6. The Role of Rodents in Emerging Human Disease: Examples from the Hantaviruses and Arenaviruses

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Abstract

Because of the severity and the dramatic nature of the diseases they cause, the rodent-borne haemorrhagic fever viruses recently have received considerable attention from ecologists and health scientists. During the past five years, researchers have identified at least 25 'new' hantaviruses and arenaviruses, all associated with murid rodents, and coevolutionary theory suggests that many additional virus–host associations await discovery. Basic research on the ecology of hantavirus and arenavirus reservoir species is providing information of practical importance for reservoir control and disease prevention. Studies of reservoir geographic distribution and habitat associations help define potential disease-endemic areas and more precisely identify the spacial variation in relative risk to humans. Cross-sectional and longitudinal studies of reservoir populations help define mechanisms of viral transmission and identify the relationship between environment, reservoir populations, and human disease. Integrated results from a variety of reservoir studies can be combined with data from satellite images to provide models that can help scientists predict specific times and places of increased risk to human populations. Biologists and pest control specialists who work with reservoir species may be at increased risk of infection with rodent-borne viruses unless appropriate safety guidelines are followed.

Keywords

Rodents, infectious disease, rodent-borne disease, zoonoses, haemorrhagic fever, arenavirus, hantavirus

Introduction

As the chapters in this volume amply illustrate, rodents—as pests—are responsible for considerable economic loss, through damage to crops, food stores and human property. Rodents, as carriers of diseases transmitted to humans (rodent-borne zoonoses), are also responsible for considerable economic loss in terms of decreased worker productivity and health-care costs. The most important negative impact of rodent-borne diseases, the loss of human health and lives, can be assigned no price tag.

Although the specific theme of this chapter is the application of basic research on rodent biology and ecology toward public health goals, the goals of pest management personnel and public health practitioners are similar. Whether to prevent economic loss or to prevent disease, we seek to control rodent populations, prevent their access to human food and other products, prevent their access to our dwellings, and minimise their contact with humans.

Accomplishment of these objectives is facilitated by a thorough understanding of the biology and ecology of the target species. In this chapter, I will (1) introduce the extent and severity of the human disease problem caused by the rodent-borne haemorrhagic fever viruses; (2) use examples from the hantaviruses and arenaviruses to illustrate the broad nature and potential for expansion of the rodent-borne disease problem; (3) illustrate how a structured basic research program can provide data that may assist in the management of rodent host populations and the prevention of human disease; (4) discuss the implications of our increasing awareness of severe rodent-borne diseases and the understanding of their transmission patterns in terms of the safety measures recommended for mammalogists and vertebrate pest control specialists working in disease-endemic areas; and (5) provide an up-to-date list of the rodent-borne haemorrhagic fever viruses, their reservoir hosts, and the host distributions, so that rodent biologists can assess their particular risk and take appropriate precautions.

Emerging Infectious Diseases

In 1967 the Surgeon General of the United States, William H. Stewart, declared that it was time to "close the book on infectious diseases" and start paying more attention to chronic ailments. In 1998, Surgeon General David Satcher, speaking to the United States Congress, addressed the "continuing threat of emerging infectious diseases", singling out infectious disease as the number one killer worldwide. Even in the United States, according to Dr. Satcher, the death rate from infectious diseases, excluding acquired immune deficiency syndrome (AIDS), rose by 22% between 1980 and 1992. What factors are responsible for this stark difference in perspective coming from two surgeons general? What are emerging infectious diseases? Why are they suddenly becoming important?

The term 'emerging infectious disease' applies to two groups of illnesses: those caused by previously unknown agents that are being recognised at an increasing rate, such as AIDS, Lyme disease and hantavirus pulmonary syndrome, and those that represent the re-emergence of previously

described diseases in drug-resistant or more virulent forms, such as tuberculosis, malaria, and the illnesses due to *Escherichia coli* 0157:H7 (Institute of Medicine, 1992). The recent awareness of emerging infectious diseases is due to several factors. The development of antibiotic resistance is one. Others include rapid transportation, that quickly brings victims of remotely acquired diseases into heavily populated cities, improved diagnosis, and physician education. Another important factor is our rapidly expanding population with the resulting incursion of humans into remote, natural habitats where previously unknown diseases have existed for many years in cycles involving wild-animal hosts. Some of these diseases of wild animals, the zoonotic diseases, can be transmitted to humans. Rodents, because of their tremendous diversity, social behaviour, opportunistic life history, high reproductive potential, periodically high population densities, and peridomestic affinities, are among the most important natural reservoirs for zoonotic diseases. A review published in 1995 described approximately 60 zoonotic diseases, or groups of associated diseases, for which rodents serve as hosts for the etiologic agent (Hugh-Jones et al. 1995). The rodent-borne haemorrhagic fevers represent one such group.

Because of our phylogenetic relatedness to them, other mammals are the most likely animals with which humans may be expected to share pathogens. Rodents are the most diverse group of mammals, comprising nearly half of the 4,600 species in the class. It is likely that only a small proportion of the organisms infecting rodents would cause disease in humans. Nevertheless, the potential number of agents is vast. The disease agents that infect the house mouse (*Mus musculus*) have been relatively well studied because of its use as a laboratory animal. Although it does not claim to be comprehensive, a recent report (Committee on Infectious Diseases of Mice and Rats, 1991) provides a discussion of about 40 bacteria, viruses, and parasites that cause disease in *M. musculus*. These agents are described mostly from populations of mice that have not been outside of the relatively sterile environment of the laboratory for many generations. Thus, the potential for pathogen diversity may be much greater in populations of sylvatic species. It is certainly not unreasonable to suspect that every species of wild rodent might harbour as many, if not more, potential disease agents.

In the natural host, coevolution likely has lead to a relatively benign relationship between host and pathogen. The death or severe illness of the host is rarely to the evolutionary benefit of a parasite. When other animals (including humans) come into contact with rodents, the possibility of a cross-species infection occurs. The response of the human immune system to these novel agents is unpredictable. In many cases the pathogen will be cleared rapidly by the immune response and no disease occurs. Some pathogens may be pre-adapted to hide from the human immune system (e.g. human immunodeficiency virus). Others might elicit a strong immune response, but that response might, itself, result in severe pathology to the host. Such is the case with the rodent-borne haemorrhagic fever viruses.

The Rodent-Borne Haemorrhagic Fevers

The magnitude of the potential for human disease involving rodent-borne agents is largely unknown. However, one group for which considerable progress has been made in recent years is the rodent-borne haemorrhagic fever viruses. An awareness of the distribution of these viruses and their disease potential is becoming increasingly important to rodent biologists and management personnel. In this chapter I will provide brief descriptions of the most important of the known viruses, the recognised diseases caused by each, and their general distributions. Additional details concerning their importance for wildlife biologists (Childs et al. 1995), identification and distribution of the reservoir species (Mills and Childs 1999), and epidemiology of the diseases (Peters et al. 1996; Peters et al. 1999; Enría et al. 1999) can be found in other sources.

The rodent-borne viral haemorrhagic fevers are caused by two groups of viruses, the hantaviruses and the arenaviruses. Although they are both negative-stranded, enveloped ribonucleic acid (RNA) viruses, the two groups are not closely related taxonomically. The hantaviruses constitute the genus *Hantavirus*, within the family Bunyaviridae; the arenaviruses constitute the family Arenaviridae. Nevertheless, these two groups of viruses share several important characteristics. Both cause severe haemorrhagic fever in humans. The hantaviruses cause hantavirus pulmonary syndrome (HPS) in the New World and haemorrhagic fever with renal syndrome (HFRS) in the Old World. The arenaviruses cause the South American hemorrhagic fevers in the New World, and Lassa fever in the Old World. These diseases are the cause of significant morbidity and mortality. There may be 200,000 cases of HFRS each year in Asia, primarily in China and Korea (McKee et al. 1991). Lassa virus is responsible for as many as 300,000 human infections each year in West Africa (McCormick et al. 1987). Secondly, each virus in both families is usually associated with a specific rodent host, of the family Muridae, in which it establishes a chronic, persistent infection that involves the sporadic or persistent shedding of large quantities of infectious virus into the environment in urine, faeces or saliva. These characteristics of the infection are key to the transmission of the virus, both from rodent to rodent, and from rodent to human. Humans are believed to be infected most frequently via the inhalation of infectious aerosols of rodent excreta or secreta. Other likely but less frequent routes of infection include direct contact of broken skin or mucous membranes with contaminated rodent fluids or fomites, ingestion of contaminated food, or the bite of an infected rodent. Transmission within host populations may be by a variety of horizontal and vertical mechanisms, but evidence from field studies indicates that horizontal transmission, and perhaps, specifically aggressive encounters between adult male rodents, may be an important mechanism (Glass et al. 1988; Mills et al. 1992, 1997b).

Haemorrhagic Fever with Renal Syndrome

HFRS is the term applied collectively to a suite of diseases of varying severity caused by hantaviruses in Asia and Europe. The

diseases are characterised by fever, chills, myalgia, and varying degrees of haemorrhage and renal compromise with 1% to 15% mortality. The viruses are carried by rodent hosts of the murid subfamilies Murinae (Old World rats and mice) and Arvicolinae (voles), and the distributions of the diseases generally coincide with the distributions of the host species (Mills and Childs 1999). A summary of the viruses, the known diseases, and approximate distribution of the reservoirs is provided (Appendix 1).

The prototype hantavirus, Hantaan virus, gained worldwide attention during the Korean conflict, when over 3,000 United Nations troops contracted a severe form of HFRS, then referred to as Korean haemorrhagic fever (KHF). However, the disease, which has variously been referred to as epidemic hemorrhagic fever, hemorrhagic nephrosonephritis, Churilov's disease, and Songo fever, has been recognised for many years in Asia (McKee et al. 1991; Peters et al. 1999). A Chinese medical text from 960 AD may describe compatible symptoms. The disease was noted by Soviet scientists as early as 1913, and outbreaks continued to be described by the Soviets as well as among Japanese troops in Manchuria during the 1930s. The etiologic agent of KHF was not described until the late 1970s when Ho Wang Lee isolated a virus from the lungs of the striped field mouse (*Apodemus agrarius*) captured on the banks of the Hantaan River near the border between North and South Korea (Lee et al. 1978). Currently, Hantaan virus is responsible for perhaps 200,000 cases of HFRS each year, in China, Korea, and the Russian Far East (McKee et al. 1991).

Epidemics are seasonal with an autumn peak, coinciding with the maximum agricultural activity and probably maximum host population density. Cases occur predominantly among adult men in rural habitats; many cases are among farmers, forest workers and soldiers in the field (McKee et al. 1991; Peters et al. 1999).

Seoul virus, which is found nearly worldwide in association with its cosmopolitan host, the Norway rat (*Rattus norvegicus*), is responsible for a relatively mild form of HFRS (Lee et al. 1980). Although Seoul virus has been detected in rats throughout most of the range of the species, most confirmed cases of HFRS caused by Seoul virus have been restricted to Korea, Russia, and China. Reasons for the apparent lack of disease in other parts of the world are unknown, but may include inadequate case finding. A search in one United States city revealed three suspected cases (Glass et al. 1994).

Dobrava virus, hosted by the yellow-necked field mouse (*Apodemus flavicollis*), is responsible for a severe form of HFRS in the Balkans. Dobrava virus may be associated with *A. agrarius* in the Baltic region (Plyusnin et al. 1997; Peters et al. 1999).

Although several hantaviruses are hosted by arvicoline rodents in Asia and Europe, only one is known to be associated with human disease. Puumala virus, carried by the bank vole (*Clethrionomys glareolus*), is the etiologic agent for a mild form of HFRS called nephropathia epidemica (NE). NE is endemic to Scandinavia, western Europe, and European Russia. Several additional hantaviruses, some only recently discovered, are associated with murine and arvicoline rodents in Asia and Europe

(Appendix 1). These viruses have not been definitively associated with human disease, but extensive studies are lacking.

Hantavirus Pulmonary Syndrome

HPS is a New World hantavirus disease characterised by a flu-like prodrome involving fever, myalgia, and malaise, which rapidly progresses to cardiopulmonary compromise that may end in death in about 50% of cases in spite of aggressive hospital care.

In early 1993, only a single autochthonous hantavirus was known from the New World: Prospect Hill virus (Lee et al. 1982), which is associated with the meadow vole, *Microtus pennsylvanicus*. It still has not been associated with any human disease. The seemingly sudden appearance of HPS in the spring of 1993 led to the isolation of Sin Nombre virus (SNV; Elliott et al. 1994) and its association with the deer mouse (*Peromyscus maniculatus*; Nichol et al. 1993; Childs et al. 1994). Armed with a specific case definition and the molecular and serologic tools and reagents necessary to detect SNV, physicians and mammalogists quickly discovered that HPS was a pan-American disease, and that numerous species of New World sigmodontine and arvicoline rodents serve as hosts for a plethora of hantaviruses. Currently, approximately 21 viruses have been described in association with about as many host species occurring from Canada to Patagonia (Appendix 1 and Figure 1). About half of these viruses are known human pathogens. All of those viruses responsible for HPS are hosted by rodents of the murid subfamily Sigmodontinae. In addition to the United States and Canada, HPS has now been documented in Argentina, Chile, Paraguay, Uruguay, Brazil, and Bolivia, and hantavirus or hantavirus antibody has been demonstrated in rodents from Peru, Venezuela, Costa Rica and Mexico.

The South American Haemorrhagic Fevers

The South American haemorrhagic fevers currently consist of four recognised diseases that are clinically similar. They are characterised by an insidious prodrome of fever, malaise, muscle aches, and retroorbital headache, which may be followed by hypotension, conjunctival injection, petechiae on the throat, chest, and axillary area, dizziness, and tremors. Severe cases demonstrate bleeding from gums and mucous membranes, shock, coma, and convulsions (Enría et al. 1999). Mortality may be 10% to 33%. With a single possible exception, the New World arenaviruses for which the reservoir is known are all associated with sigmodontine rodents (Appendix 2).

The first arenaviral haemorrhagic fever to be recognised and, to date, the best studied is Argentine haemorrhagic fever (AHF). The disease was described in 1953 (Arribalzaga 1955) and the etiologic agent, Junín virus, was described in 1958 (Parodi et al. 1958). Several hundred to over a thousand cases of AHF were confirmed each year on the central Argentine Pampa from the discovery of the disease until the recent development of a vaccine.

Cases are predominantly in adult men from rural areas, and epidemics are seasonal, occurring in the fall—coinciding with the harvest of principal crops (corn and soybeans) and maximum densities of the

Figure 1.
Geographic locations of the currently recognised New World hantaviruses, as of 1 October 1998 (from Mills and Childs 1998).

principal reservoir, the corn mouse (*Calomys musculinus*). The introduction of an effective treatment using immune plasma decreased the mortality from 15–30% to less than 1%, and the recent use of a highly efficacious vaccine in the AHF-endemic area has resulted in a substantial reduction in the numbers of reported cases (Maiztegui et al. 1998).

Bolivian hemorrhagic fever (BHF), caused by Machupo virus, was described following several clusters of cases in 1959. The 2,000–3,000 cases of naturally acquired BHF have all been from the Beni Department of north-western Bolivia. Sporadic cases predominantly involve adult males from rural environments (Kilgore et al. 1995), but several large outbreaks have been associated with high densities of the reservoir, *Calomys callosus*, in and around villages. Unlike its congener, *C. musculinus* (which is strictly associated with grassland and agricultural habitats), *C. callosus* can be found in close association with human dwellings. An outbreak in the town of San Joaquín in 1963–1964 ended abruptly after two weeks of continuous trapping in homes, during which 3,000 *C. callosus* were captured (Kuns 1965), and an ongoing program of rodent trapping in villages in the BHF-endemic area may be, at least in part, responsible for the scarcity of cases since 1974 (PAHO 1982).

Venezuelan haemorrhagic fever, described in 1989 (Salas et al. 1991), is caused by Guanarito virus, an arenavirus hosted by the cane mouse, *Zygodontomys brevicauda*. Recognised cases have been restricted to rural areas of southern Portuguesa and northern Barinas states. The highest risk of disease is among adult male farm workers, and the greatest numbers of cases occur between November and January (Manzione et al. 1998).

Finally, an arenaviral haemorrhagic fever caused by Sabiá virus is known from a single naturally acquired case near Sao Paulo, Brazil, in 1990 (Coimbra et al. 1994). Nothing is known about the reservoir, or the potential endemic area.

Old World Arenaviral Haemorrhagic Fevers

Lassa fever, which is endemic to West Africa, is the only recognised arenaviral haemorrhagic fever in the Old World. Although the magnitude and geographic extent of the cases are poorly known, Lassa virus probably causes 100,000 to 300,000 cases and 5,000 deaths annually (McCormick et al. 1987). The virus has been isolated from humans or rodents in Nigeria, Sierra Leone, Guinea, and Liberia, but serologic surveys show that Lassa or Lassa-like viruses are present in at least 10 other African countries (Peters et al. 1996; Appendix 1). Two or more species of the *Mastomys natalensis* species complex appear to serve as the reservoir for Lassa virus. At least eight species of *Mastomys* occur in Africa south of the Sahara, and their distribution and relationships are poorly understood (Robbins and Van Der Straeten 1989). A 32-chromosome species, *Mastomys huberti*, has been described as being found in dwellings, while a 38-chrom-osome species, *Mastomys erythroleucus*, was found in the surrounding bush areas; both species were frequently infected with Lassa virus with a prevalence of about 30% (McCormick et al. 1987).

Lymphocytic choriomeningitis (LCM), caused by the arenavirus lymphocytic

choriomeningitis virus (LCMV), is associated with the house mouse (*M. musculus*) throughout much of its worldwide range. LCMV usually produces a syndrome of fever and myalgia (sometimes complicated by meningitis), which is rarely serious, but infections during pregnancy have been associated with serious, even fatal complications to neonates (Peters et al. 1996). LCM is not considered a viral haemorrhagic fever and will not be discussed further. Nevertheless the disease may be much more common than is diagnosed, and biologists and pest control practitioners should be aware of the risk. Detailed reviews have been published (Jahrling and Peters 1992; Peters et al. 1996; Enría et al. 1999).

Potential Virus Diversity

The rate of discovery of new haemorrhagic fever viruses has increased almost exponentially in recent years. In the Americas, for instance, the number of known autochthonous hantaviruses has increased from one, in 1993, to over 21 in 1998 (Figure 1). The rate of discovery of new hantaviruses and arenaviruses is not slowing, and theoretical considerations suggest that we may recognise only a small proportion of the potential diversity. In general, each hantavirus and arenavirus appears to be associated with a single species of murid rodent host. The hantaviruses are associated with the Murinae, the Sigmodontinae, and the Arvicolinae; the arenaviruses with the Murinae and the Sigmodontinae. Furthermore, the phylogenetic relationships among the viruses (with some exceptions for the Arenaviridae) are generally mirrored by the phylogenetic relationships among the rodent hosts (Bowen et al. 1997; Mills et al. 1997a; Schmaljohn and Hjelle 1997). This pattern suggests that there was an ancestral hantavirus and arenavirus associated with an ancestral murid rodent, before the subfamilial lineages diverged, over 20 million years ago, and that the viruses have been co-speciating and co-evolving along with their rodent hosts since that time. Implicitly, the maximum potential number of hantaviruses and arenaviruses would be one for each of the 143 species of Arvicolinae, 529 species of Murinae, and 423 species of Sigmodontinae (numbers of species from Musser and Carleton 1993). Indeed, some species (e.g. *Sigmodon alstoni*, *Sigmodon hispidus*, *Bolomys obscurus*; Appendix 1) are known to host an arenavirus and a hantavirus. Nevertheless, it is unlikely that this maximum number of viral species will be found. Virus extinctions are very likely to have occurred in some murid lineages. For instance, some well-studied species (e.g. *M. musculus*, and *C. musculinus*) appear not to be associated with a hantavirus. It is also likely, however, that some trans-species 'host jumping' may have occurred over time (Bowen et al. 1997; Morzunov et al. 1998), thus further increasing the potential diversity of viruses.

Ecological Studies of Reservoir Species

Just as control of pest populations for economic reasons depends upon an understanding of the biology and ecology of pest species, the control or prevention of rodent-borne disease largely depends upon understanding the biology and ecology of

the host. Several basic research studies of the ecology of virus reservoir species during the past 12 years have provided information that potentially can be very useful for risk assessment and directed intervention in disease control.

In an earlier paper (Mills and Childs 1998) we reviewed some of these studies and outlined a series of directed goals toward the understanding of reservoir ecology as it relates to human disease. After initial identification of the reservoir host, these goals include (a) determining the potential disease-endemic area by identifying the geographic distribution of the host, and the range of infection by the pathogen within the host distribution; (b) more precisely defining relative human risk by determining the distribution of the host and pathogen among the distinct habitats on a regional scale; (c) investigating potential mechanisms of transmission of the pathogen within host populations; (d) conducting long-term prospective studies to elucidate the temporal patterns of infection in host populations; and (e) integrating data from reservoir studies toward the development of a predictive model that would allow the early identification of specific times, places, and conditions that may lead to increased rodent populations, or increased infection in rodent populations that can cause elevated risk of human disease. Although specifically directed at understanding rodent ecology in relation to human disease, many of these goals (especially a, b, d, and e) are applicable to studies of economic pests. In this section, the above-listed goals are used as a structural basis, while providing examples from studies and theoretical problems specific to the hantaviruses and arenaviruses, to illustrate the value of basic research toward the practical goal of preventing and controlling human disease caused by rodent-borne pathogens.

Defining disease-endemic areas

One of the most basic pieces of information for designing and directing a prevention program for any disease is a precise knowledge of the geographic area where a disease may occur (the potential endemic area). Prevention efforts, such as public education and reservoir control, must be directed throughout this area, while efforts outside the area represent wasted time and money. For any rodent-borne disease, the geographic distribution of the reservoir defines the maximum potential endemic area of the disease. For many rodent species in North America, the distributional ranges are precisely known and are available in the literature (Hall and Kelson 1959). Following the identification of the deer mouse as the reservoir for SNV (Childs et al. 1994), scientists consulted the published distribution of *P. maniculatus* in North America (Carleton 1989), and realised that the potential endemic area for HPS caused by SNV could encompass most of the North American continent. Education of physicians and increased surveillance soon confirmed that sporadic cases of HPS occurred throughout the range of the deer mouse in the United States. For other rodent species, in less extensively studied parts of the world, these distributions are poorly defined. This is the case with several important hantavirus and arenavirus reservoir species in South America. For example, the published distribution for *C. musculinus*, reservoir of Junín virus,

includes central and northern Argentina (Redford and Eisenberg 1992). Nevertheless, during recent ecological investigations of Laguna Negra virus on the Chaco of Paraguay (Yahnke et al. 1998), *C. musculinus* was frequently captured. A concerted effort, as well as multi-disciplinary studies that include health scientists, ecologists, and systematists, will be essential to define accurately the distributional ranges of important reservoir species.

For some host–virus systems (e.g. *P. maniculatus* and SNV), the host appears to be infected throughout its geographic range. In other cases, the distribution of the virus may include only a small portion of the range of the host. In those cases, the identification of the geographic area in which the host and the pathogen both occur provides a more precise definition of the potential disease-endemic area. While *C. musculinus* occurs throughout central and northern Argentina (and apparently western Paraguay), the AHF-endemic area occupies only a very limited region of the central Argentine Pampa (Maiztegui et al. 1986). Limited searches for Junín virus in *C. musculinus* populations outside the endemic area have been unsuccessful (Mills et al. 1991). *Calomys laucha* also occurs from central Argentina through south-eastern Bolivia, western Paraguay, and west-central Brazil (Musser and Carleton 1993), yet Laguna Negra virus apparently occurs only on the Chaco of Paraguay (Johnson et al. 1997, Mills and Childs 1998). Populations of *C. laucha* in Paraguay and central Argentina appear to be disjunct, and it is possible that the populations of *C. laucha* in Argentina are genetically distinct and will not support infection with Laguna Negra virus.

Populations of *C. musculinus* appear to be continuous across the boundary of an expanding AHF-endemic area (Maiztegui et al. 1986). The spatially restricted but expanding distribution of Junín virus within a continuous host population suggests recent introduction of Junín virus or recent genetic changes in the virus, host, or both populations. Reasons for the lack of coincidence in host and virus distributions are likely to be diverse and involve host genetics, geographic boundaries, and local extinctions in subpopulations. The elucidation of these factors, which will require collaboration among ecologists, virologists, geneticists, and systematists, will contribute to our understanding of host–virus coevolution, the relationships among rodent species, and the properties of host systems that are required to support long-term maintenance of viral symbionts. On the practical side, these studies will allow the precise definition of the geographic areas in which humans are at risk for specific diseases.

Defining habitat associations

In addition to the large geographic patterns discussed above, host and pathogen populations may vary on regional or local scales. Many species of rodents demonstrate distinct local habitat preferences, which may have practical implications for disease transmission as well as reservoir management. The risk of human disease may be more precisely defined by describing differences in host distribution, population densities, and prevalence of infection among the distinct habitats represented in a local area. Even for species that are considered

opportunists or generalists, habitat studies may yield useful information.

The deer mouse is considered a habitat generalist and has been reported as occurring in nearly every dry-land habitat in North America (Burt and Grossenheider 1976). A habitat study conducted in the south-western United States confirmed that *P. maniculatus* occupied all of the major habitats represented (Mills et al. 1997b). Nevertheless, the prevalence of infection with SNV varied significantly among habitats, being lowest at the altitudinal and climatic extremes (desert and alpine tundra) and highest at the middle altitude habitats such as chaparral, grassland, and piñon-juniper woodland. The last habitat is where most HPS cases in the south-western United States have occurred. Similar results were demonstrated by a study in Nevada and California (Boone et al. 1998). Results such as these can be applied by public health scientists to define more precisely the relative risk of disease to humans living, working, or pursuing recreational activities in various habitats.

The corn mouse, *C. musculinus*, has historically been considered a denizen of corn fields, as its common name implies. Junín virus has been thought to be transmitted to farmers working in those crop fields during the mechanised harvesting process (Carballal et al. 1988). Recently however, habitat studies conducted in the AHF-endemic area demonstrated a distinct preference by *C. musculinus* for the relatively stable, weedy border habitats (fence lines and roadsides) adjacent to the crop fields (Figure 2).

These results suggest a need to reconsider the possible places and mechanisms of transmission of Junín virus to humans. They also suggest a specific intervention mechanism for decreasing the incidence of AHF: periodically burning or cutting the weedy border habitats to eliminate the preferred habitat for the reservoir host. Habitat studies conducted for other

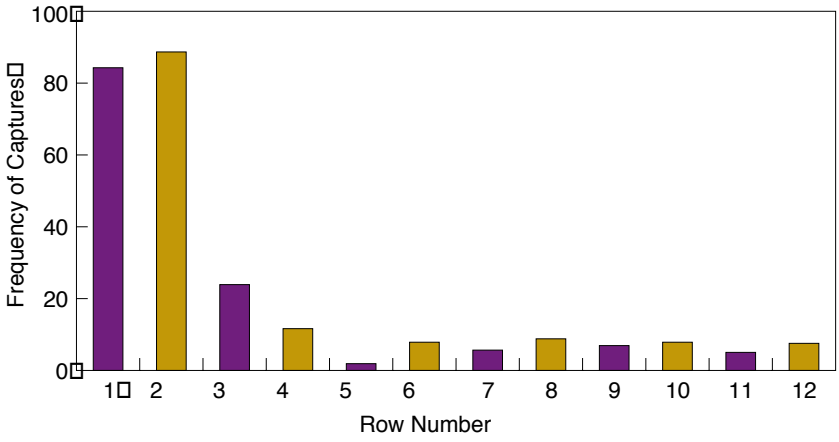

Figure 2.
Cumulative numbers of captures within each of 12 rows of traps of a 12 by 12 trapping grid located in crop fields and adjacent roadside habitat in central Argentina, March 1998 to August 1990. Rows 1 and 2 are roadside habitat; rows 3 through 12 are in crop fields.

reservoir species might suggest similar approaches. Identifying mechanisms of transmission

Basic field studies of reservoir demography have provided important clues to the specific mechanisms of virus transmission within host populations. Field studies with SNV (Mills et al. 1997b) and Black Creek Canal virus (Glass et al. 1998) have shown a J-shaped curve of antibody prevalence with host age. This pattern suggests that the young of infected females are born with maternal antibody, which is lost within a few weeks. Infection is then acquired by some horizontal mechanism later in life. Field data have also demonstrated a positive correlation between scars and the prevalence of infection (Glass et al. 1988). The more aggressive males may have a much higher prevalence of infection than females (Mills et al. 1992; Mills et al. 1997b). Thus, an important, specific mechanism of virus transfer within reservoir populations may be aggressive encounters among adult male animals. Laboratory studies have indicated that lymphocytic choriomeningitis and Lassa viruses are maintained by vertical transmission mechanisms (Childs and Peters 1993). However preliminary field data have demonstrated an age-associated acquisition of antibody in *Mastomys* populations in Guinea (A.H. Demby and 10 others, unpublished data). This and similar disparities between laboratory and field results for Junín virus (Mills et al. 1992) may indicate that laboratory results may not always be applicable to natural field conditions and that field studies are important for testing predictions based on laboratory results.

Long-term studies

Perhaps the greatest amount of useful information about reservoir populations and host–virus dynamics is achieved through the use of longitudinal mark–recapture studies (Mills et al. 1999b). These studies involve the establishment of multiple permanent trapping plots, which are operated at defined intervals (usually monthly for disease studies) for several consecutive nights. Captured rodents are measured, sampled (e.g. blood and oral swab), identified with a permanent mark or number, and released at the site of capture. In subsequent trapping events, animals are repeatedly captured, measured, and sampled. In this way, changes in community structure and population densities — as well as individual growth rates, movement, reproductive condition, and infection status —are measured over time. Simultaneous monitoring of environmental variables, such as temperature, rainfall, and growth and cover by vegetation, provides clues concerning environmental changes that are related to changes in reservoir populations and, subsequently, changes in risk of human disease.

Mark–recapture studies have helped to elucidate the temporal population dynamics of host virus infection for the reservoirs of Seoul and Prospect Hill viruses (Childs et al. 1987), Puumala virus (Niklasson et al. 1995), Junín virus (Mills et al. 1992), and SNV (Douglass et al. 1996; Mills et al. 1999b). The cited studies and others in progress are helping to elucidate the associations among environmental conditions, rodent population densities, prevalence of infection in reservoir populations, and human disease risk.

The incidence of several rodent-borne diseases is related to changes in density of reservoir populations. Large year-to-year fluctuations in population density are characteristic of rodent populations of many species. Northern Hemisphere arvicolines, such as the reservoir for Puumala virus (*C. glareolus*), undergo regular population cycles with a periodicity of 3–4 years, although the causes for the cycles are still unclear (Krebs and Myers 1974; Niklasson et al. 1995). The year-to-year incidence of HFRS caused by Puumala virus was shown to be correlated with the density of *C. glareolus* in Russia and Scandinavia (Niklasson et al. 1995).

Regular population cycles are not known in rodents from the Northern Hemisphere tropics or anywhere in the Southern Hemisphere. However, periodic, dramatic increases in the density of some rodent populations do occur. These population irruptions are generally associated with unusual climatic conditions, which result in abundant food supplies and ideal or prolonged conditions for reproduction. A three-year longitudinal study of *C. musculinus* in Argentina demonstrated a clear positive association between reservoir population density and the magnitude of AHF epidemics (Figure 3).

The associated environmental conditions were a relatively benign winter, followed by a wet summer, which apparently resulted in unusually lush vegetation and abundant food supplies (Mills et al. 1992).

The outbreak of HPS in the south-western United States in 1993 was preceded by an El

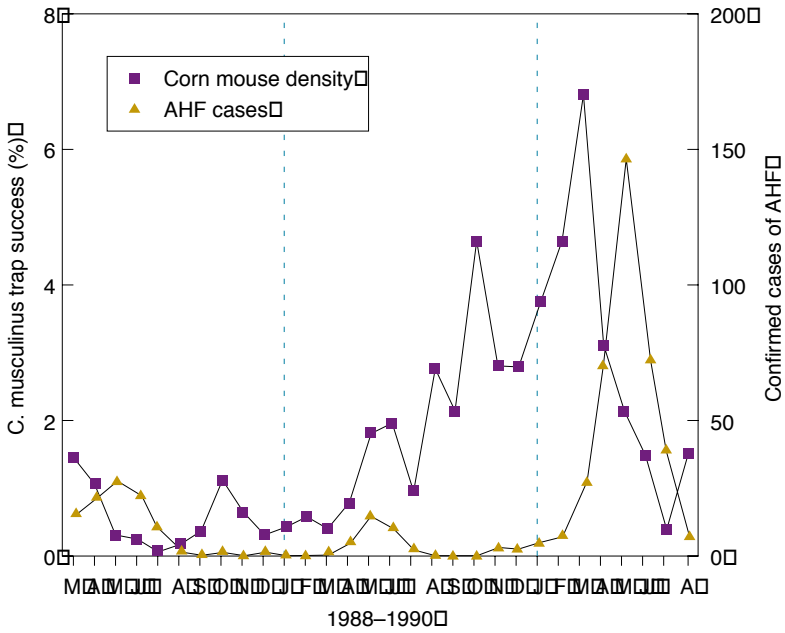

Figure 3.
Mean numbers of captures of *Calomys musculinus* per 100 trap nights (trap success) and numbers of cases of Argentine haemorrhagic fever (AHF) in central Argentina, March 1998 to August 1990. Reprinted with permission from Mills et al. (1992).

Niño Southern Oscillation (ENSO) event, which resulted in unusually warm winters and high rainfall in affected areas. It has been hypothesised that the HPS outbreak was a direct result of increases in rodent populations and increases in prevalence of SNV infection among high-density reservoir populations (Parmenter et al. 1993). Although intuitively attractive, no longitudinal monitoring of rodent populations and infection status was in place in the area of the outbreak, so this hypothesis cannot be confirmed. Subsequent to the outbreak, however, the Centers for Disease Control and Prevention, in collaboration with several local universities, initiated a series of longitudinal mark–recapture studies in the south-western United States (Mills et al. 1999b). These studies were in place to document environmental changes and associated increases in reservoir populations in some areas of the south-west in response to an ENSO event in 1997/1998 (T.L. Yates, K.D. Abbott, C.H. Calisher and M.L. Morrison, unpublished data). These increases in reservoir populations have been associated with increased numbers of HPS cases in the south-western United States. As of August 1998, there have been about 14 cases in the four-state area of Arizona, Colorado, New Mexico, and Utah, in comparison to 2, 2, and 4, for the same time periods in 1995, 1996, and 1997, respectively (Centers for Disease Control and Prevention, unpublished data).

A recent outbreak of HPS in southern Chile was apparently preceded by a dramatic increase in local populations of the reservoir of Andes virus (*Oligoryzomys longicaudatus*). Causes for the rodent irruption are unclear, but may be related to an unusually benign winter or to the flowering of a local species of bamboo, an event that may occur only every 40 years and that provides abundant food for the granivorous *O. longicaudatus* (Murúa et al. 1996; Toro et al. 1998). Longitudinal studies are currently being planned and initiated in Chile and Argentina to follow the environmental variables associated with changes in population density and infection status in *O. longicaudatus* populations and the relation of these variables to human disease.

An important key to being able to predict the relative risk of diseases to humans is understanding the conditions that lead to increased virus transmission and increased prevalence of infection in host populations. Infection appears to be associated with behavioural events involving the interactions of individual rodents. Given the pattern of horizontal transmission demonstrated for many hantaviruses and arenaviruses, it might be predicted that increasing population densities should result in increased rodent-to-rodent contact and a higher prevalence of infection in host populations. In fact, however, investigators are frequently unable to show a correlation between rodent population density and prevalence of infection in rodent populations (Mills et al. 1992; Douglass et al. 1996; Bond et al. 1998; Boone et al. 1998). The problem with these approaches may be in seeking an instantaneous, linear relationship between density and antibody prevalence. In strongly seasonal environments, the effects of seasonal reproduction and horizontal transmission of virus may result in an alternation of peaks in population density and prevalence of infection. In Sweden, the population density of

C. glareolus was highest in autumn (Niklasson et al. 1995), while the prevalence of antibody to Puumala virus in these populations was highest in the spring, and correlated with vole population density the previous fall. A similar pattern of alternating peaks in density and antibody prevalence was observed for populations of *Apodemus azarae* infected with Pergamino virus in Argentina—rodent density was highest in the fall, antibody prevalence was highest in the spring (Schmidt et al. 1998). This pattern has also been observed for *P. maniculatus* populations infected with SNV in Colorado (Calisher et al. 1999), and *Peromyscus boylii* infected with a Sin Nombre-like virus in Arizona (Abbott et al. 1999). This delayed-density-dependent prevalence of infection may be typical for viruses transmitted by horizontal mechanisms in seasonal environments. Autumn populations display peak densities because of the culmination of the spring/summer reproductive effort; yet the population consists primarily of young of the year that have not yet been infected, or are only recently infected and do not yet have detectable antibody. The cessation of reproduction and over-winter mortality results in a population nadir in the spring, but at that time the population consists exclusively of older adults, which are more likely to be infected. In an autumn during which particularly high population levels occur, crowding would presumably lead to more intraspecific contacts, more virus transmission events, and a proportionally higher antibody prevalence the following spring (Niklasson et al. 1995; Mills et al. 1999a). Research leading to an understanding of the conditions that lead to increased virus transmission and prevalence of infection in host populations will improve the ability of public health scientists and modellers to predict increases in the risk of human disease.

Predictive models of disease risk

Perhaps the most important practical application of studies of reservoir populations is to integrate the data from these studies into a predictive model that would allow public health practitioners to identify specific times and places where conditions may pose a threat to the public health. Such a model (Figure 4) assumes that the risk of human disease is related to rodent population density and prevalence of infection; rodent populations are affected by the quality of the biotic environment (e.g. habitat quality and food supply); and the abiotic environment (e.g. edaphic factors and weather) influences rodent populations both directly (e.g. direct effects of cold temperatures on survival) and indirectly (through their effect on habitat quality and food supply; Mills and Childs 1998). It is not possible to have scientists continuously measuring rodent populations and environmental variables wherever rodent-borne diseases occur. However, this may not be necessary.

Recent studies using satellite imaging and geographic information systems have demonstrated that remotely monitored vegetation indices can help predict the changing risk of human disease in sites as far away as East Africa (Linthicum et al. 1987), and the south-western United States (Boone et al. 1998; Cheek et al. 1998). The success of these mathematical models will depend upon the accuracy of the parameter estimates, and the accuracy of the estimates,

in turn, will depend upon data collected by investigators conducting basic field and laboratory research into the ecology and biology of the rodent reservoirs.

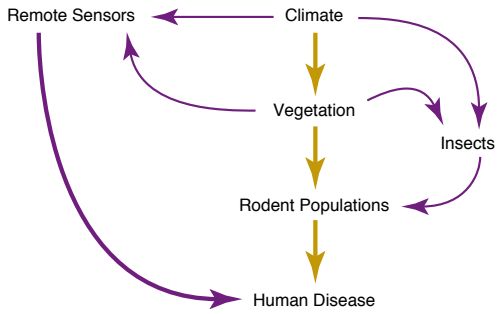

Figure 4.
Simplified schematic model of relationships among ecosystem components within an endemic area for a rodent-borne human disease. Remote sensors (satellites) may be used for detecting changes in the ecosystem components which may lead to increased risk of disease. From Mills and Childs (1998).

The Risk to Rodent Biologists

In the United States, the sudden realisation that wild rodents are the reservoir for potentially lethal disease has resulted in significant changes in the way many rodent biologists conduct their research and teaching. Mammalogy classes avoid the handling of sigmodontine rodents by students, the establishment of laboratory colonies from wild captured individuals of known reservoir species is strictly controlled, and researchers who handle reservoir rodents are prudent to follow safety guidelines.

The chance of contracting HPS by handling New World sigmodontine rodents appears to be low. Nevertheless, the disease is sufficiently severe to warrant strict safety measures for the general public (CDC 1993), and there is evidence that wildlife biologists are at increased risk. Among the first 100 cases of HPS in the United States, three were in wildlife biologists, and although a recent serosurvey of over 1,000 American mammalogists demonstrated that the risk of infection with SNV appeared to be low (less than 1%), risk increased with the number of *Peromyscus* that investigators had handled during their careers (Armstrong et al. 1994). A study of Finnish mammalogists showed a more striking relationship. Although no mammalogist with less than five years of experience had antibody to Puumala virus, 40% of those who had trapped voles for more than 10 years had antibody (Brummer-Korvenkontio et al. 1982). These results suggest that Puumala virus is more easily transmitted to humans than is SNV (although because of the high mortality of SNV, about half of those infected would not be available for sampling). Fortunately, nephropathia epidemia is a relatively mild disease. The murine- and sigmodontine-associated HFRS, HPS, Lassa fever, and South American haemorrhagic fevers can be much more severe and can lead to fatalities in 15–50% of cases. Relatively simple safety precautions will minimise the risk of infection to biologists and are highly recommended for all researchers handling all known viral haemorrhagic fever reservoir species.

Standard precautions have been promulgated for investigators conducting field studies, which may involve handling reservoir species for haemorrhagic fever viruses. These guidelines, which were developed during field studies of Junín virus in Argentina and the sigmodontine

hantaviruses in the Americas, have been published in English (Mills et al. 1995a,b) and in Spanish (Mills et al. 1998). Briefly, investigators should wear rubber gloves when handling traps containing captured animals, and the traps should be handled in a manner that will prevent or minimise contact with rodent excretions or secretions and inhalation of potentially infectious aerosols of these materials. If captured rodents are transported, the traps containing them should be placed in airtight plastic bags. These bags subsequently should be opened and the rodents handled only in an isolated outdoor area by personnel wearing protective equipment (latex gloves, gowns or overalls, respirators fitted with high-efficiency particulate air filters, and goggles). Handling rodents outdoors is preferred in order to take advantage of the disinfectant properties of natural ultraviolet light and the rapid dilution of aerosols in open circulating air. Rodents should be anesthetised before handling to prevent bites and production of aerosols, and the use of sharp instruments such as needles and scalpels should be avoided when possible. Instruments, working surfaces, and traps should be decontaminated using an appropriate disinfectant (e.g. 5% hospital strength Lysol, or 10% household bleach in water), and contaminated gloves, disposable gowns, and wastes should be autoclaved or burned. Rodent carcasses kept for museum specimens can be decontaminated by fixing in 10% formalin for at least 48 hours.

Pest control workers should be alert to the possibility of inhalation of infectious aerosols when working in closed structures, which may be infested by hantavirus or arenavirus reservoir species. The doors and windows of such structures should be opened, and the building allowed to air out for at least 30 minutes before beginning work. Clean-up of these structures should be conducted so as to avoid the creation of aerosols. Nesting materials or contaminated areas should be wetted down with disinfectant, and floors should be mopped, not swept (CDC 1993).

Hantavirus infection in laboratory rodent colonies has resulted in extensive outbreaks of human disease (Kulagin et al. 1962). Precautions when initiating laboratory colonies from wild rodents that are known reservoir species for hantaviruses or arenaviruses should include quarantine as defined cohorts and serologic screening upon capture, and again after 30 days (Mills et al. 1995b).

The rodent-borne haemorrhagic fever viruses are only one example of many zoonotic agents that are likely to be hosted by rodents. In this chapter they have been used as an example to illustrate the potential diversity of rodent-borne disease agents. Although the diseases they cause are dramatic, the risk to researchers can be minimised by the adherence to relatively simple safety guidelines. Researchers studying these agents have amassed a large amount of new data during the last 5–6 years. Continued basic research into the ecology of these host–virus systems promises to provide useful models for understanding host–pathogen coevolution, transmission processes in natural populations, and the relationship of environmental factors to host populations, pathogen transmission patterns, and human disease.

Acknowledgments

Thanks to Barbara Ellis for graphics, and to Barbara Ellis, Jamie Childs, Tom Ksiazek, and C.J. Peters for helpful comments on the manuscript.

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Appendix 1. Currently recognised hantaviruses and the diseases they produce, the small mammal host species and host distribution. Nomenclature and distributions from Wilson and Reeder (1993).

Host subfamily	Reservoir	Virus	Disease	Distribution of reservoir
Murinae	*Apodemus agrarius*	Hantaan	HFRS	C. Europe, S to Thrace, Caucasus, and Tien Mtns; Amur River through Korea, to E. Xizang and E. Yunnan, W. Sichuan, Fujiau, Taiwan.
	A. flavicollis	Dobrava	HFRS	England, Wales; NW Spain, France, Denmark, S. Scandinavia through European Russia, Italy, Balkans, Syria, Lebanon, Israel; Netherlands
	Bandicota indica	Thai	not known	Sri Lanka, India, Nepal, Burma, S. China, Taiwan, Thailand, Laos, Vietnam; introduced to Malay Peninsula and Java
	Rattus norvegicus	Seoul	not known	Nearly worldwide
Arvicolinae	*Clethrionomys glareolus*	Puumala	not known	France and Scandinavia to Lake Baikal, S to N Spain, N Italy, Balkans, W Turkey, N Kazakhstan; Britain, SW Ireland
	C. rufocanus	not named	not known	Scandinavia through Siberia to Kamchatka, S to Ural Mtns, Altai Mtns, Mongolia, Transbaikal, N. China, Korea, N. Japan
	Lemmus sibericus	Topografov	not known	Palearctic from White Sea, W Russia, to Chukotski Peninsula, NE Siberia, Kamchatka; Nearctic from W Alaska E to Baffin Island, Hudson Bay, S in Rocky Mtns to C. British Columbia
	Microtus arvalis	Tula	not known	Spain through Europe to Black Sea and Kirov region, Russia; Orkney Islands, Guernsey, and Yeu (France)
	M. rossiaemeridionalis	Tula	not known	From Finland E to Urals, S to Caucasus, through Ukraine E to Rumania, Bulgaria, S. Yugoslavia, N Greece, NW Turkey
	M. californicus	Isla Vista	not known	SW Oregon through California, USA, to N Baja California, Mexico
	M. fortis	Khabarovsk	not known	Transbaikal and Amur Region S though Nei Mongol and E China to lower Yangtze Valley and Fujian

Appendix 1. (Cont'd) Currently recognised hantaviruses and the diseases they produce, the small mammal host species and host distribution. Nomenclature and distributions from Wilson and Reeder (1993).

Host subfamily	Reservoir	Virus	Disease	Distribution of reservoir
Arvicolinae (cont'd)	*M. ochrogaster*	Bloodland Lake	not known	EC Alberta to S Manitoba, Canada S to N Oklahoma and Arkansas E to C Tennessee and W Virginia, USA
	M. pennsylvanicus	Prospect Hill	not known	C Alaska to Labrador, Newfoundland, Prince Edwards Island; S in Rocky Mtns to New Mexico, Great Plains to N Kansas, Appalachians to N Georgia, USA
Sigmodontinae	*Bolomys obscurus*	Maciel	not known	S Uruguay and EC Argentina
	Calomys laucha	Laguna Negra	HPS	N Argentina and Uruguay, SE Bolivia, W Paraguay, WC Brazil
	Oligoryzomys chacoensis	Bermejo	not known	W Paraguay, SE Bolivia, WC Brazil, N Argentina
	O. flavescens	Lechiguanas	HPS	SE Brazil, Uruguay, Argentina
	O. longicaudatus	Andes	HPS	Andes of Chile and Argentina
	O. longicaudatus?	Oran	HPS	Andes of Chile and Argentina
	O. microtis	Rio Mamore	not known	C Brazil, contiguous lowlands of Peru, Bolivia, Argentina
	Oryzomys palustris	Bayou	HPS	SE USA
	Peromyscus leucopus	New York	HPS	C and E USA into S and SE Canada, S to Yucatan Peninsula, Mexico
	P. maniculatus	Sin Nombre	HPS	Alaska across N Canada, S through USA to S Baja California and NC Oaxaca, Mexico
	Reithrodontomys megalotis	ElMoro Canyon	not known	SC British Columbia and SE Alberta, Canada, W and NC USA, S to N Baja California, and interior Mexico to C Oaxaca
	R. mexicanus	Rio Segundo	not known	S Tamaulipas and WC Michoacan, Mexico S to Panama; Andes of Columbia, Ecuador
	Sigmodon alstoni	Caño Delgadito	not known	NE Colombia, N and E Venezuela, Guyana, Surinam, and N Brazil
	S. hispidus	BlackCreek Canal	HPS	SE USA, interior Mexico to C Panama, N Colombia and N Venezuela
	Unknown	Juquitiba	HPS	(Human cases from Brazil)
Non-rodent	*Suncus murinus* (insectivore)	Thotopalayam	not known	Afghanistan, Pakistan, India, Sri Lanka, Nepal, Bhutan, Burma, China, Taiwan, Japan, Indomalayan region; introduced to coastal E Africa, Madagascar, Comores, Mauritius, Reunion & coastal Arabia.

Appendix 2. Currently recognised arenaviruses and the diseases they produce, small mammal host species and host distributions. Nomenclature and distributions from Wilson and Reeder (1993).

Hostsubfamily	Reservoir	Virus	Disease	Distribution of reservoir
Murinae	*Arvicanthus* sp.	Ippy	Not known	S Mauritania, Senegal, Gambia, E through Sierra Leone, Ivory Coast, Ghana, Burkina Faso, Togo, Benin, Nigeria, Niger, Chad, Sudan, Egypt, to Ethiopia; S through N Zaire, Uganda, S Burundi, Kenya, S Somalia & Tanzania, to E Zambia
	Mastomys natalensis	Mopeia	Not known	S Africa as far north as Angola, S Zaire, and Tanzania
	Mastomys spp.	Lassa	Lassa fever	Africa south of the Sahara
	Mus musculus	Lymphocytic choriomeningitis	LCM	Most of world in association with humans
	Praomys sp.	Mobala	Not known	C Nigeria through Cameroon Republic and Central African Republic, S. Sudan, Zaire, N Angola, Uganda, Rwanda, Kenya, south through E Tanzania to N and E Zambia
Sigmodontinae	*Bolomys obscurus*	Oliveros	Not known	S Uruguay and EC Argentina
	Calomys callosus	Machupo	Bolivian hemorrhagic fever	N Argentina, E Bolivia, W Paraguay, WC to EC Brazil
	C. callosus	Latino	Not known	N Argentina, E Bolivia, W Paraguay, WC to EC Brazil
	C. musculinus	Junín	Argentine hemorrhagic fever	N and C Argentina, E Paraguay
	Neacomys guianae	Amaparí	Not known	Guianas, S Venezuela, N Brazil
	Neotoma albigula	Whitewater Arroyo	Not known	SE California to S Colorado to W Texas, USA, south to Michoacan & W Hidalgo, Mexico
	Oryzomys buccinatus?	Paraná	Not known	E Paraguay and NE Argentina
	O. albigularis	Pichindé	Not known	N & W Venezuela, E Panama, Andes of Colombia & Ecuador to N Peru
	Oryzomys sp.?	Flexal	Not known	Not known
	S. alstoni	Pirital	Not known	NE Colombia, N and E Venezuela, Guyana, Surinam, N Brazil

Appendix 2. (Cont'd) Currently recognised arenaviruses and the diseases they produce, small mammal host species and host distributions. Nomenclature and distributions from Wilson and Reeder (1993).

Hostsubfamily	Reservoir	Virus	Disease	Distribution of reservoir
Sigmodontinae	*S. hispidus*	Tamiami	Not known	SE USA, Mexico to C Panama, N Colombia and N Venezuela
	Zygodontomys brevicauda	Guanarito	Venezuelan hemorrhagic fever	S Costa Rica through Panama, Colombia, Venezuela, Guianas, to N Brazil; including Trinidad & Tobago and smaller islands adjacent Panama & Venezuela
	Unknown	Sabiá	Unnamed	(Human cases from Sao Paulo State, Brazil)
Non-rodent	*Artibeus* (bats)?	Tacaribe	Not known	(Isolates from bats on Trinidad and Tobago)