Ecology of Hantaviruses and Their Hosts in North America

James N. Mills,[1] Brian R. Amman,[1] and Gregory E. Glass[2]

Abstract

Since the 1993 discovery of a highly pathogenic hantavirus associated with the North American deer mouse (*Peromyscus maniculatus*), intensive ecological studies have led to many advances in our understanding of the natural history of New World hantaviruses as it relates to human disease. Seventeen named hantaviruses have been identified in North America. Field and laboratory studies of Sin Nombre and other hantaviruses have delineated host associations, geographical distributions, mechanisms of transmission, temporal infection dynamics of these viruses in host populations, and environmental factors that influence these dynamics. Using data from these studies, preliminary predictive models of the risk of hantavirus infection to humans have been developed. Improved models using satellite-derived data are under development. Multidisciplinary collaboration, integration of field and laboratory studies, and establishment and maintenance of long-term monitoring studies will be critical to continued advancement in the understanding of hantavirus–host ecology and disease prevention in humans.

Key Words: Ecology—Hantavirus—Hantavirus pulmonary syndrome—North America—Predictive models—Reservoir—Rodents—Sin Nombre virus.

Introduction

IN 1993, AN OUTBREAK OF acute respiratory distress with high case–fatality ratio led to the description of hantavirus pulmonary syndrome (HPS), the isolation of Sin Nombre virus (SNV), and the identification of its reservoir host, the deer mouse, *Peromyscus maniculatus* (Nichol et al. 1993, Childs et al. 1994, Elliott et al. 1994). With the education and increased awareness of physicians and the development of assays to diagnose infection in humans and rodents, New World hantaviruses were quickly recognized in association with a large number of rodent host species throughout the Americas. The number of hantaviruses recognized continues to increase every year. The New World hantaviruses have apparently existed undetected and have undergone cospeciation along with their cricetid (rodent family Cricetidae) hosts for millions of years (Yates et al. 2002). Currently, there are over 40 named hantavirus genotypes in the Americas with 17 of them occurring in North America. Six of the 17 are known to cause HPS and are associated with rodents native to North America (Table 1). The collective range of the rodent hosts for these pathogenic hantaviruses covers much of North America and practically all of the United States (Fig. 1).

Most of the >480 confirmed cases of HPS in 30 U.S. states (Fig. 2) are attributed to SNV, and the majority have occurred in the southwestern United States (Centers for Disease Control and Prevention [CDC], Special Pathogens Branch, unpublished data). Seventy-three cases were reported in Canada as of December 2008 (Webster et al. 2007; H. Artsob, personal communication, 2008); no HPS cases have been reported in Mexico.

Hantavirus Studies Before 1993

In 1982, Lee et al. (1982) detected antibody reactive with Hantaan virus in 48 of 161 meadow voles (*Microtus pennsylvanicus*) from Maryland. The virus they characterized (Prospect Hill virus) has not been associated with human disease. Seoul virus, which causes mild hemorrhagic fever with renal syndrome in Asia, was isolated from Norway rats (*Rattus norvegicus*) from Pennsylvania, Maryland, and Louisiana, and antibodies to SEOV were found in Norway rats in Texas and California (LeDuc et al. 1986). Although the distribution of SEOV in the United States is poorly studied, it has generally been found wherever it has been sought, suggesting that SEOV virus is associated with the Norway rat throughout its

---

[1]Division of Viral and Rickettsial Diseases, National Center for Zoonotic, Vector-Borne, and Enteric Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia.
[2]W. Harry Feinstone Department of Molecular Microbiology, The Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland.

TABLE 1. NAMED HANTAVIRUS GENOTYPES IN NORTH AMERICA AS OF MAY 2009

Virus[a]	Host species[b]	Distribution of virus	Disease	Reference
Order Rodentia, Family Muridae, Subfamily Murinae				
Seoul (SEOV)	*Rattus norvegicus*	Nearly worldwide	Mild/moderate hemorrhagic fever with renal syndrome	LeDuc et al. (1982)
Order Rodentia, Family Cricetidae, Subfamily Arvicolinae				
Prospect Hill (PHV)	*Microtus pennsylvanicus*	North America	None recognized	Lee et al. (1982)
Bloodland Lake (BLLV)	*Microtus ochrogaster*	North America	None recognized	Hjelle et al. (1995a)
Isla Vista (ISLAV)	*Microtus californicus*	North America	None recognized	Song et al. (1995)
Order Rodentia, Family Cricetidae, Subfamily Neotominae				
Sin Nombre (SNV)	*Peromyscus maniculatus*	North America	HPS	Childs et al. (1994)
New York (NYV)	*Peromyscus leucopus*	East and central USA	HPS	Hjelle et al. (1995b)
Monongahela (MGLV)	*P. maniculatus*	Eastern USA and Canada	HPS	Song et al. (1996)
Limestone Canyon (LSCV)	*Peromyscus boylii*	Southwestern USA	None recognized	Sanchez et al. (2001)
Blue River (BRV)	*P. leucopus*	Central USA	None recognized	Morzunov et al. (1998)
El Moro Canyon (ELMCV)	*Reithrodontomys megalotis*	Western USA and Mexico	None recognized	Hjelle et al. (1994)
Order Rodentia, Family Cricetidae, Subfamily Sigmodontinae				
Black Creek Canal (BCCV)	*Sigmodon hispidus (spadicipygus)*	Southern Florida	HPS	Rollin et al. (1995)
Bayou (BAYV)	*Oryzomys palustris*	Southeastern USA	HPS	Morzunov et al. (1995)
Muleshoe (MULEV)	*S. hispidus*	Texas to southern Nebraska	HPS	Rawlings et al. (1996)
Playa de Oro (OROV)	*Oryzomys couesi*	Colima, Mexico	None recognized	Chu et al. (2008)
Order Soricomorpha, Family Soricidae, Subfamily Soricinae				
Camp Ripley (RPLV)	*Blarina brevicauda*	North America	None recognized	Arai et al. (2007)
Ash River (ARRV)	*Sorex cinereus*	Minnesota, USA	None recognized	Arai et al. (2008)
Jemez Springs (JMSV)	*Sorex monticolus*	New Mexico, USA	None recognized	Arai et al. (2008)

[a]Virus nomenclature follows the 8th report of the International Committee on the Taxonomy of Viruses (Nichol et al. 2005).
[b]Host nomenclature follows Musser and Carleton (2005).
HPS, hantavirus pulmonary syndrome.

range, which includes most urban areas of the United States (LeDuc et al. 1986). Antibody to SEOV was detected in humans in the United States in the late 1980s (Childs et al. 1988a), but was only recently associated with human disease in North America (Baltimore, MD) (Glass et al. 1994).

Studies of the natural history of Prospect Hill virus and SEOV and the rodents that serve as their natural hosts in Baltimore, Maryland, were some of the earliest ecological studies of hantaviruses in the Americas (Childs et al. 1987a, 1987b, 1988b, Korch et al. 1989). These studies illuminated basic concepts of hantavirus natural history that still guide research. The highly specific relationship between hantaviruses and the rodent species that serve as reservoirs of these viruses in nature was apparent from these studies. Even in areas where Norway rats and meadow voles were syntopic, there was no evidence for cross-infection (Korch et al. 1989). The frequent detection of SEOV by reverse transcriptase (RT)–polymerase chain reaction or virus isolation from tissues of antibody-positive rodents was considered evidence that rodents of that species constitute the natural reservoir (Childs et al. 1987a, Arthur et al. 1992), while the sporadic occurrence of antibodies alone in rodents of syntopic species was interpreted as spillover from rodents of the primary reservoir species.

Data from laboratory and field studies led to the identification of mechanisms of SEOV transmission between Norway rats. Experimentally infected rats were much more susceptible to SEOV infection by intramuscular than by aerosol inoculation (Nuzum et al. 1988). Field studies demonstrated an association between acquisition of scars and acquisition of antibody, implicating aggressive interactions (e.g., biting) as a mode of intraspecific transmission of SEOV (Glass et al. 1988). Finally, seroconversion in the field occurred nearly uniformly throughout the year, rather than seasonally, as would be expected if arthropod transmission was involved (Childs et al. 1987b).

Ecological Studies, 1993 to Present

Although antibodies to hantaviruses were detected as early as the mid-1980s in rodents of several species of native North American (Cricetidae) rodents (Tsai et al. 1985), the implications of this finding were not understood until the association of SNV with HPS was discovered in 1993. In the wake of the 1993 HPS outbreak, field studies were designed to achieve a series of goals concerning hantavirus/host ecology and the risk of hantavirus infection in humans (Mills and Childs
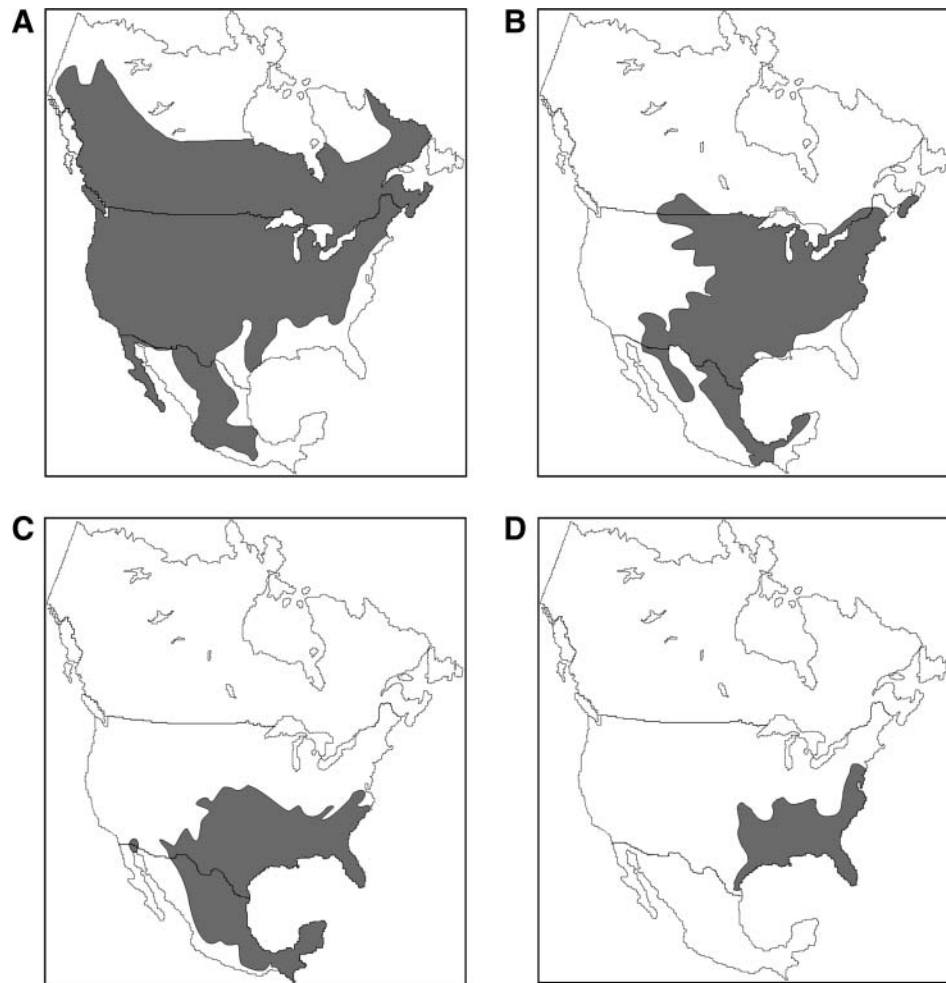
FIG. 1. North American geographic ranges of rodents of four species of hantavirus reservoir hosts that carry hantaviruses known to be human pathogens. (**A**) Deer mouse (*Peromyscus maniculatus*; Carleton 1989), host of Sin Nombre virus. (**B**) White-footed mouse (*Peromyscus leucopus*; Carleton 1989), host of New York virus. (**C**) Hispid cotton rat (*Sigmodon hispidus*), host of Black Creek Canal and Muleshoe viruses (Hershkovitz 1955, Hall and Kelson 1959). (**D**) Rice rat (*Oryzomys palustris*), host of Bayou virus (Wolfe 1982).

1998). These goals initially included identification of the virus–host associations and extended to surveys (cross-sectional studies) designed to identify the potential HPS endemic areas and high-risk habitats, and to determine mechanisms of viral transmission within rodent host populations. Longitudinal studies were initiated to understand the temporal dynamics of hantavirus infection in rodent host populations and to identify environmental factors associated with these temporal dynamics. Currently, data from the cross-sectional surveys and longitudinal studies are being used to build predictive models with the goal of identifying environmental conditions associated with increased transmission of hantaviruses in host populations before these conditions lead to increased disease risk in human populations.

Cross-Sectional (Short-Term) Studies

The goals of the earliest studies were to extend our knowledge of the geographical distribution and natural host range of SNV and other hantaviruses. Host and virus identification in North America often derived from human case follow-up studies (Childs et al. 1994, Hjelle et al. 1995b, Rollin et al. 1995, Rawlings et al. 1996, Ksiazek et al. 1997). Several hantaviruses not associated with human disease were discovered as a result of investigations of HPS cases associated with other hantaviruses (Rawlings et al. 1996), during the course of long-term ecological studies of rodent populations (Sanchez et al. 2001), or by examination of rodent tissues archived in the freezers of museums in the United States (Song et al. 1995, Arai et al. 2007, 2008). Because most North American small mammals are relatively well studied, published distribution maps were available. These maps identify the maximum potential disease endemic area for human disease under the assumption that the distribution of each virus coincides with the distribution of its rodent host. For example, cross-sectional studies showed that, although prevalence of infection varied in space, the distribution of SNV coincided with the known range of the deer mouse in North America, thus effectively outlining the potential geographical range of HPS caused by SNV (Mills et al. 1998, Drebot et al. 2000). Similarly, Bayou virus was shown to occur across much of the range of its principal host, the rice rat
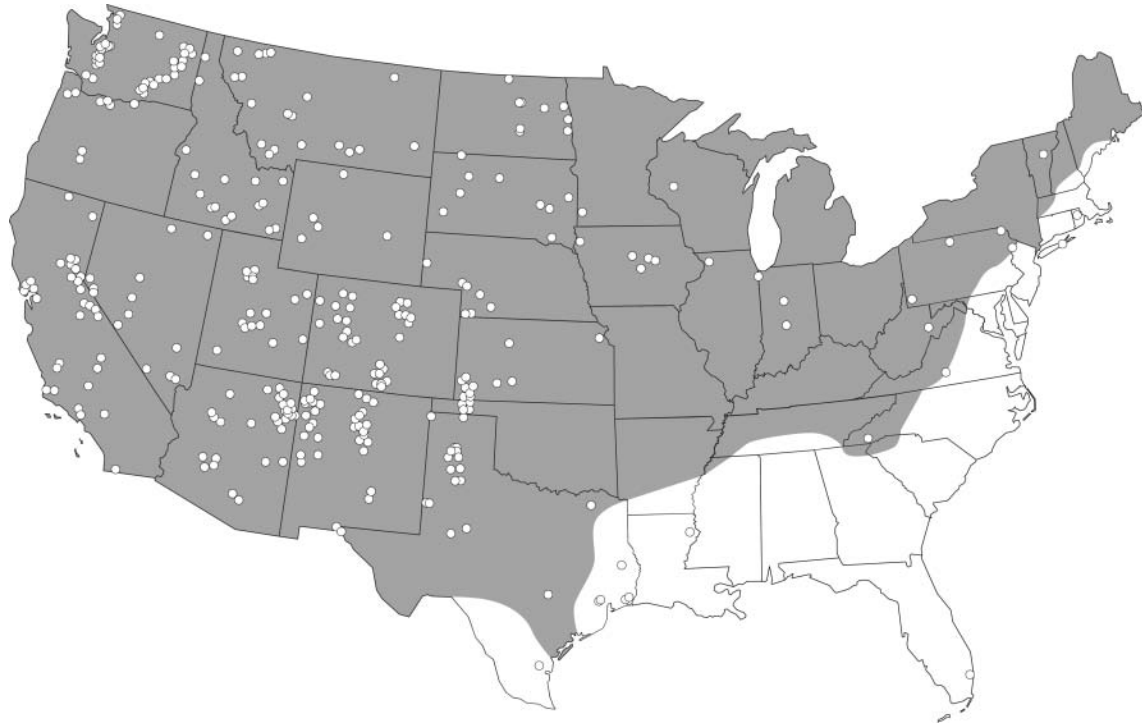
FIG. 2. White dots represent approximate sites of exposure for 480 cases of hantavirus pulmonary syndrome (HPS) confirmed in the United States (1993–2008; Centers for Disease Control and Prevention, Special Pathogens Branch, unpublished data). Shaded area represents the range of the deer mouse (*P. maniculatus*) in the United States. Cases outside the range of the deer mouse were associated with hantaviruses carried by rodents of other species (Fig. 1). For example, the HPS case in southern Florida in 1994 was caused by Black Creek Canal virus, which is principally associated with the hispid cotton rat (*S. hispidus*).

(*Oryzomys palustris*; Ksiazek et al. 1997). In contrast, although the hispid cotton rat (*Sigmodon hispidus*) is distributed throughout the southeastern United States, Black Creek Canal virus (BCCV) has been found in a limited area of southern Florida. In addition, results of a preliminary study suggest that Muleshoe virus is associated with hispid cotton rats in west Texas (Rawlings et al. 1996), suggesting that two viruses are hosted by one rodent species. An explanation for this apparent lack of a specific one-to-one relationship between host and virus may be that *S. hispidus* is a complex of species or subspecies (Musser and Carleton 2005). BCCV is restricted to the range of what has been considered *S. h. (Sigmodon hispidus) spadicipygus* on the southern tip of Florida, while Muleshoe virus may be associated with one or more forms in the western part of the range.

These distributional studies were augmented by regional studies demonstrating differences in host and virus activity and thus differences in relative risk of infection to humans among habitat types. For example, there were distinct differences in deer mouse population density and prevalence of infection with SNV among habitats and elevations in the southwestern United States (Jay et al. 1997, Mills et al. 1997). The lowest deer mouse population densities and the lowest prevalence of SNV infection (and consequently the lowest densities of SNV-infected deer mice) were in the altitudinal and climatic extremes of desert and alpine tundra, while the highest densities and prevalences were at middle altitude habitats including Great Basin scrub and pinyon-juniper woodland. These are also the biomes that are most densely populated in that area by humans (Mills et al. 1997). Habitat

distributions of other North American hantaviruses are largely unstudied.

Cross-sectional studies of the ecology of SNV, BCCV, and El Moro Canyon virus helped delineate mechanisms of rodent-to-rodent virus transmission. The association of infection with rodent age suggested horizontal transmission, as had been observed for SEOV and the Norway rat. More frequent infection in males than in females (male bias in antibody prevalence) and the association of wounding with infection (especially in males) implicated aggressive encounters among males as a likely mechanism of transmission (Mills et al. 1997, Douglass et al. 2001, McIntyre et al. 2005, Calisher et al. 2007). The existence of differences in the degree of male bias in antibody prevalence among hosts of different species suggests different mechanisms of transmission or differences in the frequency of various mechanisms of transmission among species (Mills et al. 1999a, Calisher et al. 2007); other possible mechanisms, including venereal transmission (Hinson et al. 2004), vertical transmission, mutual grooming, communal nesting (Calisher et al. 1999, Pearce-Duvet et al. 2006), and environmental contamination have not been carefully investigated.

Longitudinal Studies

Long-term studies are necessary to understand the seasonal and year-to-year patterns in hantavirus–host dynamics as well as to identify the environmental variables associated with those changing dynamics. In 1994, longitudinal mark–release–recapture studies were initiated in four states with a
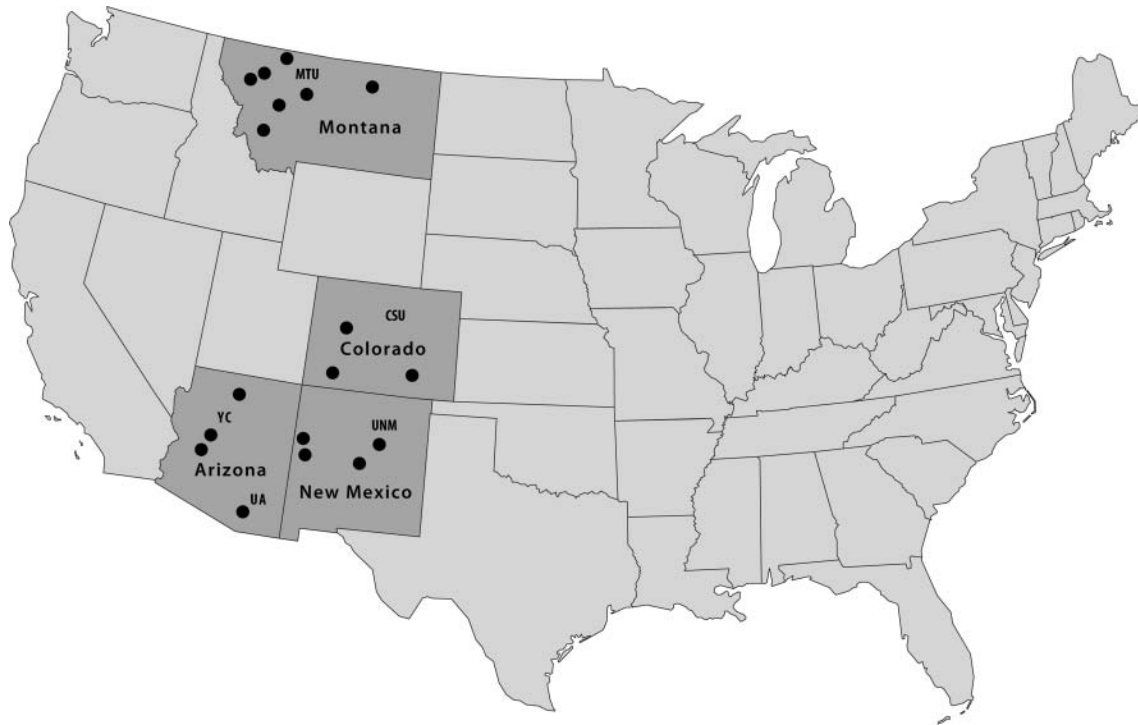
FIG. 3. Locations of long-term mark-recapture studies conducted in the United States, 1994–2006. MTU, Montana Tech University; CSU, Colorado State University; YC, Yavapai College; UA, University of Arizona; UNM, University of New Mexico.

relatively high incidence of HPS: Arizona, Colorado, Montana, and New Mexico (Fig. 3) (Mills et al. 1999b, Douglass et al. 2001). Over 13 years, these studies accumulated more than 1 million trap nights and 44,000 rodents captured. These and other long-term ecological studies (Boone et al. 2002, McIntyre et al. 2005, Safronetz et al. 2008) show that many environmental factors interact to influence host population dynamics and hantavirus transmission in North American rodents (See Fig. 4 for summary schematic).

For example, increases in reproductive success brought about by environmental regulators such as precipitation, habitat quality, and food availability influence hantavirus transmission rates within rodent populations (Mills 2005). The El Niño Southern Oscillation (ENSO) event that brought increased rainfall to the southwestern United States in 1992–1993 was hypothesized to have resulted in increased population densities and increased transmission of SNV in deer mouse populations via a bottom-up trophic cascade, leading to the 1993 outbreak of HPS (Engelthaler et al. 1999). Because no one was monitoring deer mouse populations in the southwestern United States at the time, this hypothesis remained untested until another ENSO event occurred in 1997. Investigators observed increased rainfall followed by increased vegetative cover and finally dramatically increased abundance of deer mice at trapping sites. These events were followed by 3 years of increased numbers of HPS cases in the southwestern United States (Yates et al. 2002, Mills 2005). Further studies demonstrated that the effects of rainfall can vary, depending on its interaction with other variables, including location, altitude, vegetation type, temperature, and season. For example, at a grassland site in southeastern Colorado, increased rainfall had positive effects on deer mouse

populations when temperatures were warm, but negative effects when temperatures were low (Calisher et al. 2005a). Thus, although the component "weather" is represented by a single box in Figure 4, the ultimate effect of weather as a cascade component depends upon the interaction of multiple variables that may act synergistically.

Habitat alteration or disturbance resulting in biodiversity loss can lead to local extinction of populations of rodent species that are habitat and dietary specialists and to population increases in rodents of opportunistic species, many of which are hantavirus reservoirs (Mills 2006). Hantavirus transmission in these high-density host populations is likely to increase, leading to greater risk of infection to humans. These processes in host populations may contribute to the observed negative relationship between host diversity and prevalence of infection with hantaviruses (Mills 2005, 2006). These relationships may only be apparent when long-term averages of rodent population densities and prevalences are taken into consideration.

Host populations in disturbed habitats demonstrate altered population dynamics that may lead to increased risk of infection for humans. For example, peridomestic deer mouse populations had longer breeding seasons and higher SNV infection prevalence than sylvan populations on a Montana ranch. These differences might be related to the more favorable microenvironment in and around buildings and potentially longer survival of virus deposited inside buildings (Kuenzi et al. 2001). This favorable (for mouse and virus) indoor environment might also help explain why HPS cases in the United States are frequently associated with inhabiting or cleaning closed structures with active infestations of deer mice (Armstrong et al. 1995). Although deer mice are frequent
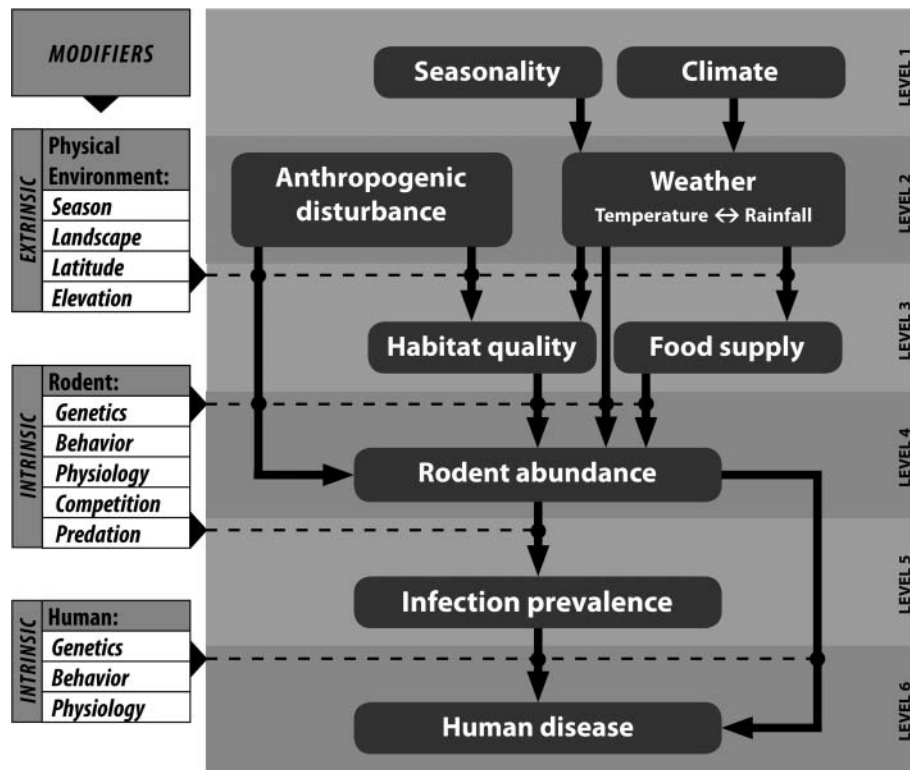
FIG. 4. Components of a bottom-up trophic cascade influencing the risk of HPS to human populations. Seasonality and climate affect local weather which, in turn, affects habitat quality and food quality and availability as experienced by rodent host populations, resulting in increases or decreases in reproductive success, growth rates, and survivorship. Rodent abundance is also affected by anthropogenic disturbance, both directly and through its effects on habitat quality. Because hantaviruses are horizontally transmitted in a density-dependent manner, infection prevalence is controlled by rodent abundance. The risk of human infection is a function of the number of infectious rodents in the environment, which is a function of both population abundance and prevalence of infection in the host population. Monitoring of components at each level (right side of graph) can have predictive value for human infection. Monitoring of lower level components provides the greatest lead time, while monitoring of higher level components provides the most accurate risk prediction. "Modifiers" on the left are variables that are extrinsic or intrinsic to host and human populations that are rarely monitored. These variables may have important influences that occur at the intersections of levels. For example, the end effect of weather on habitat quality will depend upon the landscape (e.g., soil type and cover, slope, topography, and vegetation); the effects of rodent abundance on infection prevalence are influenced by the host's genetic susceptibility, level of stress, reproductive condition, risk behavior, and interactions with other species. This is a simplified schematic and potential but poorly understood connections (e.g., the effects of level 2 and 3 components on infection prevalence) and feedback loops (e.g., negative effects of rodent abundance on food supply and habitat quality and potential negative effects of infection prevalence on rodent abundance) are omitted.

inhabitants of houses and outbuildings in rural areas, other hantavirus hosts in North America (e.g., hispid cotton rats and rice rats) only rarely are found in such environments. This contrasting behavior might help explain the relative rarity of HPS cases associated with hispid cotton rats and rice rats. This same logic suggests caution in concluding that hantaviruses associated with some North American hantavirus host taxa that have not been associated with HPS (e.g., *Reithrodontomys* spp. [harvest mice], *Microtus* spp. [voles], and even the *Soricomorpha* [shrews and moles]) are not pathogenic for humans.

Another important concept elucidated by long-term ecological investigation is the role of population density in transmission and maintenance of hantaviruses. The prevalence of infection by hantaviruses in rodent host populations frequently does not show synchronous density dependence. In fact, the highest prevalence of infection may occur during the season when the population density is lowest (Boone et al.

1998, Douglass et al. 2001). An explanation for the lack of synchronous density dependence may be that the highest host population densities occur at the end of the breeding season, when the population consists of a high proportion of young (and therefore uninfected) individuals. It has been proposed that the highest prevalence of infection might occur in the spring of the year, before the young of the year have entered the population and the population age structure is oldest. Finally, it is hypothesized that the prevalence of infection in this population is proportional to the peak population density attained during the previous breeding season. This delayed-density-dependent prevalence of infection, which was proposed to explain changes in the prevalence of Puumala virus infection in bank voles (Niklasson et al. 1995), was hypothesized as a universal phenomenon for horizontally transmitted rodent-borne pathogens in temperate habitats (Mills et al. 1999a). Delayed density dependence was recently demon-

strated in Montana deer mice. SNV antibody prevalence peaked in spring and was proportional to the peak density of deer mouse populations the previous autumn (Madhav et al. 2007). Although spring prevalence in females was much lower than in males when autumn densities were low, prevalence in females increased more rapidly at higher densities, approaching the prevalence in males at the highest densities. This suggests that female deer mice may frequently interact with other deer mice only at relatively high population densities (Madhav et al. 2007).

In contrast to SEOV in Norway rats (Childs et al. 1987b, 1988a), native North American hantavirus rodent host population densities and infection prevalences may vary greatly among years. The virus may even become extinct in some local populations (especially sites with low population densities in marginal habitats), only to be reintroduced from nearby source populations a few months or years later (Abbott et al. 1999, Calisher et al. 2005b, Kuenzi et al. 2007). This suggests that a metapopulation structure or source-sink dynamic may influence the overall pattern of hantavirus dynamics and persistence (Glass et al. 1998, Boone et al. 2000) and that habitat heterogeneity (both spatial and temporal) might serve as indicators of changing patterns of risk.

Predictive Modeling

Because there is no vaccine and no specific treatment for HPS, the best current defense measure is prevention of infection. Effective intervention relies on the identification of times and places of increased risk (Mills and Childs 1998). An important goal of longitudinal studies of hantavirus host populations has been to identify environmental factors associated with increases in host population density to develop predictive models of HPS risk for humans.

Data from longitudinal studies of SNV and deer mice demonstrated an association among increases in rodent population density at specific sites, increased virus transmission in host populations, and increases in human cases of HPS (Yates et al. 2002). Knowledge of this association allowed prediction of increased risk of human disease and the publication of advanced warning (CDC 1998, 1999), possibly resulting in reduced morbidity and loss of life. These predictions represent the use of simple models based on direct observation of rodent population trends. Although useful, such models, based on observations at levels 4 and 5 (Fig. 4), provide short lead-time and are possible only for local areas where rodent populations are being monitored. To develop models that provide greater lead-time and cover wider geographic areas, researchers have focused on environmental conditions at lower levels of the bottom-up trophic cascade hypothesized to lead to increases in rodent population density and on the use of broad-coverage satellite data capable of monitoring components at levels 2 and 3 (Fig. 4).

Because of their universal availability and long lead-time, weather data (especially rainfall) were among the first potential predictors to be explored (Yaffee et al. 2008). Although state-of-the-art forecasting tools were employed, addition of weather variables to simple density-dependent models based on counts of deer mice did not improve predictability. Part of the explanation for this result may be that the same amount of rainfall can have highly divergent effects on vegetation depending upon numerous factors, including location, slope, topography, soil type, vegetation type, and time of year. More successful models have circumvented the variable effects of rainfall by using vegetation or indicators of vegetation quality as a predictor variable.

Environmental conditions monitored by satellites identified sites likely to support increased abundance of infected deer mice in a given season (Glass et al. 2000, 2002, 2006). Some locations showed persistently favorable environmental conditions over several years (Glass et al. 2007). These sites are hypothesized to serve as "refugia"—areas where deer mice and SNV thrive—while unfavorable conditions elsewhere result in low deer mouse population densities and low prevalence (or local extinction) of SNV. These refugia would represent sources for deer mouse repopulation and reintroduction of SNV when local conditions improve (Yates et al. 2002).

Loehman et al. (manuscript in preparation) used gross primary productivity (GPP) derived from the moderate resolution imaging spectroradiometer to predict deer mouse abundance at Montana trapping sites for 5 years. Rodent abundance tracked GPP closely for 4 years, but rodent populations decreased the 5th year while GPP continued to rise. Factors not included in the model (e.g., predation, competition, or intrinsic population factors that may operate at high population densities) may have been more important in the 5th year than the factors included in the model.

Clearly, extrinsic and intrinsic factors affecting rodent population dynamics and hantavirus transmission are myriad (Fig. 4). These factors do not act independently and their interactions will add further complexity to predictive models. We believe that useful models are possible, but their development will require the considerable multidisciplinary efforts of mathematicians and ecologists and they must be based on truly long-term monitoring of rodent populations and environmental variables. These monitoring programs will be measured in decades rather than a few years.

Laboratory Studies of Hantavirus Infection in the Principal Host

Laboratory studies using pathogenic American hantaviruses in the natural host must be conducted in biosafety level (BSL)-4 laboratories or in natural outdoor enclosures by investigators wearing appropriate personal protective equipment (Botten et al. 2000). As a further complication, SNV is difficult to grow in cell culture and deer mouse–to–deer mouse SNV virus transmission in the laboratory setting has been challenging to demonstrate (Botten et al. 2002).

In the earliest laboratory studies of North American hantaviruses, Hutchinson et al. (1998, 2000) used BCCV and hispid cotton rats to confirm patterns observed in Old World hantavirus/host systems, including transient viremia, long-term presence of infectious virus in organ tissues, long-term shedding of virus in urine and saliva, and horizontal transmission of virus between cage-mates. One finding, however, contrasts with other field and laboratory studies. For other hantaviruses, pups of infected dams acquire protective maternal antibody, either *in utero* or by breastfeeding, and vertical transmission appears not to occur (Zhang et al. 1988, Dohmae and Nishimune 1995, Mills et al. 1997, Borucki et al. 2000, Botten et al. 2002, Kallio et al. 2006). BCCV, however, appears to have been transmitted from infected dams to offspring. Cotton rats used in these studies were a subspecies

from the midwestern United States (Hutchinson et al. 2000), where BCCV does not occur. In light of more recent findings concerning associations between hantaviruses and cotton rats at the subspecies level, additional experiments are needed.

For SNV in the deer mouse, investigators (Botten et al. 2002) demonstrated a very different pattern from those described above. In contrast to studies with Hantaan, Seoul, Puumala, and BCCVs, SNV shedding was not detected in urine or feces, although viral RNA was detected intermittently in saliva. Intracage transmission, which was easily demonstrated for other hantaviruses, was detected in only 1 of 46 mice exposed. The apparent poor efficiency with which SNV was shed by its host may be an important factor in the relatively low incidence of human infection (Safronetz et al. 2008).

Above we suggested that male bias in the prevalence of hantavirus infection in hosts of many species was due to gender-specific differences in behaviors that serve as risk factors for transmission, such as aggressive interactions. We also suggested that the correlation between scars and infection is because aggression leads to infection. Recent laboratory studies suggest that the cause-and-effect relationship between aggression and infection may be complex. Male Norway rats infected with SEOV were more aggressive than were uninfected males, and aggressive males had more virus in their tissues than did less aggressive males (Klein et al. 2004b). Differences in host immune response to infection also may impact the likelihood that infected individuals remain infectious. After inoculation with SEOV, male rats had more viral RNA in target organs and shed viral RNA longer than did females. This was associated with sex-related variation in the expression of genes involved with immune function (Klein et al. 2004a). The expression of key transcriptional factors and genes that encode for proinflammatory, antiviral, T cell, and Ig superfamily proteins was higher in females than in males. Conversely, males had higher expression of heat shock protein genes, suggesting elevated cellular stress. These patterns indicate that infection in males may be longer and more productive than similar infections in females. Lehmer et al. (2007) reported experimental evidence that male deer mice were less immunocompetent than females and suggested that this condition helps explain the commonly observed higher infection prevalence in males than females.

Studies suggest that regulatory T cells contribute to the persistence of hantaviruses in rodents (Easterbrook et al. 2007, Schountz et al. 2007). These cells, which suppress proinflammatory responses, were more numerous during the persistent phase of SEOV infection in male Norway rats. Inactivation of regulatory T cells caused a reduction in SEOV RNA in target organs and to decreased shedding of viral RNA in saliva (Easterbrook et al. 2007). Results consistent with regulatory T cell effects have been described in a similar system for deer mice (Schountz et al. 2007).

Synthesis and Future Directions

Over the last 14 years, the increase in our understanding of North American hantavirus–host ecology has been dramatic. Nevertheless, many challenges remain. As studies continue, relatively simple patterns that first emerged have been shown to be inaccurate or incomplete or time- or site-specific. For example, the initial generalization that ENSO events and increased rainfall lead to increases in host population density

and increased risk of human infection may be true only for the arid Southwest. The effect of rainfall on host populations cannot be considered in isolation; its interactions with many other environmental variables must be considered to achieve a predictive understanding (Mills 2005). Other patterns deduced after a few years of study, such as the linear relationship between GPP and deer mouse population density in Montana, were shown to be incorrect after longer-term investigations (Loehman et al., manuscript in preparation). Indeed, because of the stochastic nature of environmental conditions and host responses to environmental conditions, some associations (such as the negative relationship between rodent community diversity and prevalence of hantavirus infection) were only discerned by using long-term averages (Mills 2005).

Observations from laboratory studies do not necessarily hold when applied to field conditions. For example, transmission of SNV among deer mice was rare in the laboratory (Botten et al. 2002), but appears to occur readily in the field. Transmission in nature may require specific factors (e.g., environmental stressors affecting immune function, territorial boundaries, and population dominance hierarchies) that were not replicated in the laboratory. Although transmission of BCCV to offspring was observed in the laboratory (Hutchinson et al. 2000), there is no evidence that it occurs in the field (Glass et al. 1998). Nevertheless, laboratory studies can be important for helping to interpret field observations (e.g., aggression among hosts leads to infection, but the converse may also be true [Klein et al. 2004b]). The widely held assumption (principally derived from results of laboratory studies) that hantaviruses do not have important effects on host fitness has been challenged by a field study that suggests both a population effect and an individual physiological response of infection: survival of infected (antibody-positive) young deer mice was lower than that of uninfected mice, and recently infected (seroconverting) deer mice gained less weight than mice that did not seroconvert (Douglass et al. 2001, 2007). A laboratory study demonstrating that chronically infected deer mice had weaker immune responses than uninfected mice provided a possible mechanism for this reduced health (Lehmer et al. 2007). Laboratory and field studies are complementary, and accurate conclusions often require both. Finally, field studies in natural environments should be supplemented with studies in disturbed peridomestic environments where most cases of HPS are acquired (Kuenzi et al. 2001).

The recent finding of several species of insectivores that appear to host hantaviruses in many parts of the world, including North America (Arai et al. 2007, 2008), challenges our long-held assumptions about the origin and cospeciation of hantaviruses and muroid rodent hosts and opens a new field of investigation: Is there a clade of hantaviruses that has cospeciated and radiated along with the insectivore lineage? Did the insectivore hantavirus lineage derive from the muroid lineage or vice versa? Are insectivore-associated hantaviruses pathogenic for humans? Although the similarity of phylogenetic trees provides strong evidence for codivergence of hantaviruses and hosts, this is not the complete story. Virus spillover in rodents is common, even across family lines (e.g., Childs et al. 1994), and host jumping between subspecies, species, and genera has apparently occurred (Vapalahti et al. 1999, Plyusnin and Morzunov 2001). In North America, cross-

species host jumping events have been proposed for New York virus (Morzunov et al. 1998) and for Limestone Canyon virus (Sanchez et al. 2001). Cross-taxon jumps at higher taxonomic levels should be less common, but may have occurred, especially among syntopic species. It is highly unlikely that hantaviruses associated with muroid rodents and with insectivores diverged from a hantavirus associated with a common ancestor to both groups. Nevertheless, a much more recent host jumping event between these two lineages with similar ecological niches is possible. Extensive sampling and detailed phylogenetic analyses will be needed to reveal the true explanations for the patterns observed.

The practical end to ecological studies of hantaviruses is not the understanding of hantavirus–host ecology in itself, but the application of this understanding to the development of risk-reduction interventions aimed at decreasing the burden of human disease. Pathogen and host identification, delineation of endemic areas and high-risk habitats, and specification of seasonal risk patterns have obvious practical value and have been achieved for several areas in the United States. Predictive models are beginning to show increasing success (CDC 1998, 1999, Glass et al. 2006, Loehman et al. [manuscript in preparation], Luis et al. [manuscript in review]), but their continued improvement depends upon the establishment, maintenance, and continuity of long-term monitoring programs.

The need for future studies is great. Ecological studies are still lacking in the eastern United States, where SNV, New York virus, Monongahela virus, BCCV, or Bayou virus are common, and we do not know what host or virus factors are responsible for the lower incidence of human disease in the eastern United States. Most human cases of HPS are acquired from exposure to virus in peridomestic environments, and host population ecology in these habitats is different from that in more natural, undisturbed settings, yet ecological studies in these environments are still rare. The utility of field studies has been limited by the inability to control population and environmental variables, while laboratory studies suffer because of their inability to replicate natural conditions. Future field studies might employ outdoor enclosures that would provide seminatural conditions while allowing the control of some population and environmental variables such as population density, age structure, sex ratios, the availability and quality of food and water, and the presence of competitors and predators (Bagamian et al., unpublished data).

Several HPS cases in the United States have occurred very close to the border with Mexico (CDC, Special Pathogens Branch, unpublished data) and rodent species that are known to host hantaviruses that cause HPS in the United States (*P. maniculatus*, *Peromyscus leucopus*, and *S. hispidus*) occur in large areas of Mexico; yet, no HPS cases have been reported in Mexico. Mexico is home to a much higher diversity of sigmodontine and neotomine rodents than the rest of North America (Musser and Carleton 2005), and preliminary serosurveys have reported hantavirus antibodies in rodents of at least eight species (Mantooth et al. 2001, Suzan et al. 2001, Chu et al. 2008, Castro-Arellano et al. 2009). Nevertheless, except for Playa de Oro virus (Chu et al. 2008), the viruses associated with these hosts remain largely uncharacterized. The diversity, distribution, and natural history of hantaviruses in Mexico and their importance for human disease are almost completely unstudied. Our understanding of the diversity and ecology of North American hantaviruses will remain incomplete until intensive studies in Mexico are undertaken.

Although laboratory studies of SNV are difficult for reasons already mentioned, they are sorely needed. Effects of infection on hosts, the relative efficiency of potential mechanisms of transmission, host–virus specificity and the potential of secondary hosts, pathogenesis, viral shedding, viral recrudescence, and many other problems are best investigated in the controlled environment of the laboratory.

Improvements in the nascent field of predictive modeling for hantaviruses are also needed and will require the continuation, perhaps for decades, of long-term monitoring programs for host populations and environmental variables. Unfortunately, traditional funding agencies do not generally support long-term studies. We hope that the increasing recognition by ecologists and public health officials of the value of long-term monitoring programs (e.g., Institute of Medicine Workshop on Global Climate Change and Extreme Weather Events: Understanding the Potential Contributions to the Emergence, Reemergence and Spread of Infectious Disease [Institute of Medicine, 2008]) will lead to the development of needed long-term funding sources.

Acknowledgments

Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention or the Department of Health and Human Services.

Disclosure Statement

No competing financial interests exist.

References

Abbott, KD, Ksiazek, TG, Mills, JN. Long-term hantavirus persistence in rodent populations in central Arizona. Emerg Infect Dis 1999; 5:102–112.

Arai, S, Bennett, SN, Sumibcay, L, Cook, JA, et al. Phylogenetically distinct hantaviruses in the masked shrew (*Sorex cinereus*) and dusky shrew (*Sorex monticolus*) in the United States. Am J Trop Med Hyg 2008; 78:348–351.

Arai, S, Song, JW, Sumibcay, L, Bennett, SN, et al. Hantavirus in northern short-tailed shrew, United States. Emerg Infect Dis 2007; 13:1420–1422.

Armstrong, LR, Zaki, SR, Goldoft, MJ, Todd, RL, et al. Hantavirus pulmonary syndrome associated with entering or cleaning rarely used, rodent-infested structures [letter]. J Infect Dis 1995; 172:1166.

Arthur, RR, Lofts, RS, Gomez, J, Glass, GE, et al. Grouping of hantaviruses by small (S) genome segment polymerase chain reaction and amplification of viral RNA from wild-caught rats. Am J Trop Med Hyg 1992; 47:210–224.

Boone, JD, McGwire, KC, Otteson, EW, Debaca, RS, et al. Remote sensing and geographic information systems: charting Sin Nombre virus infections in deer mice. Emerg Infect Dis 2000; 6:248–258.

Boone, JD, McGwire, KC, Otteson, EW, Debaca, RS, et al. Infection dynamics of Sin Nombre virus after a widespread decline in host populations. Am J Trop Med Hyg 2002; 67:310–318.

Boone, JD, Otteson, EW, McGwire, KC, Villard, P, et al. Ecology and demographics of hantavirus infections in rodent populations in the Walker River basin of Nevada and California. Am J Trop Med Hyg 1998; 58:445–451.

Borucki, MK, Boone, JD, Rowe, JE, Bohlman, MC, et al. Role of maternal antibody in natural infection of Peromyscus maniculatus with Sin Nombre virus. J Virol 2000; 74:2426–2429.

Botten, J, Mirowsky, K, Ye, C, Gottlieb, K, et al. Shedding and intracage transmission of Sin Nombre hantavirus in the deer mouse (Peromyscus maniculatus) model. J Virol 2002; 76:7587–7594.

Botten, J, Nofchissey, R, Kirkendoll-Ahern, H, Rodriguez-Moran, P, et al. Outdoor facility for quarantine of wild rodents infected with hantavirus. J Mamm 2000; 81:250–259.

Calisher, CH, Mills, JN, Sweeney, WP, Root, JJ, et al. Population dynamics of a diverse rodent assemblage in mixed grass shrub habitat, southeastern Colorado, 1995–2000. J Wildl Dis 2005a; 41:12–28.

Calisher, CH, Root, JJ, Mills, JN, Rowe, JE, et al. Epizootiology of Sin Nombre and El Moro Canyon hantaviruses, southeastern Colorado, 1995–2000. J Wildl Dis 2005b; 41:1–11.

Calisher, CH, Sweeney, W, Mills, JN, Beaty, BJ. Natural history of Sin Nombre virus in western Colorado. Emerg Infect Dis 1999; 5:126–134.

Calisher, CH, Wagoner, KD, Amman, BR, Root, JJ, et al. Demographic factors associated with prevalence of antibody to Sin Nombre virus in deer mice in the western United States. J Wildl Dis 2007; 43:1–11.

Carleton, MD. Systematics and Evolution. In: Kirkland, GL, Layne, JN. (eds). Advances in the study of Peromyscus. Lubbock: Texas Tech University Press; 1989:7–141.

Castro-Arellano, I, Suzan, G, Leon, RF, Jimenez, RM, et al. Survey for antibody to hantaviruses in Tamaulipas, Mexico. J Wildl Dis 2009; 45:207–212.

CDC. Hantavirus pulmonary syndrome—Colorado and New Mexico, 1998. MMWR Morb Mortal Wkly Rep 1998; 47:449–452.

CDC. Update: hantavirus pulmonary syndrome—United States, 1999. MMWR Morb Mortal Wkly Rep 1999; 48:521–525.

Childs, JE, Glass, GE, Korch, GW, Arthur, RR, et al. Evidence of human infection with a rat-associated hantavirus in Baltimore, Maryland. Am J Epidemiol 1988a; 127:875–878.

Childs, JE, Glass, GE, Korch, GW, LeDuc, JW. The ecology and epizootiology of hantaviral infections in small mammal communities of Baltimore: a review and synthesis. Bull Soc Vector Ecol 1988b; 13:113–122.

Childs, JE, Glass, GE, Korch, GW, LeDuc, JW. Prospective seroepidemiology of hantaviruses and population dynamics of small mammal communities of Baltimore, Maryland. Am J Trop Med Hyg 1987a; 37:648–662.

Childs, JE, Korch, GW, Glass, GE, LeDuc, JW, et al. Epizootiology of hantavirus infections in Baltimore: isolation of a virus from Norway rats, and characteristics of infected rat populations. Am J Epidemiol 1987b; 126:55–68.

Childs, JE, Ksiazek, TG, Spiropoulou, CF, Krebs, JW, et al. Serologic and genetic identification of Peromyscus maniculatus as the primary rodent reservoir for a new hantavirus in the southwestern United States. J Infect Dis 1994; 169:1271–1280.

Chu, YK, Owen, RD, Sanchez-Hernandez, C, Romero-Almaraz, ML, et al. Genetic characterization and phylogeny of a hantavirus from Western Mexico. Virus Res 2008; 131:180–188.

Dohmae, K, Nishimune, Y. Protection against hantavirus infection by dam's immunity transferred vertically to neonates. Arch Virol 1995; 140:165–172.

Douglass, RJ, Calisher, CH, Wagoner, KD, Mills, JN. Sin Nombre virus infection of deer mice in Montana: characteristics of newly infected mice, incidence, and temporal pattern of infection. J Wildl Dis 2007; 43:12–22.

Douglass, RJ, Wilson, T, Semmens, WJ, Zanto, SN, et al. Longitudinal studies of Sin Nombre virus in deer mouse dominated ecosystems of Montana. Am J Trop Med Hyg 2001; 65:33–41.

Drebot, MA, Artsob, H, Werker, DH. Hantavirus pulmonary syndrome in Canada. Can Commun Dis Rep 2000; 26:65–68.

Easterbrook, JD, Zink, MC, Klein, SL. Regulatory T cells enhance persistence of the zoonotic pathogen Seoul virus in its reservoir host. Proc Natl Acad Sci Biol 2007; 104:15502–15507.

Elliott, LH, Ksiazek, TG, Rollin, PE, Spiropoulou, CF, et al. Isolation of the causative agent of hantavirus pulmonary syndrome. Am J Trop Med Hyg 1994; 51:102–108.

Engelthaler, DM, Mosley, DG, Cheek, JE, Levy, CE, et al. Climatic and environmental patterns associated with hantavirus pulmonary syndrome, Four Corners Region, United States. Emerg Infect Dis 1999; 5:87–94.

Glass, GE, Cheek, JE, Patz, JA, Shields, TM, et al. Using remotely sensed data to identify areas at risk for hantavirus pulmonary syndrome. Emerg Infect Dis 2000; 6:238–247.

Glass, GE, Childs, JE, Korch, GW, LeDuc, JW. Association of intraspecific wounding with hantaviral infection in wild rats (Rattus norvegicus). Epidemiol Infect 1988; 101:459–472.

Glass, GE, Livingstone, W, Mills, JN, Hlady, WJ, et al. Black Creek Canal virus infection in Sigmodon hispidus in southern Florida. Am J Trop Med Hyg 1998; 59:699–703.

Glass, GE, Shields, T, Cai, B, Yates, TL, et al. Persistently highest risk areas for hantavirus pulmonary syndrome: potential sites for refugia. Ecol Appl 2007; 17:129–139.

Glass, GE, Shields, TM, Parmenter, RR, Goade, D, et al. Predicted hantavirus risk in 2006 for the southwestern U.S. Occas Pap Mus Tex Tech Univ 2006; 255:1–14.

Glass, GE, Watson, AJ, LeDuc, JW, Childs, JE. Domestic cases of hemorrhagic fever with renal syndrome in the United States. Nephron 1994; 68:48–51.

Glass, GE, Yates, TL, Fine, JB, Shields, TM, et al. Satellite imagery characterizes local animal reservoir populations of Sin Nombre virus in the southwestern United States. Proc Natl Acad Sci Biol 2002; 99:16817–16822.

Hall, ER, Kelson, KR. The Mammals of North America. New York: Ronald Press, 1959.

Hershkovitz, P. South American marsh rats, genus Holochilus, with a summary of Sigmodont rodents. Fieldiana Zool 1955; 37:639–673.

Hinson, ER, Shone, SM, Zink, MC, Glass, GE, et al. Wounding: the primary mode of Seoul virus transmission among male Norway rats. Am J Trop Med Hyg 2004; 70:310–317.

Hjelle, B, Chavez-Giles, F, Torrez-Martinez, N, Yates, T, et al. Genetic identification of a novel hantavirus of the harvest mouse Reithrodontomys megalotis. J Virol 1994; 68:6751–6754.

Hjelle, B, Jenison, SA, Goade, DE, Green, WB, et al. Hantaviruses: clinical, microbiologic, and epidemiologic aspects. Crit Rev Clin Lab Sci 1995a; 32:469–508.

Hjelle, B, Lee, SW, Song, W, Torrez-Martinez, N, et al. Molecular linkage of hantavirus pulmonary syndrome to the white-footed mouse, Peromyscus leucopus: genetic characterization of the M genome of New York virus. J Virol 1995b; 69:8137–8141.

Hutchinson, KL, Rollin, PE, Peters, CJ. Pathogenesis of a North American hantavirus, Black Creek Canal virus, in experimentally infected *Sigmodon hispidus*. Am J Trop Med Hyg 1998; 59:58–65.

Hutchinson, KL, Rollin, PE, Shieh, WJ, Zaki, S, et al. Transmission of Black Creek Canal virus between cotton rats. J Med Virol 2000; 60:70–76.

Institute of Medicine. *Global Climate Change and Extreme Weather Events: Understanding the Contributions to Infectious Disease Emergence*. Washington, DC: National Academies Press, 2008.

Jay, M, Ascher, MS, Chomel, BB, Madon, M, et al. Seroepidemiologic studies of hantavirus infection among wild rodents in California. Emerg Infect Dis 1997; 3:183–190.

Kallio, ER, Poikonen, A, Vaheri, A, Vapalahti, O, et al. Maternal antibodies postpone hantavirus infection and enhance individual breeding success. Proc R Soc Lond 2006; 273:2771–2776.

Klein, SL, Cernetich, A, Hilmer, S, Hoffman, EP, et al. Differential expression of immunoregulatory genes in male and female Norway rats following infection with Seoul virus. J Med Virol 2004a; 74:180–190.

Klein, SL, Zink, MC, Glass, GE. Seoul virus infection increases aggressive behaviour in male Norway rats. Anim Behav 2004b; 67:421–429.

Korch, GW, Childs, JE, Glass, GE, Rossi, CA, et al. Serologic evidence of hantaviral infections within small mammal communities of Baltimore, Maryland: spatial and temporal patterns and host range. Am J Trop Med Hyg 1989; 41:230–240.

Ksiazek, TG, Nichol, ST, Mills, JN, Groves, MG, et al. Isolation, genetic diversity, and geographic distribution of Bayou virus (Bunyaviridae: *Hantavirus*). Am J Trop Med Hyg 1997; 57:445–448.

Kuenzi, AJ, Douglass, RJ, White, D, Bond, CW, et al. Antibody to Sin Nombre virus in rodents associated with peridomestic habitats in west central Montana. Am J Trop Med Hyg 2001; 64:137–146.

Kuenzi, AJ, Morrison, ML, Madhav, NK, Mills, JN. Brush mouse (*Peromyscus boylii*) population dynamics and hantavirus infection during a warm, drought period in southern Arizona. J Wildl Dis 2007; 43:675–683.

LeDuc, JW, Smith GA, Bagley, LR, Hasty, SE, et al. Preliminary evidence that Hantaan or a closely related virus in enzootic in domestic rodents. N Engl J Med 1982; 307:624.

LeDuc, JW, Smith, GA, Childs, JE, Pinheiro, FP, et al. Global survey of antibody to Hantaan-related viruses among peridomestic rodents. Bull World Health Org 1986; 64:139–144.

Lee, PW, Amyx, HL, Gajdusek, DC, Yanagihara, RT, et al. New haemorrhagic fever with renal syndrome-related virus in indigenous wild rodents in United States. Lancet 1982; 2:1405.

Lehmer, EM, Clay, CA, Wilson, E, St. Jeor, S, et al. Differential resource allocation in deer mice exposed to Sin Nombre virus. Physiol Biochem Zool 2007; 80:514–521.

Madhav, NK, Wagoner, KD, Douglass, RJ, Mills, JN. Delayed density-dependent prevalence of Sin Nombre virus antibody in Montana deer mice (*Peromyscus maniculatus*) and implications for human disease risk. Vector Borne Zoonot Dis 2007; 7:353–364.

Mantooth, SJ, Milazzo, ML, Bradley, RD, Hice, CL, et al. Geographical distribution of rodent-associated hantaviruses in Texas. J Vector Ecol 2001; 26:7–14.

McIntyre, NE, Chu, YK, Owen, RD, Abuzeineh, A, et al. A longitudinal study of Bayou virus, hosts, and habitat. Am J Trop Med Hyg 2005; 73:1043–1049.

Mills, JN. Regulation of rodent-borne viruses in the natural host: implications for human disease. Arch Virol 2005; Suppl. 19:45–57.

Mills, JN. Biodiversity loss and emerging infectious disease: an example from the rodent-borne hemorrhagic fevers. Biodiversity 2006; 7:9–17.

Mills, JN, Childs, JE. Ecologic studies of rodent reservoirs: their relevance for human health. Emerg Infect Dis 1998; 4:529–537.

Mills, JN, Johnson, JM, Ksiazek, TG, Ellis, BA, et al. A survey of hantavirus antibody in small-mammal populations in selected U.S. National Parks. Am J Trop Med Hyg 1998; 58:525–532.

Mills, JN, Ksiazek, TG, Ellis, BA, Rollin, PE, et al. Patterns of association with host and habitat: antibody reactive with Sin Nombre virus in small mammals in the major biotic communities of the southwestern United States. Am J Trop Med Hyg 1997; 56:273–284.

Mills, JN, Ksiazek, TG, Peters, CJ, Childs, JE. Long-term studies of hantavirus reservoir populations in the southwestern United States: a synthesis. Emerg Infect Dis 1999a; 5:135–142.

Mills, JN, Yates, TL, Ksiazek, TG, Peters, CJ, et al. Long-term studies of hantavirus reservoir populations in the southwestern United States: rationale, potential, and methods. Emerg Infect Dis 1999b; 5:95–101.

Morzunov, SP, Feldmann, H, Spiropoulou, CF, Semenova, VA, et al. A newly recognized virus associated with a fatal case of hantavirus pulmonary syndrome in Louisiana. J Virol 1995; 69:1980–1983.

Morzunov, SP, Rowe, JE, Ksiazek, TG, Peters, CJ, et al. Genetic analysis of the diversity and origin of hantaviruses in *Peromyscus leucopus* mice in North America. J Virol 1998; 72:57–64.

Musser, GG, Carleton, MD. Superfamily Muroidea. In: Wilson, DE, Reeder, DM, eds. *Mammal Species of the World, a Taxonomic and Geographic Reference*. Baltimore: Johns Hopkins University Press, 2005:894–1531.

Nichol, ST, Beaty, BJ, Elliott, RM, Goldbach, R, et al. Family *Bunyaviridae*. In: Fauquet, CM, Mayo, MA, Maniloff, J, Desselberger, U, et al., eds. *Virus Taxonomy: Eighth Report of the International Committee on Taxonomy of Viruses*. San Diego: Elsevier Academic Press, 2005:695–716.

Nichol, ST, Spiropoulou, CF, Morzunov, S, Rollin, PE, et al. Genetic identification of a hantavirus associated with an outbreak of acute respiratory illness. Science 1993; 262:914–917.

Niklasson, B, Hornfeldt, B, Lundkvist, A, Bjorsten, S, et al. Temporal dynamics of Puumala virus antibody prevalence in voles and of nephropathia epidemica incidence in humans. Am J Trop Med Hyg 1995; 53:134–140.

Nuzum, EO, Rossi, CA, Stephenson, EH, LeDuc, JW. Aerosol transmission of Hantaan and related viruses to laboratory rats. Am J Trop Med Hyg 1988; 38:636–640.

Pearce-Duvet, JMC, St. Jeor, SC, Boone, JD, Dearing, MD. Changes in Sin Nombre virus antibody prevalence in deer mice across seasons: the interaction between habitat, sex, and infection in deer mice. J Wildl Dis 2006; 42:819–824.

Plyusnin, A, Morzunov, SP. Virus evolution and genetic diversity of hantaviruses and their rodent hosts. Curr Top Microbiol Immunol 2001; 256:47–75.

Rawlings, JA, Torrez-Martinez, N, Neill, SU, Moore, GM, et al. Cocirculation of multiple hantaviruses in Texas, with characterization of the small (s) genome of a previously undescribed virus of cotton rats (*Sigmodon hispidus*). Am J Trop Med Hyg 1996; 55:672–679.

Rollin, PE, Ksiazek, TG, Elliott, LH, Ravkov, EV, et al. Isolation of Black Creek Canal virus, a new hantavirus from *Sigmodon hispidus* in Florida. J Med Virol 1995; 46:35–39.

Safronetz, D, Drebot, MA, Artsob, H, Cote, T, et al. Sin Nombre virus shedding patterns in naturally infected deer mice (*Peromyscus maniculatus*) in relation to duration of infection. Vector Borne Zoonot Dis 2008; 8:97–100.

Sanchez, AJ, Abbott, KD, Nichol, ST. Genetic identification and characterization of Limestone Canyon virus, a unique *Peromyscus*-borne hantavirus. Virology 2001; 286:345–353.

Schountz, T, Prescott, J, Cogswell, AC, Oko, L, et al. Regulatory T cell-like responses in deer mice persistently infected with Sin Nombre virus. Proc Natl Acad Sci Biol 2007; 104:15496–15501.

Song, JW, Baek, LJ, Nagle, JW, Schlitter, D, et al. Genetic and phylogenetic analyses of hantaviral sequences amplified from archival tissues of deer mice (*Peromyscus maniculatus nubiterrae*) captured in the eastern United States. Arch Virol 1996; 141:959–967.

Song, WM, Torrez-Martinez, N, Irwin, W, Harrison, FJ, et al. Isla Vista virus—a genetically novel hantavirus of the California vole *Microtus californicus*. J Gen Virol 1995; 76:3195–3199.

Suzan, G, Ceballos, G, Mills, J, Ksiazek, TG, et al. Serologic evidence of hantavirus infection in sigmodontine rodents in Mexico. J Wildl Dis 2001; 37:391–393.

Tsai, TF, Bauer, SP, Sasso, DR, Whitfield, SG, et al. Serological and virological evidence of a Hantaan virus-related enzootic in the United States. J Infect Dis 1985; 152:126–136.

Vapalahti, O, Lundkvist, A, Fedorov, V, Conroy, CJ, et al. Isolation and characterization of a hantavirus from *Lemmus sibiricus*: evidence for host switch during hantavirus evolution. J Virol 1999; 73:5586–5592.

Webster, D, Lee, B, Joffe, A, Sligl, W, et al. Cluster of cases of hantavirus pulmonary syndrome in Alberta, Canada. Am J Trop Med Hyg 2007; 77:914–918.

Wolfe, JL. *Oryzomys palustris*. Mamm Species 1982; 176:1–5.

Yaffee, RA, Nikolopoulos, K, Reilly, DP, Crone, SF, et al. An experiment in epidemiological forecasting: comparison of forecast accuracies among different methods of forecasting deer mouse population densities in Montana. Proceedings of the 28th International Symposium on Forecasting 2008. Available at www.forecasters.org/submissions/ISF2008Robert AYaffeeCDCprojectarticle.pdf.

Yates, TL, Mills, JN, Parmenter, CA, Ksiazek, TG, et al. The ecology and evolutionary history of an emergent disease: hantavirus pulmonary syndrome. Bioscience 2002; 52:989–998.

Zhang, XK, Takashima, I, Hashimoto, N. Role of maternal antibody in protection from hemorrhagic fever with renal syndrome virus infection in rats. Arch Virol 1988; 103:253–265.

Address correspondence to:
James N. Mills
Division of Viral and Rickettsial Diseases
National Center for Zoonoses, Vector-Borne, and Enteric Diseases
Centers for Disease Control and Prevention
Atlanta, GA 30333

E-mail: jmills@cdc.gov