease sometimes appears closely related to factors besides rodent abundance, including population dynamic phase, dispersal to human habitations, and behavioral interactions
- Predators have a range of effects on rodent populations, with some species causing chronic suppression and others eliciting boom-and-bust cycles or chaos
- In interacting systems of predator, prey, and pathogen, theory predicts that the loss of predators should tend to increase the absolute and relative number of infected prey

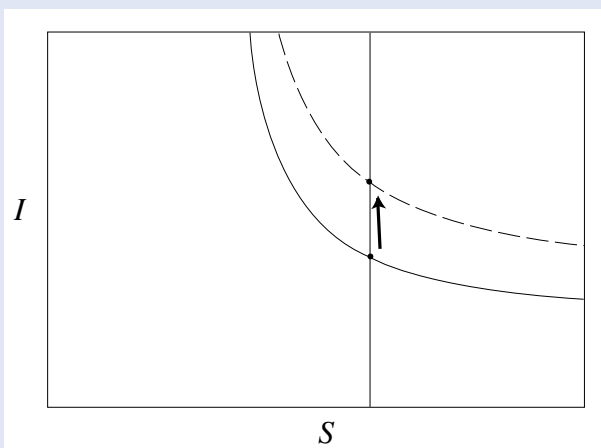
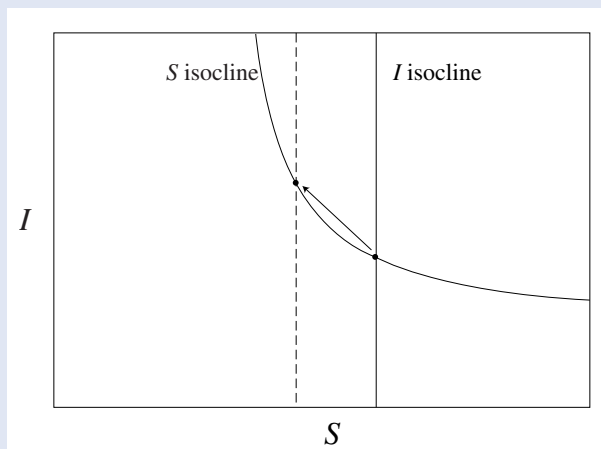
■ Linking predators to rodent-borne diseases

The viral, bacterial, and protozoal pathogens responsible for zoonotic diseases use the same basic pathways to spread within rodent populations as they use to invade

¹Institute of Ecosystem Studies, Box AB, 65 Sharon Turnpike, Millbrook, NY (rostfeld@ecostudies.org); ²Department of Zoology, University of Florida, Gainesville, FL

Panel 1. Theoretical perspectives on predator impacts on infectious disease systems

A broad range of models of systems involving a mixture of predation and parasitism suggest that one generic effect of predator reduction could be the unleashing of host–pathogen interactions in prey species, leading to emerging infectious diseases within and among host species (Dobson and Hudson 1992; Packer *et al.* 2003; RD Holt unpublished). In a general sense, predation upon a host with a specialist pathogen is asymmetrical “intraguild predation” (Polis *et al.* 1989), because the predator and pathogen in effect compete for healthy hosts, and the predator can directly kill the pathogen when it consumes infected hosts. A simple but illuminating way to illustrate how predator removal can alter disease levels is an SI (susceptible–infected) model:



(top) Reducing predation on infected individuals increases their equilibrium abundance. Solid vertical line is infected isocline, with predator; dashed line is infected isocline, without predator. (bottom) Reducing predation on healthy individuals can also increase the equilibrium abundance of infected individuals. Solid and dashed curved lines are isoclines for S, with and without predator.

$$\frac{dS}{dt} = (b - m(C))S - \beta SI + (\gamma + b')I,$$

$$\frac{dI}{dt} = \beta SI - (\gamma + m'(C))I$$

Here, b and b' are birth rates of healthy and infected hosts, γ is recovery of infected hosts, and $m(C)$ and $m'(C)$ are death rates of healthy and infected hosts, respectively. We assume that either or both death rates may increase with increasing predator abundance C . Disease transmission is density dependent, scaled by β , the rate of pathogen transmission.

If the death rate of infected hosts is sufficiently high, the pathogen regulates the host. Inspection of the model isoclines reveals that predator removal always increases both the equilibrium abundance of infected individuals (I^*), and the fraction of hosts infected ($I^*/(I^*+S^*)$). If predators mainly focus on infected hosts (for example, because they are easier to catch), the isocline for the infected portion of the population shifts to the left (top). Each infected individual lives longer in the absence of the predator, and can infect that many more individuals. If predators instead attack healthy hosts (because infected prey are poor quality, or less mobile), predator removal shifts the healthy host isocline upwards (bottom). Again, this produces more infected individuals; in effect, the host is more productive and can sustain a greater load of infection. (Although these effects arise in a wide range of epidemiological models, it should be noted that because of the complexity of predator–prey and infectious disease interactions, alternative scenarios are also feasible.)

humans. They exit a rodent host either in excreta (feces, urine or saliva) or via the bite of a blood-sucking arthropod, and enter a new host – rodent or human – through inhalation, swallowing, or skin punctures. It seems logical to assume that the greater the abundance of rodent reservoirs, the higher the potential delivery rate of pathogens from rodents into vectors or the air and water supply, and therefore the higher the risk to people of contracting the disease. If this is true, then any factor that reduces rodent density should help diminish the incidence of zoonotic disease. Rodents are preferred prey for many taxa of predators, including mammals, birds, and reptiles, and

these predators could potentially be strong limiting factors and regulators of rodent density. If so, then the presence of abundant populations of rodent predators could help protect human health. We expect this effect on theoretical grounds, irrespective of whether predators tend to attack infected or healthy prey (Panel 1).

Native predatory vertebrates appear to be particularly sensitive to human-caused disturbances of ecological systems, and are often the direct targets of reduction or eradication efforts (Turner 1996; Terborgh *et al.* 2001). The destruction of predator populations and their habitats could have unanticipated negative consequences for

human health. An alleged collapse in predator populations was postulated as a key driver of the 1993 outbreak of HPS (Epstein 2000), but this possibility has not been explored empirically. Predator collapse could be an important pathway by which human-accelerated environmental change (Likens 1991) elicits the emergence or enhancement of infectious diseases.

The scenario linking epidemics of zoonotic diseases to changes in the abundance or species composition of carnivorous vertebrates is essentially a trophic cascade (Pace *et al.* 1999), with the twist that pathogens are involved. The argument is that predators limit rodent numbers, rodent numbers limit pathogen numbers, and pathogen numbers in rodents then determine disease incidence in people (Figure 1). If accurate, the scenario suggests that human activities that reduce predator numbers will increase the incidence of zoonotic diseases. This is plausible and consistent with formal theory, but is it supported by evidence? This review assesses evidence for each link in the putative trophic cascade.

■ Is zoonotic disease linked to rodent density?

High rodent density might be expected to increase the risk of human exposure to zoonotic pathogens, irrespec-

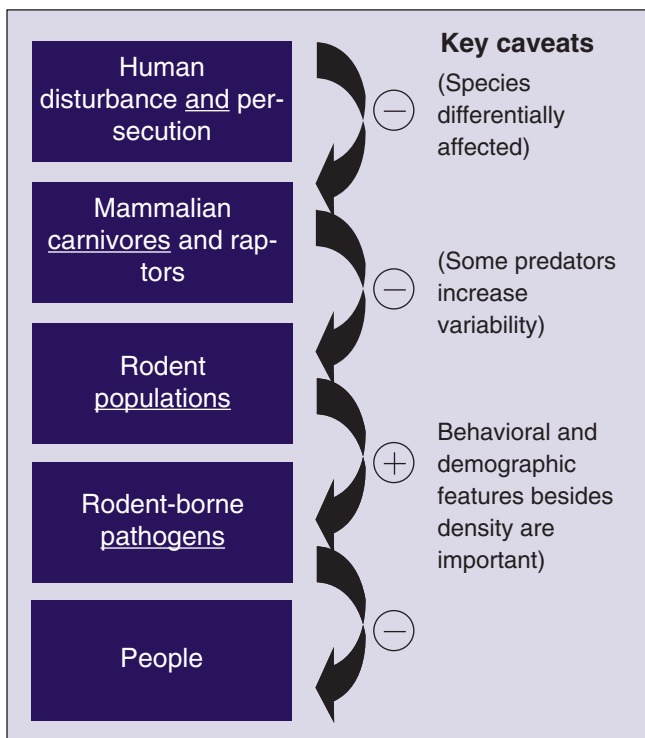


Figure 1. Conceptual diagram of the trophic cascade in which human disturbance affects health via predator reduction, increases in rodent numbers, and consequent increases in transmission of rodent-borne disease agents to people. Key entities are listed within boxes and direct interactions are denoted by arrows. Plus and minus signs indicate whether the impact of an entity is positive or negative. Key caveats to the simple, direct linkages are given on the right.



Figure 2. A female white-footed mouse (*Peromyscus leucopus*) with nursing young. This species is a reservoir for several zoonotic diseases such as Lyme disease, and is noted for its tremendous reproductive potential and dramatic population fluctuations.

tive of the type of disease agent or its mode of transmission. For disease agents transmitted directly from rodent excreta, such as hantaviruses or arenaviruses, the higher the abundance of rodents, the higher the deposition rates of pathogens into local environments, and therefore the higher the likely exposure rate. Similarly, for water-borne diseases such as leptospirosis, higher rates of pathogen delivery to water sources should result from greater numbers of rodents in the watershed. For disease agents transmitted from rodents to humans by vectors, such as Lyme disease or the plague, higher densities of rodent reservoirs should result in a higher rate of contact between vectors and reservoirs, leading to higher infection prevalence in vectors and consequently in disease risk to people (Figure 2). Note that, from a theoretical perspective, predator loss can increase both the density and frequency of infected individuals in the rodent population (Panel 1).

The relationships between rodent density and human disease are often assumed, and are theoretically reasonable, but not necessarily supported by direct evidence (Glass *et al.* 2000). Some situations may undermine or even reverse the expectation of a positive correlation between rodent numbers and disease risk for humans. For example, peaks in rodent density typically occur following seasonal or multi-year periods of high population growth rates (Hansson and Henttonen 1988). Often, populations at peak density have a high abundance of younger age classes, produced during the phase of rapid recruitment. These individuals usually show lower seroprevalence (the proportion of individuals testing positive for infection, detected with antibody blood tests). This may reflect the fact that they have simply had less time to be exposed to



Courtesy of M Benjamin

Figure 3. A cluster of adult blacklegged ticks (*Ixodes scapularis*) in the forest understory. This species is known to be the primary vector of at least two bacterial diseases (Lyme disease and human granulocytic ehrlichiosis), one protozoal disease (babesiosis), and one viral hemorrhagic disease (tick-borne encephalitis), all of which appear to use rodents as a primary reservoir.

infection. Young individuals may also be protected by maternal antibodies (Childs *et al.* 1987), or may exhibit less of the behaviors that raise infection risks in older individuals, such as mating or fighting (Glass *et al.* 1988; Mills *et al.* 1999; Yahnke *et al.* 2001).

Another situation that undermines a correlation between rodent numbers and disease transmission is when pathogen numbers are limited by factors other than abundance of their rodent hosts. In this case, infection in one habitat may reflect “spillover” from another habitat (Holt and Hochberg 2002). A third condition occurs when pathogen transmission between reservoir individuals, and from reservoirs to humans, increases with the proportion of the reservoir population that is infected, rather than with population density. In other words, transmission is frequency-dependent rather than density-dependent (Begon *et al.* 1999).

A fourth situation, pertaining to vector-borne diseases, arises when a greater abundance of rodent hosts leads to a lower incidence of humans being bitten by the vector. In essence, the arthropod vectors are so busy biting abundant rodent hosts that they only infrequently encounter and bite people. This situation is thought to be crucial in urban outbreaks of bubonic plague, where eradication of the Norway rat (*Rattus norvegicus*) reservoir when vector flea populations are abundant can result in dramatically increased attack rates by fleas on people (Keeling and Gilligan 2000). Ironically, eradication of the reservoir could cause a human disease outbreak.

Some examples demonstrate an increased risk or incidence of human disease with increases in rodent abundance. Niklasson *et al.* (1995), Escutenaire *et al.* (1997),

and Brummer-Korvenkontio *et al.* (1999) describe correlations between bank vole (*Clethrionomys glareolus*) population size and human cases of nephropathia epidemica (caused by the Puumala form of hantavirus) in Sweden, Belgium, and Finland, respectively. For HPS in the Southwestern US, outbreaks of human disease sometimes occur in high-density years of the deer mouse reservoir, but also occur in low-density mouse years (Yates *et al.* 2002). At the level of individual households, Childs *et al.* (1995) found that a high local abundance of deer mice was a significant risk factor for HPS during the original North American outbreak. Mills *et al.* (1992) observed an association between *Calomys* mice outbreaks and human cases of Argentine hemorrhagic fever. For Lyme disease in the northeastern US, interannual variation in the density of infected nymphal ticks (*Ixodes scapularis*), which is the primary risk factor for humans, increases linearly with the prior

year’s density of the main reservoir species, white-footed mice (*Peromyscus leucopus*) (Ostfeld *et al.* 2001; Figure 3).

At the same time, however, many studies of rodent outbreaks have found no evidence of associated outbreaks in human disease, despite the fact that many of these species are known reservoirs for human pathogens. Of course, it is still possible that public health professionals simply didn’t detect an increased incidence of human disease. It is also possible that there are mechanisms that decouple rodent abundance from human infection risk.

Some rodent species, such as the Norway rat reservoir of plague bacteria (*Yersinia pestis*), are commensals with people, meaning they live in close association with human habitations, whereas others, such as the deer mouse (*Peromyscus maniculatus*) reservoir of hantaviruses, usually are not. For some non-commensal rodents, notably the deer mouse, some evidence links invasions of houses, barns, and other buildings to high population density in the wild (eg Kuenzi *et al.* 2001). Therefore, the disease risk to humans can be increased when rodent behavior (in this case, dispersal and habitat selection) changes with increasing density. Conversely, without such behavioral shifts, risk to humans may not increase at higher rodent numbers.

The link between rodent density and zoonotic disease risk has been established in only a few instances, and therefore remains somewhat tenuous. Critical issues requiring further research include: (1) the relative importance of population density, population growth rate, age/sex structure, and behavior in determining the numbers or proportion of rodents infected and capable of spreading disease; (2) whether the proportion of individ-

ual rodents infected (infection prevalence) or absolute numbers infected is a better predictor of human disease risk; and (3) whether the effects of rodent demography and behavior on human disease risk varies predictably with the mode of pathogen transmission. In other words, is rodent demography a better predictor for directly transmitted diseases than for those involving vectors? Empirical efforts to address these questions may be greatly enriched when they are grounded in explicit models that link rodent demography and disease dynamics (Panel 1).

■ Do predators regulate rodent density?

This is not a new question; Elton (1942) addressed it extensively 60 years ago, and active research has continued to the present. Nevertheless, the impact of predators on rodent-borne zoonotic diseases has received little attention. It seems obvious that whenever predators attack and kill rodent prey, they are removing individuals from the population and therefore reducing numbers. But if predators largely remove individuals that would have died soon from other causes, such as disease or starvation, then the effects of predators on population dynamics would be modest or nothing, and the reduction or disappearance of predators would not alter rodent abundance. Dozens of studies in the past decade or so have shown that predators do indeed reduce rodent numbers (eg Hanski *et al.* 2001). When predators are removed or excluded with fencing, rodent populations grow larger than when predator populations are intact (Desy and Batzli 1989; Korpimäki *et al.* 2002). While it is tempting to conclude that the answer to the question is therefore “yes”, things are not that simple.

Two issues complicate our understanding of the impact of predators on rodent abundance, and consequently on rodent-borne disease agents. The first is that knowing predators reduce prey numbers is insufficient. We also need to know the relative strength of this top-down effect compared to other influences on rodent numbers. For instance, if food supply is the principal regulator of population size, then any changes in predator abundance might have only trivial effects on rodent numbers, overwhelmed by the impacts of bottom-up forces. Only a few studies have jointly manipulated predator access and other factors, such as food supply or competitor numbers, to determine their impacts on rodent populations. For voles of the genus *Microtus*, the impacts of predators and food supply are of similar magnitudes and do not interact (Desy and Batzli 1989). *Microtus* is involved in the maintenance of some human pathogens (eg Plyusnin *et al.* 1994), but it seems less of an epidemiological menace than some other rodent genera.

For those genera known to maintain and transmit many human disease agents, including *Peromyscus*, *Apodemus*, *Calomys*, *Mastomys*, and *Rattus*, much less attention has been paid, either experimentally or otherwise, to assessing whether predators are a strong regulatory force. In the case of some species, such as *P leucopus*, *P maniculatus*, and *M natalensis*, food supply apparently has an overwhelmingly strong impact on population numbers. For *P leucopus* and *Apodemus* spp, the size of the autumn crop of acorns or other tree seeds is a strong determinant of rodent density the following year, often explaining over 80% of inter-annual variation (Ostfeld *et al.* 1996; Selas *et al.* 2002). For *M natalensis* and *P maniculatus*, population numbers are strongly associated with seasonal rainfall, apparently because high precipitation increases the abundance of invertebrate prey and seed production by annual plants (Leirs *et al.* 1997; Brown and Earnest 2002; Yates *et al.* 2002). The role of predators in influencing abundance in these species is still poorly understood, despite a long history of intensive research on their population dynamics.

The second complicating issue is that population dynamics (the pattern of change in numbers through time) and correlated changes in behavior and disease incidence are arguably more important to disease transmission to humans than is population density per se. Consequently, the simple fact that predators reduce average prey numbers is an inadequate basis from which to assert unequivocally that predators protect human health. Predators can exert different types of effects on prey population dynamics. Mustelid (weasel family) predators that specialize on particular rodent prey tend to cause dramatic fluctuations in numbers (Hanski *et al.* 1993; Figure 4).



Figure 4. A stoat or short-tailed weasel (*Mustela erminea*), a specialist predator on rodents known to drive some populations through boom and bust cycles or chaotic fluctuations. This type of predator might not be protective of human health, despite having a strong effect on reservoir populations. This lack of a protective role would occur if disease outbreaks are related to rodent outbreaks, which in turn are facilitated by specialist predators.



Figure 5. The kestrel (*Falco tinnunculus*), a generalist, mobile rodent predator, is thought to regulate rodent populations at more consistently low levels. This type of predator appears most likely to protect human health by chronically suppressing reservoir populations, keeping population density low.

This occurs largely because these predator populations are tightly coupled to those of their prey. As rodent populations grow, so too do weasel populations (albeit delayed, because the conversion of prey into the next generation of weasels takes months). Long delays in the impact of prey density on predator density are well known to cause strong fluctuations in prey populations, which in the case of rodents take the form of cycles (Hansson and Henttonen 1988) or chaos (Hanski *et al.* 1993).

On the other hand, predators that are either non-specialized in prey selection and can switch between target species, such as foxes and some snakes, or are highly mobile and able to roam to find better hunting grounds, including some raptors, may sometimes regulate prey at more consistently low numbers. In both cases, because the relaxation of predation pressure on the prey follows quickly upon suppression of prey numbers, the net effect of predation is to stabilize prey dynamics. The more stable population dynamics of voles are correlated with the presence of either generalist or highly mobile predators (Klemola *et al.* 2002; Kjellander and Nordström 2003; Figure 5).

Consequently, one might predict that generalist predators protect human health by chronically suppressing rodent numbers. By eliciting strong fluctuations that include rodent outbreaks, however, specialist predators promote the transmission of rodent-borne pathogens to people during population peaks. Whether this hypothesis

is correct depends on how much the pattern of population dynamics of rodent reservoirs influences disease incidence and human exposure, a topic dealt with above. In any event, the hypothesis remains untested.

■ Does anthropogenic predator loss increase zoonotic disease risk?

Human activities such as habitat destruction, conversion, and fragmentation, the spread of diseases from livestock and companion animals, pesticide use, and direct exploitation such as bushmeat consumption, are clearly reducing both the abundance and diversity of predatory vertebrates worldwide (Terborgh *et al.* 2001). If the reduction or loss of predator species releases epidemiologically important rodent species from predator limitation and pathogen levels increase (Panel 1), then the impact on human health will be negative (Figure 1). Granting that at least certain types of predators may regulate rodent reservoir populations, as discussed above, determining the epidemiological consequences of predator

loss requires that we know both which predators are most heavily impacted by human activities, and what their effects are on rodent reservoirs.

The most obvious victims of habitat destruction, domestic animal diseases, toxic pesticides, and direct exploitation are the top carnivores, including the large felids, canids, ursids, raptors, and large snakes. Tigers, jaguars, wolves, cougars, and grizzly bears require large expanses of pristine habitat; African lions, wild dogs, and cheetahs have been decimated by introduced pathogens such as canine distemper virus; large felids, canids, and ursids have been persecuted by hunters and poachers around the world; and pesticides like DDT have caused severe declines in raptor populations (Voss *et al.* 2000). In contrast, the anthropogenic impacts on smaller native predators are known in only a few cases. Black-footed ferrets (*Mustela nigripes*) were nearly driven extinct by a combination of habitat destruction and introduced canine distemper (Williams *et al.* 1988). Some small mustelid species appear to decline with the conversion of forested landscapes to agricultural use (Rosenblatt *et al.* 1999). Shrikes seem to be disappearing worldwide, and anecdotal evidence suggests that snake numbers fall near human habitations.

Although the large mammalian predators listed above may sometimes kill rodents, their primary prey consists of larger animals. Therefore, it is likely that the loss or reduction of large carnivores has, at best, a modest direct impact

on rodent populations. On the other hand, several recent studies indicate that the loss of large carnivores has profound impacts on the remaining biota, although usually only indirectly (Estes *et al.* 1998; Terborgh *et al.* 2001). One recently described direct effect of the loss of top carnivores (wolves, cougars, bears) is a greater abundance of somewhat smaller carnivores such as coyotes, foxes, and domestic cats, a phenomenon called “mesopredator release” (Crooks and Soule 1999). These mesopredators are more likely than the top predators to consume rodents and regulate their numbers. For example, several studies have shown a strong impact of domestic cats on rodent populations in suburban and rural areas (Dyckowski and Yalden 1998). However, human activities that directly or indirectly promote populations of mesopredators such as cats cannot always be assumed to control rodent populations and the pathogens they transmit. For instance, Childs (1986) found that urban cats tended to kill non-breeding rats, which were unlikely to be infected with hantavirus. Nevertheless, a possible indirect effect of the loss of large carnivores is a decrease in abundance of rodents, and potentially, in the risk of human exposure to zoonotic disease. To our knowledge, this supposition remains untested.

In areas where the large carnivores have been missing for decades or longer – the sad reality in many regions of the world – the critical question is how human activities affect the remaining predators. Assuming that the more carnivorous the species, the greater the requirements for large, undisturbed areas, habitat destruction might cause universal declines in predators, irrespective of their size (but see Crooks 2002). Clearly, further studies on the impacts of human activities on smaller carnivores are warranted.

■ What do we know and what don't we know?

As is often the case in ecology, predicting the specific consequences of human-caused degradation of natural systems becomes difficult when we consider the complexity of the systems. Here we have evaluated the assertion that human health is protected when populations of rodent predators (largely carnivores and raptors) are unhindered by human activities, liberating them to regulate their rodent prey and thereby reducing the spread of pathogens from rodents to people. Beyond the fact that many human disease agents use rodents as a natural reservoir, this assertion remains largely untested. More information is needed on the importance of rodent density (vs age structure, behavior, and other factors) for disease dynamics, and thus on human disease risk; on the impacts of different species of predators on rodent populations; and on the impacts of human activities on the various predatory species, as modified by their interactions with each other.

Despite the unknowns, however, some generalities appear to be emerging. Rodents, including domesticated

species in the pet trade, will continue to act as a source of human infection. Monkeypox transmission from Gambian giant rats (*Cricetomys gambianus*) and prairie dogs (*Cynomys sp*) are only the most recent of numerous examples. It seems likely that disease transmission will be reduced when rodent populations remain at chronically low density and away from human habitation, and will grow with increasing density, magnitude of fluctuations, and tendency to invade human dwellings. Generalist or highly mobile predators seem likely to be most effective in regulating rodent numbers at these low levels, whereas specialist predators of limited mobility appear responsible for dramatically fluctuating rodent populations. Medium-sized mammalian predators and raptors are the top candidates to play a strong regulatory role for rodents.

Habitat destruction and degradation, as well as direct exploitation via hunting and trapping, disproportionately affect larger, more carnivorous species of vertebrates. Where top predators still exist, these environmental insults might have the paradoxical effect of reducing rodent numbers by releasing mesopredators (including domestic cats) from regulation by their larger counterparts. However, where top predators have already been reduced or eradicated and environmental degradation has proceeded further, environmental disruptions are more likely to release rodents from regulation through the loss of native mesopredators. The articulation of specific hypotheses, nested within a clear conceptual and theoretical framework that incorporates the essential complexity of ecological systems, will allow us to assess more easily the relationship between human-caused environmental change and zoonotic disease.

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