The Ecology and Evolutionary History of an Emergent Disease: Hantavirus Pulmonary Syndrome

TERRY L. YATES, JAMES N. MILLS, CHERYL A. PARMENTER, THOMAS G. KSIAZEK,
ROBERT R. PARMENTER, JOHN R. VANDE CASTLE, CHARLES H. CALISHER, STUART T. NICHOL,
KENNETH D. ABBOTT, JONI C. YOUNG, MICHAEL L. MORRISON, BARRY J. BEATY, JONATHAN L. DUNNUM,
ROBERT J. BAKER, JORGE SALAZAR-BRAVO, AND CLARENCE J. PETERS

In the spring of 1993, a previously undescribed disease emerged in the Southwest, killing 10 people during an 8-week period in May and June. Early during an infection, victims experienced flu-like symptoms for several days, but their condition suddenly and rapidly deteriorated as their lungs filled with fluids; death usually occurred within hours of the onset of this crisis period. There was no cure, no successful medication or treatment, and the disease agent (virus, bacterium, or toxin) was completely unknown. For the first few weeks, the mortality rate was 70%.

Researchers from many disciplines immediately focused on the outbreak, attempting to identify the agent and understand the causes and dynamics of the disease. Within weeks, scientists at the Centers for Disease Control and Prevention (CDC) identified the agent as a previously unknown hantavirus (Bunyaviridae), subsequently named Sin Nombre virus, or SNV (Nichol et al. 1993). Because hantaviruses were known to be transmitted by rodents, investigators undertook an intensive small mammal field sampling campaign in the Four Corners region of New Mexico and Arizona. Shortly thereafter, CDC identified the viral reservoir host as a common and widely distributed rodent, the deer mouse, *Peromyscus maniculatus* (figure 1; Childs et al. 1994). During the identification period, on the medical side, physicians and medical staff made rapid progress in developing treatment methods to stabilize and sustain patients through the crisis period, thereby substantially improving patient survivorship; nonetheless, the mortality rate fell only to about 40%, where it remains today.

The emergence of this new disease prompted many questions about its history, causes, and dynamics. Was this a newly

EVIDENCE FROM TWO EL NIÑO EPISODES IN THE AMERICAN SOUTHWEST SUGGESTS THAT EL NIÑO–DRIVEN PRECIPITATION, THE INITIAL CATALYST OF A TROPHIC CASCADE THAT RESULTS IN A DELAYED DENSITY-DEPENDENT RODENT RESPONSE, IS SUFFICIENT TO PREDICT HEIGHTENED RISK FOR HUMAN CONTRACTION OF HANTAVIRUS PULMONARY SYNDROME

Terry L. Yates (e-mail: tyates@unm.edu) is a professor in the Departments of Biology and Pathology at the University of New Mexico, Albuquerque, NM 87131. Cheryl A. Parmenter, Robert R. Parmenter, John R. Vande Castle, Jorge Salazar-Bravo, and Jonathan L. Dunnum are with the Department of Biology and the Museum of Southwestern Biology, University of New Mexico. James N. Mills, Thomas G. Ksiazek, Stuart T. Nichol, and Joni C. Young are with the Centers for Disease Control and Prevention, Atlanta, GA 30333. Charles H. Calisher and Barry J. Beaty are with the Arthropod-borne and Infectious Diseases Laboratory, Foothills Campus, Colorado State University, Fort Collins, CO 80523. Kenneth D. Abbott is with the Department of Biology, Yavapai College, Prescott, AZ 86301. Michael L. Morrison is with the Department of Wildlife and Fisheries Sciences, University of Arizona, Tuscon, AZ 85721. Robert J. Baker is with the Department of Biology and The Museum, Texas Tech University, Lubbock, TX 79409. Clarence J. Peters is with the Department of Pathology, University of Texas Medical Branch, Galveston, TX 77555. © 2002 American Institute of Biological Sciences.

Figure 1. Rodent reservoir of Sin Nombre virus, the deer mouse (Peromyscus maniculatus). *The virus is shed in rodent feces, urine, and saliva and is believed to be transmitted to humans via inhalation of an aerosolized mixture of virus, feces, and dried urine particles. Photograph: Linda Broome.*

evolved virus or one that had been present, but undetected, before 1993? If the latter, why was there an epidemic in 1993? Why did the outbreak occur in the Southwest? Could the outbreak have been the result of an accidental release of a military biowarfare agent, as suggested in a *Scientific American* news report (Horgan 1993), or even a deliberate bioterrorist attack? If the outbreak was a natural phenomenon, what factors contributed to its onset, and could future outbreaks be predicted to allow preemptive public health warnings? Were there other related, though undiscovered, hantaviruses that cause human diseases in North America or other parts of the world?

While considerable progress has been made on many of these questions over these last 9 years, many details remain elusive. However, the insights acquired to date reveal a long evolutionary history between rodents and viruses, as well as a complex series of interactions among present-day climate phenomena, ecosystem processes, rodent population dynamics, and virus epidemiology.

The coevolution of Western Hemisphere rodents and hantaviruses

Hantaviruses are a group of negative-stranded RNA (ribonucleic acid) viruses, some of which are known to be highly pathogenic for humans. Before the 1993 outbreak in the United States, diseases caused by hantaviruses were thought to be largely restricted to Europe and Asia. The population biology, systematics, and natural history of the genus *Hantavirus* are poorly understood, with most of our knowledge of this species group restricted to those forms that cause medical problems for humans. These disease-causing species include such Old World species as Hantaan, Puumäla, Seoul, and Dobrava viruses (Lee et al. 1978, Brummer-

Korvenkontio et al. 1980, Lee et al. 1982, Avsiv-Zupanc et al. 1992). All of these viruses are associated with European and Asian species of rodents in the family Muridae (see box 1), and each causes hemorrhagic fever with renal syndrome.

Since the discovery of SNV, some 25 additional hantaviruses have been described from the New World (figure 2; Schmaljohn and Hjelle 1997, Peters et al. 1999). In the United States, cases of hantavirus pulmonary syndrome (HPS), the human disease caused by hantavirus infection, have been attributed to newly recognized hantaviruses in Florida, New York, Louisiana, and Texas (Peters et al. 1999), and other hantaviruses not known to cause human disease have been associated with other sigmodontine and arvicoline hosts, including the harvest mouse *Reithrodontomys megalotis* (Hjelle et al. 1995); the brush mouse *P. boylii* (Sanchez et al. 2001); and three species of meadow mice (voles) *Microtus ochrogaster* (Schmaljohn and Hjelle 1997), *M. californicus* (Song et al. 1995), and *M. montanus* (Rowe et al. 1995). Fourteen newly recognized hantaviruses, many of which are pathogenic in humans (Peters et al. 1999), have been detected in countries throughout Central and South America. These data suggest that as yet unknown hantaviruses are most likely present in other murid rodent hosts in North and South America and elsewhere in the world, especially in poorly studied regions of Africa and Asia.

Recent comparisons of published phylogenies of viruses of the genus *Hantavirus* with phylogenies of murid rodents reveal a high degree of concordance between hantavirus and rodent trees, which suggests a long coevolutionary history (figure 3; Nichol 2000, Plyusnin and Morzunov 2001). Such an association is the basis for the prediction that most, if not all, major murid lineages will have a closely associated han-

Figure 2. New World species of hantavirus. Those listed in red are known human pathogens.

Box 1. The current status of Muroid rodents nomenclature.

Taxonomic levels assigned to the various extant groups of muroid rodents have fluctuated historically from those in Alston (1876) to those in Musser and Carleton (1993). For the sake of simplicity, we adhere to the conclusion expressed by Musser and Carleton, because their classification becomes a heuristic tool for future reference. Even a meager understanding of the phylogenetic relationships among muroid rodents is just emerging. We have included the elements of the muroid classification of Simpson (1945) and contrasted them with the classifications of Musser and Carleton (1993). The extinct tribe Copemyine (figure 4) comprised the earliest relatives of the present-day sigmodontine murid rodents in North and South America.

Simpson (1945)	Musser and Carleton (1993)	Common name, muroid rodents
Super family Muroidea	Family Muridae	
Cricetidae	Subfamily Cricetinae	Hamsters
	Subfamily Calomyscinae	Mouse-like hamsters
	Subfamily Mystromyinae	White-tailed mouse
	Subfamily Sigmodontinae	New World rats and mice
	Subfamily Myospalacinae	Zokors
	Subfamily Nesomyinae	Malagasy rats and mice
	Subfamily Lophiomyinae	Crested rat
	Subfamily Arvicolinae	Voles, lemmings, and muskrats
	Subfamily Gerbillinae	Gerbils, jirds, and sand rats
Muridae	Subfamily Murinae	Old World rats and mice
	Subfamily Dendromurinae	African climbing mice, gerbil mice, fat mice, and forest mice
	Subfamily Petromyscinae	Rock mice, climbing swamp mouse
	Subfamily Cricetomyinae	Pouched rats and mice
	Subfamily Otomyinae	Vlei rats, karoo rats, and whistling rats
Spalacidae	Subfamily Spalacinae	Blind mole rats
Placanthomyidae	Subfamily Platacan thomyinae	Malabar spiny mouse and blind tree mouse
Rhizomyidae	Subfamily Rhizomyinae	Bamboo rats and African mole rats

Note: The majority of common names are from Carleton and Musser (1984) or Simpson (1945).

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tavirus lineage. Given our recent experience with known hantaviruses, many of these yet to be discovered viruses may be human pathogens.

From these data, we further suggest that the New World hantaviruses all had an Asian origin (figure 4), most likely arriving in North America sometime in the early Miocene with their Copemyine rodent hosts (a now extinct tribe of the early murid rodents; Baskin 1989). If this hypothesis is correct, early North American hantaviruses radiated with their rodent reservoirs throughout North America, many into the rapidly expanding grasslands of that period. Entrance into South America would have been 7–9 million years ago via the Panamanian Archipelago or land bridge. Some species, such as the Bayou virus and the Black Creek Canal virus, may have reinvaded North America from the south at a later date with their hosts, the rice rat (*Oryzomys* spp.) and cotton rat (*Sigmodon* spp.). Hypothesized dispersal and differentiation patterns are shown in figure 4. If these relationships are correct, an extensive complex of hantaviruses has been present in the Western Hemisphere for millions of years; thus, SNV could not be a newly introduced virus in the southwestern United States.

Sin Nombre virus and hantavirus pulmonary syndrome—a newly evolved human disease?

The close evolutionary association among these hantaviruses and their rodent reservoirs and the known natural-history tendencies of these rodents to exploit grasslands and human-generated disturbances are not sufficient to explain the 1993 outbreak, nor to definitively establish the presence of SNV in North America before that year. To determine whether SNV was historically present in this region before 1993, we first tested blood from 740 cryogenically preserved *P. maniculatus* samples collected before 1993 and archived in two university research collections: the Museum of Southwestern Biology at the University of New Mexico and The Museum at Texas Tech University. Ninety-nine (13.4%) of the tested samples (dating back to 1979), from locations distributed widely throughout North America, were found to have polyclonal antibodies reactive with SNV. Amplification of genomic RNA from frozen, archived *P. maniculatus* heart and lung tissues by reverse transcriptase polymerase chain reaction and sequencing of selected individuals confirmed that these earlier samples contained SNV.
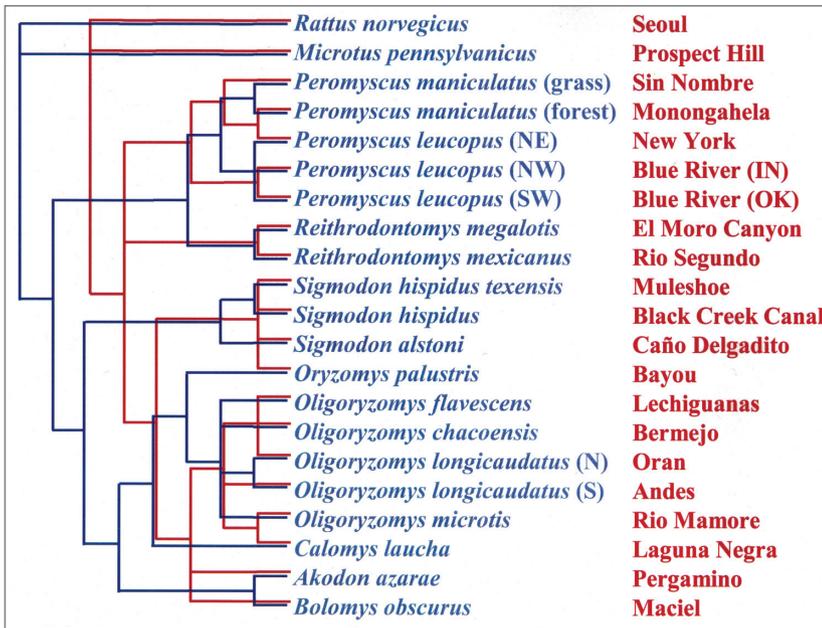
Figure 3. Phylogenetic relationships of hantaviruses (red) compared with their rodent hosts (blue). Virus phylogenies are based primarily on the M-segment genome but include some S-segment data as well. The rodent phylogeny is based on cytochrome b mitochondrial DNA sequence. The virus phylogeny was obtained from Plyusnin and Morzunov (2001) and citations therein. The rodent phylogeny was obtained from Smith and Patton (1999).

In addition, we conducted a retrospective analysis for SNV infections in cryogenically preserved tissues (blood from the heart muscle) of rodents collected on the Sevilleta Long Term Ecological Research (LTER) site in central New Mexico from 1989 to 1993. These analyses revealed that SNV was present at only one small area in the Sevilleta LTER site in 1989 but had spread across the 100,000 hectares (ha) of the Sevilleta National Wildlife Refuge (NWR) to rodents in all adjacent habitats by the fall of 1991. Finally, reexamination of numerous archived human medical records dating back to the 1970s, coupled with testing of preserved tissues from hospital patients who had exhibited symptoms similar to HPS, resulted in several confirmed cases of HPS (Zaki et al. 1996). Hence, the large number of cases of HPS that occurred in 1993 did not appear to involve a new viral genotype, only one that was merely first identified in that year.

The cause of the 1993 HPS outbreak—an ecological hypothesis

Even before it was known that SNV had probably existed in the Southwest for millennia and that genetically indistinguishable strains of SNV had been associated with HPS cases before 1993, researchers were investigating the origins of the 1993 outbreak. Because HPS was a rodent-borne disease, one of the first avenues of investigation was to determine the status of regional rodent reservoir populations. If rodent populations were at high densities in the vicinity of HPS cases (in New Mexico and Arizona), and if substantial proportions of these rodent populations were infected with SNV, then basic epidemiological theory would suggest an increased HPS caseload because of the increased probability of contagion events (rodent–human contacts).

Field research teams from the University of New Mexico's Museum of Southwestern Biology, the New Mexico Department of Health, and the CDC began sampling the composition and abundance of rodent assemblages in and around houses and workplaces of HPS patients (the most likely locations for HPS infection) and in nearby similar "control" houses and workplaces where no HPS infections had been reported. The data from these studies indicated that on average, 30% of the rodents in all locations were infected with SNV, but that the rodent capture success rate (expressed as a proportion of the numbers of captured rodents to the numbers of traps set) was significantly higher in HPS case locations (17.3%) than in control locations (8.3% to 12.7%) (Childs et al. 1995). These results indicated that the presence of greater numbers of infected rodents in human dwellings was associated with increased risk of human hantavirus infection.

Figure 4. Hypothesized routes of dispersal for New World rodents of the family Muridae. Arrows pointing to diamonds indicate the approximate geographic location of the first fossil for the indicated extinct genera (⚥), Copemys and Abelmoschomys, and the oldest fossil of the extant genus Auliscomys (Sigmodontinae). Estimates of geological age of fossils are presented as millions of years ago (mya). Other arrows indicate hypothesized routes of dispersal, with times estimated as mya.

But were the regional rodent population sizes in the spring of 1993 any different from previous years' populations? That is, what was different about 1993 compared with other years, when no HPS outbreak was observed? To explore the possibility that ecological or other environmental factors might have been responsible for the outbreak, researchers at the Sevilleta LTER site in New Mexico joined the investigation in June 1993. Although no long-term ecological studies of rodents were being conducted in the Four Corners region of New Mexico or Arizona, such studies were under way at two sites that geographically bracketed the HPS outbreak region: the Sevilleta National Wildlife Refuge in central New Mexico and Canyonlands National Park in southeastern Utah.

The Sevilleta LTER rodent studies, begun in 1989, indicated that several species of *Peromyscus* had undergone large density increases (3- to 20-fold) between 1992 and 1993; these increases had been observed in all habitat types on the Sevilleta NWR (which is composed of grasslands, desert scrublands, juniper savannas, and piñon–juniper woodlands; see *http://sevilleta. unm.edu* for 1989–2001 data). The hypothesized cause of this *Peromyscus* population explosion was a trophic cascade, initiated by the El Niño of 1992 (Parmenter et al. 1993). In New Mexico, the El Niño–Southern Oscillation (ENSO) phenomenon causes increased precipitation during fall, winter, and spring. Data from the National Oceanic and Atmospheric Administration have shown that fall–spring precipitation (September through May) in this region responds to extremes in the ENSO phenomenon, with warm phase episodes (El Niño events) and cold phase episodes (La Niña events) producing wet and dry cycles during the fall–spring periods, respectively (Molles and Dahm 1990, Swetnam and Betancourt 1990, Redmond and Koch 1991, Molles et al. 1992). Fall–spring precipitation in this region increased by 55% in El Niño years and decreased by 50% in La Niña years, when compared with years when neither extreme prevailed, over the past 80 years. Summer "monsoon" precipitation in this region is generally not influenced by ENSO. The additional El Niño fall–spring precipitation, which recharges soil moisture and promotes enhanced spring primary production, would have increased food resources for rodents (e.g., forb and grass seeds, nuts, acorns, berries, green vegetation, and arthropods) and would lead eventually to increased rodent population sizes—that is, a "trophic cascade."

The trophic cascade hypothesis was formulated using the limited Sevilleta LTER data from 1989 to 1993 (Parmenter et al. 1993), although subsequent years of field studies have contributed additional data to the analyses (figure 5). In the grasslands of the Sevilleta NWR, fall–spring precipitation amounts were positively correlated with primary produc-
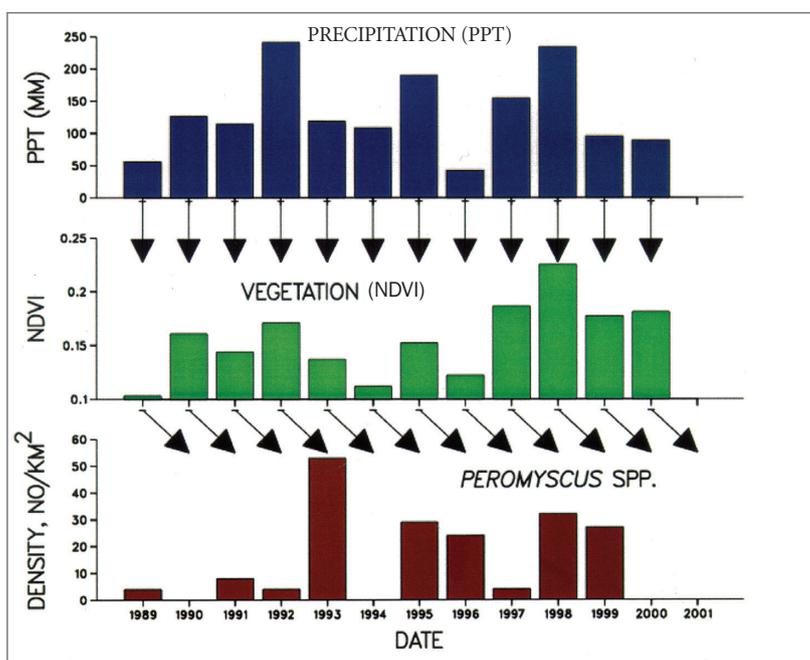

Figure 5. Sevilleta Long Term Ecological Research (LTER) data for fall–spring precipitation (September through May), spring maximum vegetation productivity (normalized difference vegetation indices [NDVI] from AVHRR [Advanced Very High Resolution Radiometer] satellite imagery), and spring Peromyscus *spp. densities (number per square kilometer [km²]) from the McKenzie Flats grasslands of the Sevilleta National Wildlife Refuge, New Mexico. Note the close correspondence of pattern dynamics between the temporal increases and decreases of precipitation and NDVI values.* Peromyscus *densities also display a significant 1-year lag relationship with precipitation.*

tion, as measured using normalized difference vegetation indices (NDVI) from AVHRR (Advanced Very High Resolution Radiometer) satellite imagery ($r = 0.651$, $df = 10$, $p < .025$). These precipitation amounts also were significantly correlated with springtime *Peromyscus* densities 1 year later ($r = 0.797$, $df = 9$, $p < .01$; figure 5). This 1-year lag period allowed the rodents to undergo several reproduction cycles, thereby increasing their population densities up to the observed maximum levels. Thus, the Sevilleta NWR *Peromyscus* population increase in 1993 appeared to be in concordance with the trophic cascade hypothesis.

The next step was to apply the trophic cascade hypothesis to the precipitation and *P. maniculatus* data from Canyonlands National Park, northwest of the HPS outbreak area. An analysis of the precipitation data from Moab, Utah, showed that the 1992 El Niño had no effect on precipitation amounts relative to previous years; the 1991–1992 period was at or below the long-term precipitation average. Deer mouse density data from 1992–1993 also showed no significant response; densities remained virtually unchanged (mean ± SE [standard error]: 1992 density = 2.6 mice ± 0.7 per ha, 1993 density = 2.4 mice ± 0.6 per ha, $n = 4$ trapping sites; Parmenter et al. 1993). Concomitantly, there were no human HPS cases in Utah during 1993.
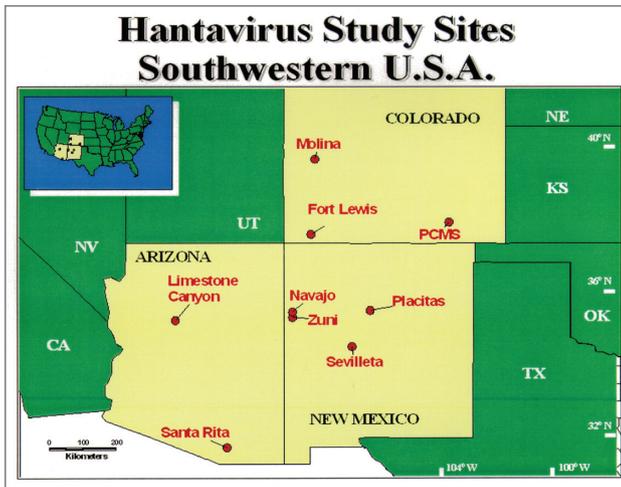
Figure 6. Longitudinal study site locations for rodents and hantavirus in the southwestern United States.

The limited data from both the Sevilleta NWR and Canyonlands National Park were consistent with predictions of the trophic cascade hypothesis: In areas where the 1992 El Niño enhanced precipitation, *Peromyscus* densities increased following a 1-year lag period, while in areas without enhanced precipitation, densities remained essentially unchanged. The precipitation record for the 1989–1993 period in the Four Corners area of New Mexico (Shiprock, NM) was then examined, and precipitation amounts were found to have been greatly enhanced by the 1992 El Niño (Parmenter et al. 1993). Although no long-term rodent data were available within the HPS outbreak area proper, the presence of unusually high precipitation amounts in 1992 may have led to increases in rodent densities in the Four Corners area (as it did in the Sevilleta NWR areas). Higher rodent densities would have facilitated greater SNV infection rates among the reservoir species, thereby triggering the HPS outbreak as human–rodent contacts grew.

Finally, as often happens with rodent population explosions, the *Peromyscus* densities at the Sevilleta NWR and in other areas of New Mexico rapidly declined during the summer of 1993 and had returned to preoutbreak levels by autumn 1993 (Parmenter and Vigil 1993). New human HPS cases also declined precipitously during the summer of 1993, and with the exception of an occasional case, the 1993 HPS outbreak in the Four Corners was essentially over by August.

The 1997–1998 El Niño—a second test

Given the striking associations among the ENSO phenomena, plant productivity, and increased murid population densities, we hypothesized that risk of human infection with SNV was directly correlated with deer mouse population density, the latter in turn driven by plant primary productivity, which in the Southwest was positively associated with fall–spring precipitation. If it was true that El Niño periods resulted in increased precipitation in this region, then relative human risk of hantaviral infection should be predictable based on this cli-

matic variable and on increases in deer mouse population density.

To test these hypotheses, we began longitudinal studies of rodent communities at sites in New Mexico, Arizona, and Colorado (figure 6). The sites, which covered a range of southwestern habitats and latitudes, were chosen to provide accurate data on changes in rodent absolute density by species (Mills et al. 1999, Parmenter et al. 1999, Parmenter et al. 2003). Vegetation types included desert grassland at the Sevilleta (New Mexico) and the Santa Rita (Arizona) sites; piñon–juniper woodland at the Placitas, Navajo, and Zuni sites (New Mexico); high-desert scrub and piñon–juniper woodland at the Molina site (Colorado); short-grass prairie at the Piñon Canyon Maneuver Site (Colorado); and piñon–juniper and chaparral at the Limestone Canyon (Arizona) and Fort Lewis (Colorado) sites. Elevations ranged from 1800–2500 meters (m) and latitudes from 32º to 40º north. The New Mexico and Arizona sites were live-trapped monthly, while the Colorado sites were sampled at more irregular intervals because of heavy snow cover at some sites during much of the year. All small mammals were identified by species and sex, eartagged, weighed, measured, and examined for ectoparasites. Blood samples were taken the first time each rodent was captured during each trapping period. Blood samples were tested for antibodies to SNV, using enzyme-linked immunosorbent assays (ELISA; Feldmann et al. 1993).

During the study period, population densities and SNV antibody prevalence varied greatly through time and by geographic location (Mills et al. 1999). Populations began a rapid decline at all sites in 1994 and had reached extremely low levels by the La Niña spring of 1996 (e.g., the Zuni site shown in figure 7). The number of infected deer mice declined as well, with no infected rodents detected at four of the nine sites.

Deer mouse population densities at all sites seemed to stabilize at low densities throughout the La Niña period of early 1996. Deer mice disappeared completely from our Placitas, Sevilleta, and Navajo sites in New Mexico. The brush mouse, *P. boylii,* which was the most common small mammal at the Placitas site in 1994, disappeared for almost 2 years. Deer mouse densities at other sites (e.g., Zuni, NM) fell to only 1 to 3 animals per hectare, with an SNV antibody prevalence at or near zero. The Colorado sites maintained low populations of deer mice, with seroprevalence levels generally below 10%.

During the spring of 1997, New Mexico experienced an unusually wet period, although this was not attributable to the ENSO phenomenon. However, a second El Niño began to form in the 1997–1998 period, and precipitation again increased above long-term averages. As predicted by the trophic cascade hypothesis, murid rodent population densities began to increase at all sites, and by January 1998, deer mouse population densities had increased from an average of 1 per ha to almost 20 per ha at some locations (figure 7). Piñon mouse (*P. truei*) populations responded to the El Niño effect as well, reaching population densities as high as 30 per ha in north-

western New Mexico, for a combined density of deer mice and piñon mice in this region of almost 50 per ha. Vegetation "greenness" indices (AVHRR NDVIs) for our study area in western New Mexico reached a 10-year high in spring 1998, with the NDVI peaking at 0.32 and surpassing the 1992 El Niño spring NDVI of 0.28 (the mean ± SE of the spring NDVI for non–El Niño years [1989–1991, 1993–1996] was 0.261 ± 0.007). These data again suggested that the increase in rodent numbers was the result of an increase in plant primary productivity that was associated with the increased fall–spring precipitation.

Predicting the second hantavirus outbreak

Given that the 1994–1998 results were highly consistent with the predictions of our trophic cascade hypothesis, it followed that there would be a greater risk of HPS in the region, if risk to humans was directly correlated with higher rodent population density and increased virus prevalence. As a result, the combination of favorable environmental conditions and concomitant high densities of rodent populations shown by these studies prompted the CDC to issue public health warn-

ings of increased risk of HPS in the southwestern United States in the spring of 1998 (CDC 1998). As figure 7 illustrates, in 1998 there were more human infections with SNV in the Four Corners area of New Mexico and Arizona than there had been in the previous 3 years combined, but not as many as in 1993. The following spring, overall rodent densities were lower than they had been in the spring of 1998, yet surprisingly, the number of HPS cases was double that of the previous spring (CDC 1999). An examination of the serological data from rodents during this period (figure 7) revealed a possible explanation that added another time lag to the trophic cascade hypothesis. Although overall rodent density was much lower than it was during the previous spring, the density of SNV-infected rodents was an order of magnitude higher than at any other time during the study period. Thus, risk of human exposure to SNV was associated with two characteristics of rodent reservoir populations: population density and prevalence of SNV infection (CDC 1998).

Following the 1997 buildup of deer mouse densities, SNV antibodies were first detected in these populations in June 1998, and antibody prevalence began to increase rapidly in the fall and winter of that year (figure 7). Rodent populations re-
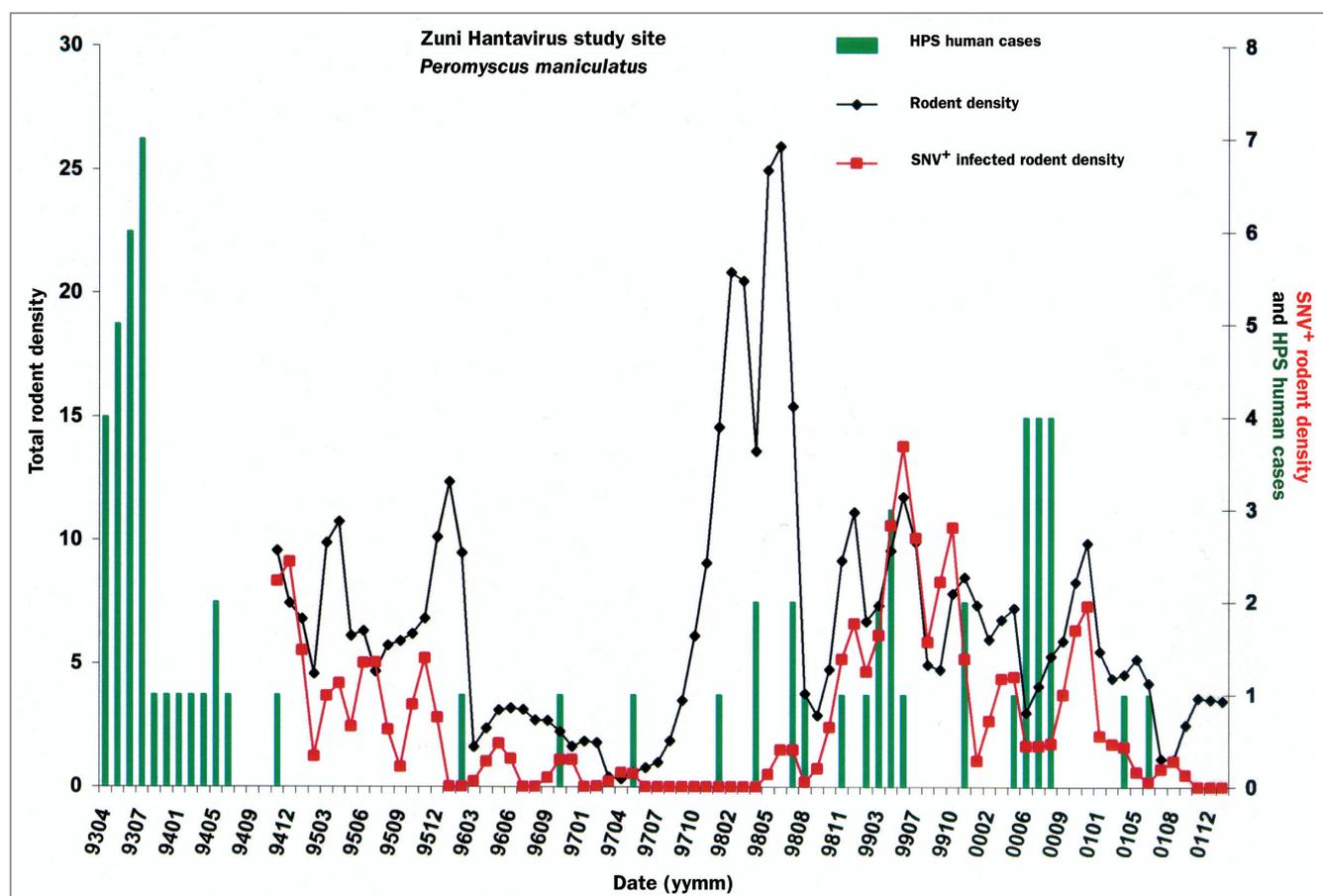

Figure 7. Mean densities of deer mice from two studies sites near Zuni, New Mexico (black line), and densities of deer mice infected with Sin Nombre virus (SNV) at the same localities (red line). Hantavirus pulmonary syndrome (HPS) cases (green histograms) are reported from the five counties surrounding Zuni in the Four Corners region (McKinley, Cibola, and San Juan Counties in New Mexico and Navajo and Apache Counties in Arizona). Rodent density values are 3-month running means of two replicate trapping sites.
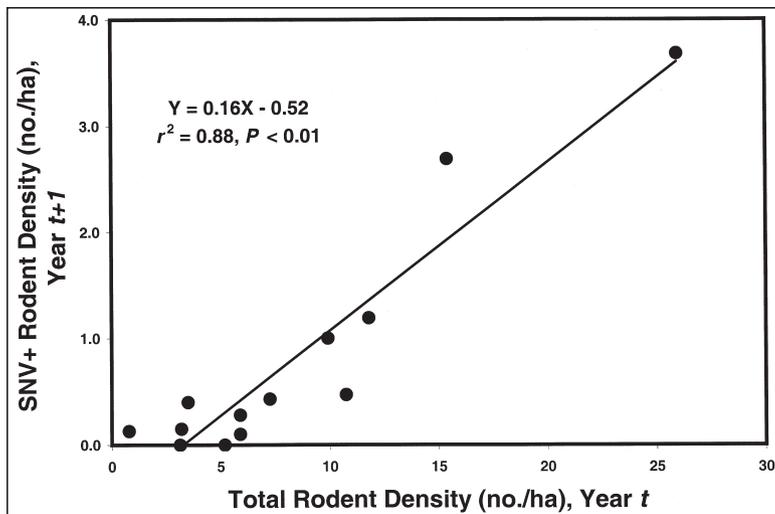
Figure 8. Densities of deer mice infected with Sin Nombre virus (SNV) at any given time are correlated with total deer mouse densities 1 year earlier. Data are from 1995 to 2002 at the Zuni site shown in figure 7. Values are the maximum total densities during spring (March–June) and summer (July–September) during a given year (t) correlated with the SNV-positive densities 1 year later (t+1).

gained some of their losses during the winter of late 1998 and early 1999, and the number of mice that were SNV positive continued to increase. The density of SNV antibody-positive deer mice at the Zuni site (and other sites) in New Mexico increased 10-fold by July 1999 (compared with the year before), despite a much lower total rodent population density. The increase in density of infected mice was paralleled by the highest numbers of HPS cases diagnosed since 1993 in this region. Despite the lower numbers of deer mice, cases of HPS continued to be reported during 1999 and by July, seven more cases had been confirmed in the five counties surrounding Zuni. Southwestern Colorado contributed two cases during this period as well.

The pattern observed for the 2000–2001 period was similar to the one observed for 1999–2000, and even more human cases were reported during 2000 than before. This pattern is consistent with the delayed density-dependent hypothesis of infection prevalence in hantavirus reservoir populations (Mills et al. 1999), which maintains that prevalence of infection in reservoir populations should be proportional to the population densities reached during the previous reproductive season. A correlation analysis between the maximum total deer mouse densities (spring and summer seasons) and the densities of SNV-positive deer mice 1 year later produced a highly significant relationship (figure 8). The addition of this delay results in the greatest disease risk to humans, in this case a full 2 to 3 years after the initial precipitation input into the ecosystem. Finally, in late 2001, rodent densities had declined to relatively low levels, SNV-infected rodent densities had dropped to near zero, and no new HPS cases had been reported.

Thus, the patterns we observed in both El Niños (1992–1993 and 1997–1998) with respect to the dynamics of precipitation, plant productivity, rodent densities, SNV prevalence, and HPS cases appeared consistent with the trophic cascade hypothesis. Additional corroboration of these patterns comes from a recent retrospective analysis of HPS cases in the Southwest that showed significant correlations between the temporal occurrences of HPS cases and antecedent El Niño precipitation conditions (Hjelle and Glass 2000).

Additional complexity in the ecology of hantavirus outbreaks

Prevalence of infection in rodent populations, therefore, is another step in the cascade, with SNV prevalence continuing to increase in the rodent population even as the population density decreases. Although it can be argued that for a horizontally transmitted virus (i.e., viral transmission moves from adult rodent to adult rodent, rather than from mother to offspring [vertical transmission]), higher levels of infection are to be expected as the population ages, it is also true that more infected individuals in the population provide greater risk of human infection. At the same time, and perhaps more important, a higher density of infected rodents provides a higher baseline of infection, which in turn can trigger an epizootic when the next population surge occurs. We believe it is this latter rodent population dynamic, a surge in a population with an existing high virus prevalence, that presents the greatest risk to humans, because not only is the density of infected rodents increasing rapidly, but also many additional individuals may be infected that have yet to seroconvert and thus are not detectable by immunoassays. It is probable that these mice are shedding maximum quantities of virus while dispersing into new habitats, and therefore pose the greatest risk to humans.

The actual prevalence of infection depends on many factors and may be roughly proportional to the population density of the previous year (Mills et al. 1999). At some of our sites, deer mice populations maintained a chronic low prevalence of infection even at very low densities, while at other sites the virus became locally extinct (Abbott et al. 1999, Calisher et al. 1999, Kuenzi et al. 1999, Parmenter et al. 1999). The latter populations presumably became infected because of immigration of infected young adults from adjacent populations, a condition enhanced by landscape-level increases in rodent population densities.

The mild winters and increased snowfall that are associated with El Niño events also improve adult survivorship throughout the winter, providing a higher density of both infected and uninfected rodents as a starting point in the next year (figure 7). The second and third years following an El Niño episode may pose as high a risk (or higher) to humans if there are more infected mice present. However, based on the Zuni data, it appears that surges in density of SNV-infected mice in 1999 and

2000 were associated with corresponding increases in HPS cases. The increased number of human cases in 1998, however, suggests that density of infected animals may increase more rapidly in some populations than others, possibly because of the presence or absence of virus or differences in initial infection levels. Determining the location and biological characteristics of these viral refugial populations on the regional landscape may prove key to developing accurate models for forecasting outbreaks of HPS.

The dynamics of human risk for HPS over the past 9 years, although showing strong correlations with the effect of El Niño and a delayed density dependence with rodent populations, still exhibit many features more characteristic of nonlinear phenomena than linear ones. The strength of various environmental signals in terms of geographic scale and duration clearly plays an important role. The similarity between the 1993 outbreak and the more recent one is a good example. Both showed a direct and strong response to the trophic cascade, beginning with an increase in fall–spring precipitation and continuing with increases in plant productivity, rodent population density, density of SNV-infected rodents, and, finally, HPS cases: The 1992 El Niño event was followed by numerous HPS cases in 1993, and the 1998 episode was followed by increased human disease in 1999. The incidence of HPS following the former outbreak, however, diminished rapidly in our Zuni study area, dropping from 24 cases in 1993 to 7 in 1994 and to 0 in 1995. In contrast, the pattern of human infection was fairly persistent across the 1998–2000 episode, with 7, 9, and 13 HPS cases in 1998, 1999, and 2000, respectively.

Clearly, the dynamics involving rodent population density alone are not sufficient to explain these differences. The greatest risk of SNV human infection occurs in all cases, regardless of rodent population density, on the positive side of the slope of increasing density of SNV-infected rodents. It appears that although a relationship exists initially between rodent density and risk, the duration of this risk depends on whether or not one or more thresholds are achieved in subsequent years. Our data suggest that, although general rodent population dynamics and numbers of human cases in our Zuni study area were comparable between 1993–1994 (31 cases) and 1998–2000 (29 cases), the epidemiological circumstances were different during these two episodes, which resulted in a different response in the latter case. SNV infection levels in rodent populations rose to higher levels at our study sites in 2000 than at the same sites in 1995, 2 years after the first observed human cases. The explanation for this difference is unclear at this time, but it may be related to the increased summer monsoon moisture of 1999 or to the relatively mild winter of 1999 (or both), which promoted higher levels of rodent overwinter survivorship. Although on a broad regional scale, the trophic cascade triggered by increased precipitation increases the risk of human disease, the actual risk to humans is highly localized and depends on a complex series of variables. These variables include landscape heterogeneity, microclimatic differences, rodent disease, local food abundance, and competition. Such complexity will have to be taken into account before a predictive model of HPS risk can be developed on a fine-grained scale. The degree to which public health warnings in 1998 may have reduced the number of cases in that year should also be investigated.

Of course, ecological and evolutionary forecasting can safeguard the public health against hantaviral and other zoonotic disease outbreaks only insofar as researchers understand the biological complexity of natural and human-dominated ecosystems.

Large-scale, long-term, multidisciplinary studies are needed to advance that understanding, as well as to determine whether foreign or genetically modified pathogens are being introduced into our ecosystems. The large number of new hantavirus species discovered in the New World alone since 1993 serves to illustrate how little we know of the biological diversity around us and emphasizes the urgent need to inventory life on Earth.

Acknowledgments

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