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Regulation of Rodent-Borne viruses in the natural host: implications for human disease

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Summary. Prevalence and transmission rates of rodent-borne viruses within host populations vary in time and space and among host-virus systems. Improving our understanding of the causes of these variations will lead to a better understanding of changes in disease risk to humans. The regulators of prevalence and transmission can be categorized into five major classes: (1) Environmental regulators such as weather and food supply affect transmission rates through their effect on reproductive success and population densities. (2) Anthropogenic factors, such as disturbance, may lead to ecosystem simplification and decreased diversity. These changes favor opportunistic species, which may serve as reservoirs for zoonotic viruses. (3) Genetic factors influence susceptibility of mice to infection or capacity for chronic shedding and may be related to population cycling. (4) Behavioral factors, such as fighting, increase risk of transmission of some viruses and result in different patterns of infection between male and female mice. Communal nesting may result in overwinter transmission in colder climates. (5) Physiologic factors control host response to infection and length of time the host remains infectious. Risk prediction is difficult because these regulators are numerous and often interact, and the relative importance of each varies according to the host species, season, year, and geographic location.

Introduction

In the collection of papers included in this special issue, we seek to further our understanding of the emergence and persistence of infectious viral diseases "from nature" that impact human health. Our common objective, to alleviate human suffering and improve public health, can be approached at multiple levels. The treatment of disease in humans, although important, should be a last resort. Elimination of the disease agent from nature usually is not possible. A third approach, which often is much more achievable, is to prevent the disease agent from making the jump from the natural reservoir to humans. This approach requires accurate risk prediction and development and targeting of effective preventive measures

which, in turn, require a detailed knowledge of the ecology and epizootiology of the hosts and vectors of zoonotic viruses. Studies of the dynamics of viral infection in natural host populations require a wide variety of methodologies, many of which are not commonly taught to students in public health science. Nevertheless, as human populations grow and continue to expand into formerly undisturbed natural habitats, these studies become increasingly important. Their successful accomplishment will require the collaboration of scientists from a variety of disciplines, including virology, immunology, ecology, zoology, geography, and mathematics. In this review, I will draw upon data from recent and on-going multidisciplinary studies that have increased our understanding of the regulation of rodent-borne viruses in natural host populations and relate these findings to the understanding and prevention of human disease.

Factors that influence or "regulate" the transmission and prevalence of infection of rodent-borne viruses in natural hosts are numerous and cover the full range of the biology and ecology of the host species. The space allotted to this article will allow only a general coverage of the major categories of these factors and a few examples of each.

For purposes of this article, I will define regulators as those factors that affect the transmission and prevalence of rodent-borne viruses in their natural hosts. In this context, regulation is not precise in the way that a precision instrument regulates temperature, pressure, or flow rate. Regulators in natural systems are factors that influence outcomes in ways that are difficult to quantify; their total effects vary according to their interactions with a myriad of other ecological regulators, making outcomes difficult to predict. Nevertheless, the better we understand these "regulators" the better we will be able to predict times and places of increased risk for zoonotic diseases or to develop effective interventions and target them appropriately. For convenience, I have divided factors that contribute to the prevalence and transmission of rodent-borne viruses in their hosts into five general, but overlapping, classes (Table 1). I will briefly describe each of these classes and provide illustrations, drawing from experience with the hantaviruses and arenaviruses.

Table 1. Principal categories of regulators of viral transmission in natural host populations

	Natural environmental: Weather, habitat quality, food supply
II	*Anthropogenic*: Human disturbance or alteration of habitat
III	*Genetic*: Variation among individuals or populations
IV.	*Behavioral*: Actions that affect transmission
V.	*Physiological*: Physiological predisposition or response of organism to infection

Environmental regulators

Environmental regulators such as weather, habitat quality, and food supply affect transmission rates through their effect on reproductive success and population densities. Hantavirus pulmonary syndrome (HPS) is a severe respiratory disease with high mortality [15, 25]. The great majority of HPS cases in the United States are caused by Sin Nombre virus (SNV), which is hosted by the deer mouse (*Peromyscus maniculatus*). It is widely believed that the first recognized outbreak of HPS in the southwestern United States in 1993 was associated with unusual environmental conditions that resulted in high risk of human disease [41]. The often repeated story is that the 1993 El Niño Southern Oscillation (ENSO) event brought unusually high rainfall to the arid Southwest, populations of deer mice increased dramatically, prevalence of infection increased as a consequence of these high population densities, the probability of humans encountering infected mice increased, and this produced the outbreak of HPS [41]. This scenario is logical but has been largely conjecture, because no one was specifically measuring deer mouse populations at the time. Since then, however, investigators supported by the Centers for Disease Control and Prevention have been tracking deer mouse population density and prevalence of infection with hantaviruses at several collection sites in the western United States [14, 32]. Figure 1A–C show the relationship between numbers of HPS cases in the southwestern United States during 1994–2003 and deer mouse populations, prevalence of infection with SNV using, as an index, values from four mark-recapture plots in northwestern New Mexico. There was another ENSO event in 1997, and investigators recorded increased rainfall, increased cover of green vegetation, and increased numbers of deer mice preceding increased numbers of HPS cases in 1998 Fig. 1A [41]. As predicted, the increased numbers of deer mice was followed by an increase in the prevalence of infection in host populations (with a delay of about a year; Fig. 1B). Nevertheless, neither the increase in deer mouse density nor the increase in prevalence above background levels temporally coincided with the increase in human cases. Perhaps most important is the comparison with the absolute number of infected deer mice (Fig. 1C). This index remained low when the number of human cases was low, but once the index rose above a certain threshold, human cases simultaneously increased. Although there does not appear to be a linear relationship (at this index site), this index remained above threshold levels throughout the period of increased risk in the Southwest. These observations allowed the successful prediction of high disease risk for human populations in the spring of 1998 [8, 9] and the spring of 1999 [9].

Thus it appears that rainfall was an environmental regulator of SNV transmission in rodent populations, and although the quantitative relationship was obscure, in qualitative terms, more rain appeared to translate to more virus and higher risk. Nevertheless, generalizing that conclusion even to other areas of the Southwest might not be appropriate.

At a grassland site in southeastern Colorado, investigators have been monitoring rodent populations and SNV since 1994 [3, 4]. Pinyon Canyon Maneuver Site

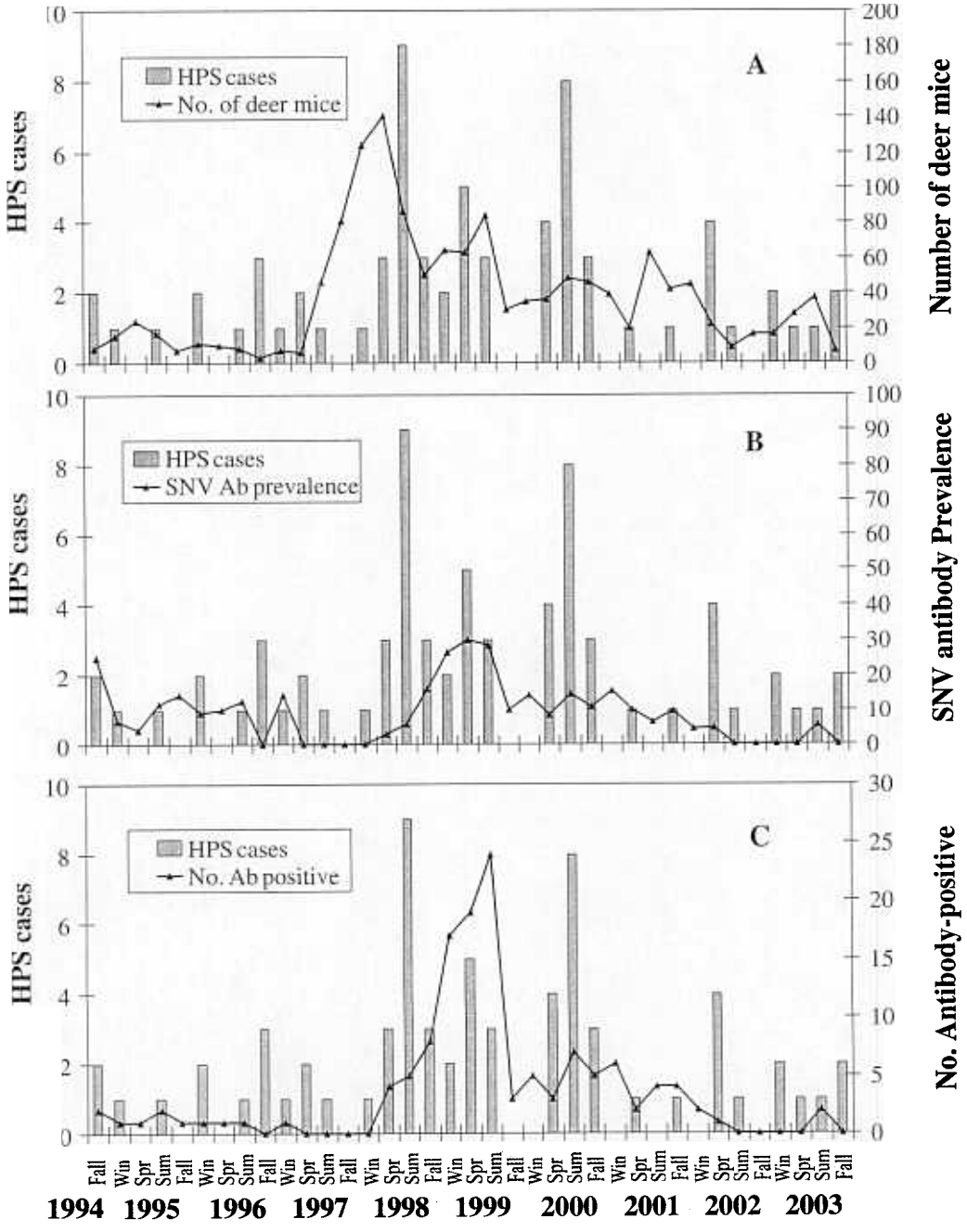

Fig. 1. Quarterly numbers of cases of hantavirus pulmonary syndrome (bars) compared with statistics describing host (deer mouse) populations at two long-term, mark-recapture sites in northwestern New Mexico, 1994–2003: (**A**) absolute numbers of deer mice captured, (**B**) prevalence of antibody to Sin Nombre virus in deer mouse populations, (**C**) absolute numbers of antibody-positive deer mice captured. After Yates et al. [41]

(PCMS) is a scrub grassland site with a different climatic regime from northwestern New Mexico. Spring and summer at PCMS have relatively high rainfall (50-yr means = 108 and 115 mm, respectively), while fall and winter are dry (means = 39 and 34 mm, respectively). Temperature patterns show a warm spring and summer (mean maximums = 27 and 32 °C; mean minimums = 7 and 13 °C) and a cold fall and winter (mean maximum = 15 and 12 °C; mean minimum = −4 and −7 °C). Thus the autumn and winter are cold and dry while spring and summer are warm and rainy. Deer mouse population dynamics at PCMS showed strong seasonal variation (Fig. 2A). There was a nadir in summer; populations increased in fall to a winter peak as the young of the year entered the trappable population, then declined again in spring to a summer trough. There were two exceptions to this pattern. In the fall of 1997 when the population should have begun to increase, it abruptly crashed. This crash coincided with a cold autumn, when rainfall was >300% of the normal value. The population recovered to resume its normal cycle

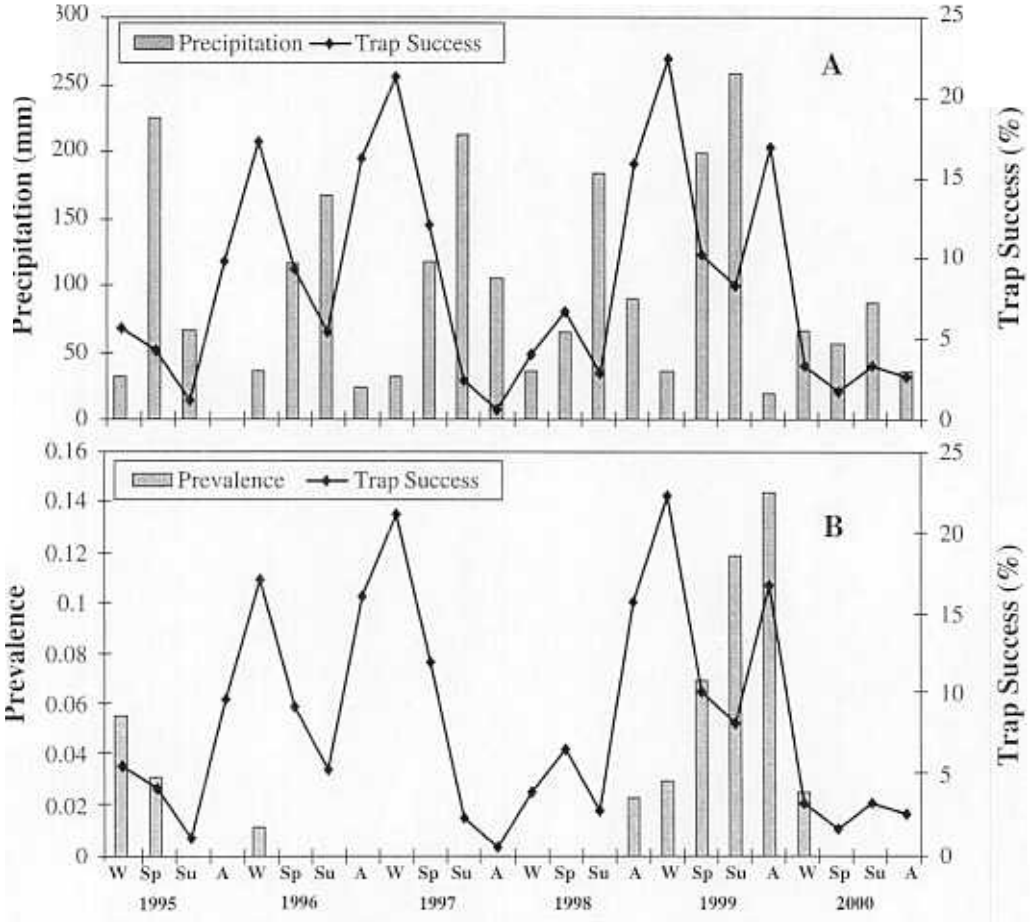

Fig. 2. Population dynamics of deer mice compared with (A) quarterly cumulative precipitation and (B) prevalence of antibody to Sin Nombre virus at a mark recapture site in southeastern Colorado. After Calisher et al. [3, 4]

in 1998 and into 1999, but the population abruptly crashed again in the winter of 2000, coincident with rainfall that was 150% of normal. The population showed no sign of recovery the following fall, following an extreme drought in spring and summer when rainfall was only 40% of normal. Thus, in the summer, *low* rainfall was associated with a negative effect on deer mice and, in the winter, *high* rainfall had a negative effect.

These host population dynamics appeared to have a great effect on the prevalence of SNV (Fig. 2B). Virus that was present at moderate prevalence disappeared from the population coincident with the drought and population nadir in summer 1995, was still absent during the population crash of 1997, but had recovered by 1999. The virus again appeared to become locally extinct following the population crash in winter 2000.

An important lesson from these observations is that regulators cannot be viewed independently. The effect of one important environmental regulator (rainfall) may vary, and even reverse direction, depending upon the season and upon its interaction with other environmental factors, such as temperature.

Anthropogenic regulators

Anthropogenic disturbance can result in dramatic changes in environmental conditions to which populations must adapt, move on, or die out. Certain opportunistic, more generalist, species may thrive under such disturbed conditions while more specialist, sylvatic species cannot survive. Thus the composition of rodent assemblages changes, usually becoming relatively species depauperate, restricted to a few opportunistic species whose population densities may increase dramatically under release from competitive pressures. This has been shown repeatedly, in relation to agriculture, ranching, and deforestation [7, 12, 27, 36, 37]. How might such disturbance affect viral infection in rodent hosts and subsequent risk to humans?

Kuenzi et al. [26] have been studying deer mouse population dynamics in sylvan and peridomestic habitats since 1996. They found several differences in populations inhabiting disturbed peridomestic situations as compared to those in more natural sylvan sites (Table 2). For example, the breeding season was about 2 months longer in peridomestic sites, and the prevalence of infection with SNV was 50% greater in deer mouse populations in peridomestic sites. Most

Table 2. Characteristics of deer mouse populations: Montana, 1996–1999, after Kuenzi et al. [26]

	Peridomestic	Sylvan
Mean breeding season (months)	~8.5	~6.5
Mean antibody prevalence	24.5% (490/2003)	16.5%* (302/1845)

*$p < 0.0001$ Chi square with Yates correction

human exposures to SNV occur in the peridomestic environment (Centers for Disease Control and Prevention, unpublished data). Thus anthropogenic disturbance can be a regulator of hantavirus infection in hosts, and subsequent risk to humans.

Decreasing natural biodiversity (usually brought about through anthropogenic disturbance) has been hypothesized to result in increasing risk for various diseases in human populations. This concept has been frequently cited in the popular press, and there has been some treatment of the hypothesis in the scientific literature [19]. Nevertheless, such treatments have remained largely theoretical, because few data are available for testing hypotheses. Using Lyme disease as a model system, Ostfeld and others [33, 34, 38] developed a general theoretical model for vector-borne diseases (the dilution effect hypothesis). The basic theory is that vertebrate communities with high species diversity will contain a greater proportion of incompetent reservoir hosts that deflect feeding vectors away from the most competent reservoirs, thereby reducing both infection prevalence in the vector and human disease risk [33].

Hantaviruses are frequently transmitted by aggressive encounters between individual rodents [18, 31]. Because most rodent species are dead-end hosts for hantaviruses, we hypothesized that hantaviruses might be transmitted more efficiently in rodent communities of lower diversity. We tested this hypothesis by relating the average antibody prevalence in the dominant hantavirus reservoir species to the average diversity indices at our longitudinal study sites in the southwestern United States. The Simpson's diversity index calculated for the rodent assemblage at each site explained 86% of the variation in hantavirus antibody prevalence (Fig. 3). This analysis provides evidence that simplification of ecosystems may result in increased transmission of some directly transmitted rodent-borne viruses.

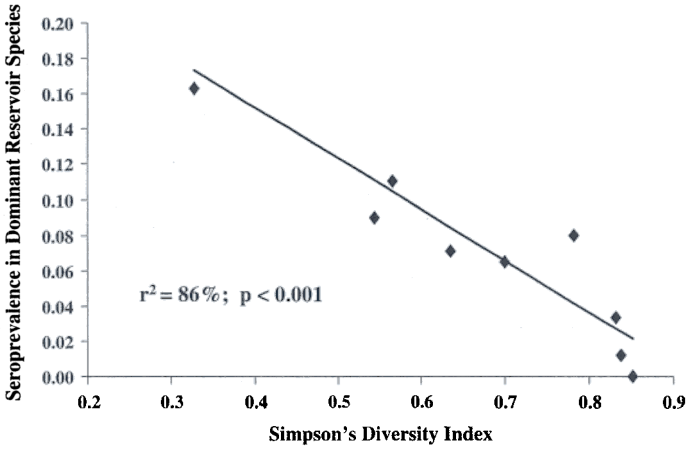

Fig. 3. Prevalence of antibody reactive with Sin Nombre virus in the principal host species compared with diversity of the small mammal assemblage at 10 mark-recapture sites in the southwestern United States. 1994–2000

Genetic regulators

The susceptibility and response of a reservoir host to infection with a zoonotic agent is largely determined by genetics [10]. Perhaps the most fundamental example of this is the coevolved pattern of asymptomatic, chronic infection and long-term viral shedding characteristic of hantavirus-host systems. This close co-adaptation is highly specific, in some cases even to the level of subspecies. The cotton rat (*Sigmodon hispidus*) has been divided into 12 geographically restricted subspecies in North America [20]. Black Creek Canal hantavirus is found only in association with *S. h. spadycipygus*, which is restricted to extreme southern Florida. Muleshoe hantavirus appears to be associated with *S. h. texianus* which occurs in eastern and central Texas, Oklahoma, and Kansas. Laguna Negra hantavirus is found only in association with populations of *Calomys laucha* in Paraguay, Bolivia, and N. Argentina [21, 35, 40]. A disjunct population of the same species in central Argentina appears to be free of infection with Laguna Negra virus (J. Mills, S. Levis, unpublished data). The experiments have not been done to determine whether this situation is a historical accident or due to genetic differences in susceptibility among populations of *C. laucha* [28]. In one case however, genetic differences within the same geographic population of a host seem to determine response to infection with an arenavirus. Based on results of laboratory inoculations, Johnson [22] proposed a model of Machupo virus infection in its host, *Calomys* sp. Laboratory studies indicated that Machupo virus was transmitted venereally among adult mice; and that newly infected dams gave birth to chronically infected pups. For adults however, there was a genetically controlled, split response to infection. Type B individuals cleared infection and had normal litters; type A's became chronically infected and females were effectively sterile. The varying interactions of the virus with these two genotypes were hypothesized to result in a cycling of host populations and to consequently varying risk to humans.

Mammalogists often classify small mammals into two categories based on life-history patterns [17]. Mammals representing generalist, opportunistic species are relatively common, highly fecund, rapidly maturing, highly mobile, and they are habitat and dietary generalists. These species often take advantage of disturbed conditions, reproducing to very high densities in a short period of time. These species are generally favored by disturbed, low-diversity conditions which they quickly colonize and in which they may reach high densities while conditions are favorable. On the other hand, specialist species are less fecund and relatively slow growing, making a larger investment in parental care. They usually require a specific and relatively narrow range of stable environmental conditions and food resources, are found in conditions of high diversity, and usually disappear following anthropogenic disturbances. Opportunistic, anthrophilic species make up a relatively small proportion of the 1000+ recognized species of Murid rodents [39]. Yet, a large percentage of reservoir hosts for rodent-borne viruses are what would be considered opportunistic species. Of 32 recognized hantavirus and arenavirus hosts, 18 were considered opportunistic, 10 were not, and 4 were

not categorized because of insufficient data (J. Mills and D. Carroll, personal experience). There are two possible explanations for this pattern. It is possible that sylvatic species may harbor an equal number of zoonotic viruses but we may have selectively recognized those viruses associated with opportunistic, peridomestic species because those are the species most likely to come into contact with humans and to be associated with human disease. On the other hand, it is possible that there is something different about the (genetically determined) life history of opportunistic species that makes them more likely to have evolved and maintained relationships with zoonotic viruses (e.g., their relatively greater aggressiveness, high fecundity, or propensity to achieve very high population densities).

Behavioral factors

Certain specific behaviors have been shown to be associated with the transmission of hantaviruses and arenaviruses within host populations. Venereal transmission, which has been suggested for Machupo virus [22], implies a certain seasonality (assuming that breeding in host populations is seasonal) and thus predictable variation in risk for human populations. Transmission of some other arenaviruses (e.g., Junín virus) and hantaviruses in host populations seems to be associated with a different behavioral mechanism. Antibody in host populations is more common in males than in females, and is more common in larger, older animals [1, 5, 14, 29], implying horizontal transmission by a mechanism that favors males. Field studies have provided data that may identify that specific mechanism. Mammalogists frequently use the presence of scars as indicators of aggressive interactions among individuals. Field studies have shown that males more frequently have scars than do females and antibody-positive males are much more likely to have scars than are antibody negative males [14, 29]. This suggests that a frequent mechanism of transmission of these viruses in host populations is by fighting and inflicting bite wounds.

As might be expected from the hypothesized route of transmission, seroconversions to hantaviruses occur during the breeding season in many areas. In Arizona male brush mice seroconvert to Limestone Canyon virus throughout the breeding season, but only rarely in winter [1]. In high-altitude areas in Colorado, there is a second peak in seroconversions during mid winter [5]. This suggests a second behavioral mechanism of transmission, perhaps associated with communal nesting and mutual grooming during cold weather. An understanding of these different mechanisms of transmission is important if we are to develop accurate models of virus transmission and human risk.

A second behavioral characteristic that has important implications for human risk is habitat selection, which can be viewed on a regional scale, or on a micro (local) scale. On a regional scale, we found that deer mice were found in every major biome represented in the southwestern United States, from desert to alpine tundra. Furthermore, at least some deer mice infected with SNV were found in all of these habitat types. Nevertheless, the relative density of deer mice and especially the relative density of antibody-positive deer mice varied widely among

habitat types. The lowest densities and prevalences were found in the altitudinal and climatic extremes (desert and alpine tundra) and the highest densities and prevalences were found in the middle altitude habitats, such as pinyon-juniper woodland and great basin scrub [30]. Although I have placed this example in the behavioral category, much of the pattern may also be due to physiological tolerances. Regardless, knowledge of these differences allows a more accurate prediction of risk to humans living or traveling in various habitat types.

On a micro scale, habitat selection can be an important determinant of viral transmission among rodent hosts and from rodent hosts to humans. I have discussed the propensity of some rodents (such as deer mice) for peridomestic habitats, where they are more frequently antibody-positive than they are in sylvan habitats. Argentine hemorrhagic fever (AHF), caused by Junín virus, is associated with farming activities in rural Argentina. Descriptions of the epidemiology of AHF have stated that farmers are infected while working in crop fields [6]. However, during a three-year longitudinal study, we found that the reservoir for Junín virus, *Calomys musculinus*, was largely restricted to the more stable weedy roadsides and fencerows between crop fields. Its congener, *C. laucha* was frequently found in crop fields [29]. This pattern of habitat partitioning between the two closely related species may be very important epidemiologically. It may help explain lack of infection with Junín virus in *C. laucha*, it suggests a specific high-risk habitat for contracting AHF, and it suggests a potential mitigation practice – cutting or burning the weeds along the roadsides and fence lines that separate crop fields.

Physiological regulators

As mentioned above, infections with many hantaviruses and some arenaviruses are more frequent in male mice, and seroconversions are generally more frequent in the breeding season. Transmission of virus within host populations is also greater under more crowded conditions [16, 29, 31]. As explained above, these characteristics are due, at least in part, to behavioral factors. On the other hand, evidence is accumulating that physiological mechanisms might also contribute to this pattern of infection. Stress, associated with crowding, has been associated with immunosuppression in many animals, including some hantavirus host species (*Microtus*, *Rattus*, *Clethrionomys glareolus*) [11, 13, 24]. Increases in sex hormones, especially testosterone and corticosterone, have been clearly associated with immunosuppression in several species [2, 42]. Finally, the balance between type A and type B response to infection with Machupo virus was dose dependent [22]. It stands to reason, therefore, that the frequency of transmission and infection also might vary according to the degree of immunosuppression of the host.

Above, I suggested that the correlation between scars and infection status in hantavirus and arenavirus host rodents means that aggression leads to infection. Recent evidence suggests, however, that the cause and effect relationship between aggression and infection may not be as simple as it appears. Klein et al. [23] showed

that male rats in the chronic stage of infection with Seoul virus were more likely to attack intruders and they spent more time fighting with them than did uninfected males. Furthermore, aggressive males had more virus in tissues (including testes and adrenal glands) than did less aggressive males.

Many other physiological factors may be related to viral infection, viral shedding, and viral persistence. These include those related to social interactions, nutrition, environmental conditions (e.g., temperature and rainfall), intake of plant secondary chemicals, and even the pH or presence of protein in the urine (which may be influenced by diet). Our knowledge of these potential relationships is scant.

In summary, regulators of viral infection in natural hosts are numerous. Most of these regulators have been inadequately studied and remain poorly understood. These regulators do not act independently; their total effect varies according to their interactions with other regulators. Nevertheless continued research and improved understanding of these regulators is important. The better we understand these regulators, the better we will be able to predict changes in disease risk to human populations, develop effective intervention programs, and appropriately and most efficiently target these intervention efforts.

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