Hantaviruses: A Global Disease Problem

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Hantaviruses are carried by numerous rodent species throughout the world. In 1993, a previously unknown group of hantaviruses emerged in the United States as the cause of an acute respiratory disease now termed hantavirus pulmonary syndrome (HPS). Before then, hantaviruses were known as the etiologic agents of hemorrhagic fever with renal syndrome, a disease that occurs almost entirely in the Eastern Hemisphere. Since the discovery of the HPS-causing hantaviruses, intense investigation of the ecology and epidemiology of hantaviruses has led to the discovery of many other novel hantaviruses. Their ubiquity and potential for causing severe human illness make these viruses an important public health concern; we reviewed the distribution, ecology, disease potential, and genetic spectrum.

The genus Hantavirus, family Bunyaviridae, comprises at least 14 viruses, including those that cause hemorrhagic fever with renal syndrome (HFRS) and hantavirus pulmonary syndrome (HPS) (Table 1). Several tentative members of the genus are known, and others will surely emerge as their natural ecology is further explored. Hantaviruses are primarily rodent-borne, although other animal species harboring hantaviruses have been reported. Unlike all other viruses in the family, hantaviruses are not transmitted by arthropod vectors but (most frequently) from inhalation of virus-contaminated aerosols of rodent excreta (1). Human-to-human transmission of hantaviruses has not been documented, except as noted below.

The recognition of a previously unknown group of hantaviruses as the cause of HPS in 1993 is an example of virus emergence due to environmental factors favoring the natural reservoir; a larger reservoir increases opportunities for human infection. We reviewed the global distribution of hantaviruses, their potential to cause disease, and their relationships to each other and to their rodent hosts.

History of HFRS and HPS

“Hemorrhagic fever with renal syndrome” denotes a group of clinically similar illnesses that occur throughout the Eurasian landmass and adjoining areas (2,3). HFRS includes diseases previously known as Korean hemorrhagic fever, epidemic hemorrhagic fever, and nephropathia epidemic (4). Although these diseases were recognized in Asia perhaps for centuries, HFRS first came to the attention of western physicians when approximately 3,200 cases occurred from 1951 to 1954 among United Nations forces in Korea (2,5). Other outbreaks of what is believed to have been HFRS were reported in Russia in 1913 and 1932, among Japanese troops in Manchuria in 1932 (2,6), and in Sweden in 1934 (7,8). In the early 1940s, a viral etiology for HFRS was suggested by Russian and Japanese investigators who injected persons with filtered urine or serum from patients with naturally acquired disease (2). These studies also provided the first clues to the natural reservoir of hantaviruses: the Japanese investigators claimed to produce disease in humans by injecting bacteria-free filtrates of tissues from Apodemus agrarius or mites that fed on the Apodemus mice. Mite transmission was never conclusively demonstrated by other investigators, and it was not until 1978 that a rodent reservoir for HFRS-causing viruses was confirmed by investigators who demonstrated that patient sera reacted with antigen in lung sections of wild-caught Apodemus agrarius or mites that fed on the Apodemus mice. The successful propagation of Hantaan (HTN) virus in cell culture in 1981 provided the first opportunity to study this pathogen systematically (9). The history of HFRS has been explored (2,11,12).
| Species          | Disease | Principal Reservoir             | Distribution of Virus | Distribution of Reservoir |
|------------------|---------|---------------------------------|-----------------------|---------------------------|
| Hantaan (HTN)    | HFRS\(^a\) | Apodemus agrarius               | China, Russia, Korea  | C Europe south to Thrace, Caucasus, & Tien Shan Mtns; Amur River through Korea to E Xizang & E Yunnan, W Sichuan, Fujiau, & Taiwan (China) England & Wales, from NW Spain, France, S Scandinavia through European Russia to Urals, S Italy, the Balkans, Syria, Lebanon, & I srael |
| Dobrava-Belgrade (DOB) | HFRS | Apodemus flavicollis            | Balkans               |                           |
| Seoul (SEO)      | HFRS    | Rattus norvegicus               | Worldwide             | Worldwide                  |
| Puumala (PUU)    | HFRS    | Clethrionomys glareolus         | Europe, Russia, Scandinavia |                           |
| Thailand (THAI)  | nd\(^b\) | Bandicota indica                | Thailand              |                           |
| Prospect Hill (PH) | nd | Microtus pennsylvanicus         | U.S., Canada          | C Alaska to Labrador, including Newfoundland & Prince Edward Island, Canada; Rocky Mountains to N New Mexico, in Great Plains to N Kansas, & in Appalachians to N Georgia, U.S. Transbaikalia Amur region; E China |
| Khabarovsk (KHB) | nd      | Microtus fortis                | Russia                |                           |
| Thottapalayam (TPM) | nd | Suncus murinus                   | India                 | Afghanistan, Pakistan, India, Sri Lanka, Nepal, Bhutan, Burma, China, Taiwan, J apan, Indomalayan Region |
| Tula (TUL)       | nd      | Microtus arvalis                | Europe                | Throughout Europe to Black Sea & NE to Kirov region, Russia |
| Sin Nombre (SN)  | HPS\(^c\) | Peromyscus maniculatus          | U.S., Canada, Mexico  | Alaska Panhandle across N Canada, south through most of continental U.S., excluding SE & E seaboard, to southernmost Baja California Sur and to NC Oaxaca, Mexico C and E U.S. to S Alberta & S Ontario, Quebec & Nova Scotia, Canada; to N Durango & along Caribbean coast to Isthmus of Tehuantepec & Yucatan Peninsula, Mexico |
| New York (NY)    | HPS     | Peromyscus leucopus             | U.S.                  |                           |

\(^a\)HFRS, hemorrhagic fever with renal syndrome
\(^b\)nd, none documented
\(^c\)HPS, hantavirus pulmonary syndrome
## Synopses

Table 1. Members of the genus *Hantavirus*, family Bunyaviridae (continued)

| Species            | Disease | Principal Reservoir          | Distribution of Virus | Distribution of Reservoir                                                                 |
|--------------------|---------|------------------------------|-----------------------|-------------------------------------------------------------------------------------------|
| Black Creek Canal  | HPS     | *Sigmodon hispidus* (cotton rat) | U.S.                  | SE U.S., from S Nebraska to C Virginia south to SE Arizona & peninsular Florida; interior & E Mexico through Middle America to C Panama; in South America to N Colombia & N Venezuela British Columbia & SE Alberta, Canada; W and NC U.S., S to N Baja California & interior Mexico to central Oaxaca |
| (BCC)              |         |                              |                       |                                                                                           |
| El Moro Canyon     | nd      | *Reithrodontomys megalotis* (Western harvest mouse) | U.S., Mexico          | SE Kansas to E Texas, eastward to S New Jersey & peninsular Florida                      |
| (ELMC)             |         |                              |                       |                                                                                           |
| Bayou (BAY)        | HPS     | *Oryzomys palustris* (rice rat) | U.S.                  | SE Kansas to E Texas, eastward to S New Jersey & peninsular Florida                      |
|                    |         |                              |                       |                                                                                           |
| Probable species:  |         |                              |                       |                                                                                           |
| Topografov (TOP)   | nd      | *Lemmus sibiricus* (Siberian lemming) | Siberia              | Palearctic, from White Sea, W Russia, to Chukotski Peninsula, NE Siberia, & Kamchatka; Neartic, from W Alaska E to Baffin Island & Hudson Bay, S Rocky Mtns to C B.C., Canada NC to S Andes, approximately to 50 deg S latitude, in Chile & Argentina |
| Andes (AND)        | HPS     | *Oligoryzomys longicaudatus* (long-tailed pygmy rice rat) | Argentina            | N Argentina & Uruguay, SE Bolivia, W Paraguay, and WC Brazil                              |
|                    |         |                              |                       |                                                                                           |
| To be named        | HPS     | *Calomys laucha* vesper mouse | Paraguay              | N Argentina & Uruguay, SE Bolivia, W Paraguay, and WC Brazil                              |
|                    |         |                              |                       |                                                                                           |
| Isla Vista (ISLA)  | nd      | *Microtus californicus* (California vole) | U.S.                  | Pacific coast, from SW Oregon through California, U.S., to N Baja California & Mexico N & C Great Plains, EC Alberta to S Manitoba, Canada, S to N Oklahoma & Arkansas, E to C Tennessee & W West Virginia, U.S.; relic populations elsewhere in U.S. & Mexico |
|                    |         |                              |                       |                                                                                           |
| Bloodland Lake     | nd      | *Microtus ochrogaster* (prairie vole) | U.S.                  | See Black Creek Canal                                                                      |
| (BLL)              |         |                              |                       |                                                                                           |
| Muleshoe (MUL)     | nd      | *Sigmodon hipidus* (cotton rat) | U.S.                  | See Black Creek Canal                                                                      |
| Rio Segundo (RIOS) | nd      | *Reithrodontomys mexicanus* (Mexican harvest mouse) | Costa Rica            | S Tamaulipas & WC Michoacan, Mexico, S through Middle American highlands to W Panama; Andes of W Colombia & N Ecuador & N Ecuador |
| Rio Mamore (RIOM)  | nd      | *Oligoryzomys microtis* (small-eared pygmy rice rat) | Bolivia              | C Brazil south of Rios Solimoes-Amazon & contiguous lowlands of Peru, Bolivia, Paraguay, & Argentina |

\[^{d}^\text{not yet isolated in cell culture}\]
\[^{e}^\text{viruses for which incomplete characterization is available, but for which there is clear evidence indicating that they are unique}\]
\[^{f}^\text{suspected host, but not confirmed}\]

Adapted from (57,72) and from (9,13,23,38,42,43,50-71)
HPS was first described in 1993 when a cluster of cases of adult fatal respiratory distress of unknown origin occurred in the Four Corners region of the United States (New Mexico, Arizona, Colorado, and Utah). The unexpected finding that sera from patients reacted with hantaviral antigens was quickly followed by the genetic identification of a novel hantavirus in patients' tissues and in rodents trapped near patients' homes (13-15).

**Prevalence and Clinical Course**

Approximately 150,000 to 200,000 cases of HFRS involving hospitalization are reported each year throughout the world, with more than half in China (16). Russia and Korea also report hundreds to thousands of HFRS cases each year. Most remaining cases (hundreds per year) are found in Japan, Finland, Sweden, Bulgaria, Greece, Hungary, France, and the Balkan countries formerly constituting Yugoslavia (16). Depending in part on which hantavirus is responsible for the illness, HFRS can appear as a mild, moderate, or severe disease (Table 2). Death rates range from less than 0.1% for HFRS caused by Puumala (PUU) virus to approximately 5% to 10% for HFRS caused by HTN virus (16). The clinical course of severe HFRS involves five overlapping stages: febrile, hypotensive, oliguric, diuretic, and convalescent; it is not uncommon, however, for one or more of these stages to be inapparent or absent. The onset of the disease is usually sudden with intense headache, backache, fever, and chills. Hemorrhage, if it occurs, is manifested during the febrile phase as a flushing of the face or injection of the conjunctiva and mucus membranes. A petechial rash may also appear, commonly on the palate and axillary skin folds. Sudden and extreme albuminuria, around day 4, is characteristic of severe HFRS. As the febrile stage ends, hypotension can abruptly develop and last for hours or days, during which nausea and vomiting are common.

One-third of deaths occur during this phase because of vascular leakage and acute shock. Almost half of all deaths occur during the subsequent (oliguric) phase because of hypervolemia. Patients who survive and progress to the diuretic phase show improved renal function but may still die of shock or pulmonary complications. The final (convalescent) phase can last weeks to months before recovery is complete (3,5,12).

More than 250 cases of HPS have been reported throughout North and South America. Although the disease has many features (e.g., a febrile prodrome, thrombocytopenia, and leukocytosis) in common with HFRS (Table 2), in HPS capillary leakage is localized exclusively in the lungs, rather than in the retroperitoneal space, and the kidneys are largely unaffected. Most of the 174 cases of HPS in the United States and Canada have been caused by Sin Nombre (SN) virus. In HPS, death occurs from shock and cardiac complications, even with adequate tissue

| Disease                  | Pathogens | Distinguishing Characteristics* |
|-------------------------|-----------|---------------------------------|
| HFRS (moderate-severe)  | HTN, SEO, DOB | hemorrhage +++/++++ azotemia/ proteinuria ++/+ conjunctival injection -/+ eye pain/myopia -/herLand |
| Death rate              |           | 1%-15%                          |
| HFRS (mild)             | PUU       | hemorrhage +/azotemia/ proteinuria +/ conjunctival injection -/ eye pain/myopia - herLand |
| Death rate <1%          |           |                                 |
| HPS (prototype)         | SN, NY    | hemorrhage +/azotemia/ proteinuria +/ conjunctival injection -/ eye pain/myopia - |
| Death rate >40%         |           |                                 |
| HPS (renal variant)     | BAY, BCC, Andes | hemorrhage +/azotemia/ proteinuria +/ conjunctival injection -/ eye pain/myopia - |
| Death rate >40%         |           |                                 |

*Minimum/maximum occurrence of the characteristic: - rarely reported; + infrequent or mild manifestation; ++, ++++, ++++ more frequent and severe manifestation.
outbreaks in Scandinavia and the HPS outbreak in the Four Corners region of the United States were associated with natural rodent population increases, followed by invasion of buildings by rodents (27,28). The ecologic events that led to 1994 and 1996 outbreaks of Andes virus-HPS in Patagonia, a region in southern South America, are being investigated. Human interventions, such as the introduction of Old World plant species (e.g., rosas mosquetas and Scottish brougham) to Patagonia, with associated alteration in rodent population dynamics, have been suggested as possible factors. Recent fires and a mild winter in Argentina’s Rio Negro and Chubut Provinces may also have had a positive effect on the carrier rodent, the collilargo, Oligoryzomys longicaudatus (M. Christie and O. Pearson, pers. comm).

Although the aerosol route of infection is undoubtedly the most common means of transmission among rodents and to humans, virus transmission by bite may occur among certain rodents (29) and may also occasionally result in human infection (30) (often inside a closed space, such as a rodent-infested grain silo, garage, or outbuilding used for food storage). Epidemiologic investigations have linked virus exposure to such activities as heavy farm work, threshing, sleeping on the ground, and military exercises. Indoor exposure was linked to invasion of homes by field rodents during cold weather or nesting of rodents in or near dwellings (16,31). Genetic sequencing of rodent- and patient-associated viruses has been used to pinpoint the precise locations of human infections, which has supported the role of indoor exposure in hantavirus transmission (32,33). Many hantavirus infections have occurred in persons of lower socioeconomic status because poorer housing conditions and agricultural activities favor closer contact between humans and rodents. However, suburbanization, wilderness camping, and other outdoor recreational activities have spread infection to persons of middle and upper incomes.

Nosocomial transmission of hantaviruses has not been documented until very recently (34) and must be regarded as rare. However, viruses have been isolated from blood and urine of HFRS patients, so exposure to bodily fluids of infected persons could result in secondary transmission. Only rarely have multiple North American HPS cases been associated with particular households or buildings. During recent outbreaks of HPS in South America, however, clustering of cases in
households and among personal contacts appeared to be more common (M. Christie, pers. comm.). During a recent outbreak of Andes-virus-associated HPS in Patagonia, a Buenos Aires physician apparently contracted the infection after minimal exposure to infected patient blood (34; D.A. Pirola, pers. comm.). An adolescent patient in Buenos Aires apparently contracted hantavirus infection from her parents, who were infected in Patagonia. This unprecedented observation of apparent person-to-person spread of a hantavirus clearly requires laboratory confirmation, especially by careful comparative analysis of the viral sequences (32,33).

Hantaviruses have also caused several laboratory-associated outbreaks of HFRS. Laboratory-acquired infections were traced to persistently infected rats obtained from breeders (35-37), to wild-caught, naturally infected rodents (38-40), or to experimentally infected rodents (39). No illnesses due to laboratory infections have been reported among workers using cell-culture adapted viruses, although asymptomatic seroconversions have been documented (40).

Antigenic and Genetic Diversity among Hantaviruses

Hantaviruses have been characterized by a combination of antigenic and genetic methods. For viruses propagated in cell culture, the plaque-reduction neutralization test is the most sensitive serologic assay for differentiation (44,45); nine hantaviruses have been defined by this test: HTN, Seoul (SEO), PUU, Prospect Hill, Dobrava-Belgrade (DOB), Thailand, TPM, SN, and BCC viruses (44-48). Genetic relationships among hantaviruses are mirrored in their antigenic properties. A direct correlation between genetic and antigenic relationships is difficult; however, it can be assumed that the plaque-reduction neutralization test measures differences in the M segment gene products, i.e., the G1 and G2 envelope glycoproteins. Comparing the deduced G1 and G2 amino acid sequences, therefore, may provide clues to the antigenic as well as genetic diversity among hantaviruses.

Of characterized hantavirus isolates, SEO virus is the most genetically homogeneous. Isolates of SEO virus, regardless of their geographic origin, display M segment nucleotide and deduced amino acid sequence homologies of approximately 95%, and 99%, respectively (41,47). A reported exception, the R22 isolate from China, had a slightly lower homology;
however, the original data suggest that an error in the nucleotide sequence, resulting in a frame shift reading error, may account for almost all of the additional changes. PUU virus isolates vary the most, with M segment nucleotide and amino acid sequence homologies of 83% and 94% observed between a Finnish and Russian isolate. HTN virus also appears to be quite stable in nature. Comparing the M segment sequences of prototype HTN virus (from *Apodemus*) and those of two human isolates obtained at a 6-year interval from HFRS patients in Korea produced nucleotide and deduced amino acid sequence homologies of 94% and 97%, respectively (48). For SN virus, comparing the complete M or S segment sequences of three strains from California or New Mexico produced homologies of 87% to 99%. Partial nucleotide sequence comparisons of the M or S segments of SN viruses from adjacent counties in California, detected in deer mice captured 19 years apart, were 97.5% homologous (49). Similarly, a retrospective analysis of archived tissue samples collected in Mono County, California, in 1983 showed viruses with partial M and S segment nucleotide sequence homologies of about 87% with SN from an 1993 HPS patient from New Mexico (50). In all cases, the amino acid sequences encoded by these genes differed between cognate proteins by much less than 5%. These values are similar to those observed among strains of HTN virus. Studies have just begun to appear in which the nature of quasispecies in natural rodent hosts is defined (43,51). Such investigations should provide more definitive data concerning the genetic diversity among hantaviruses in nature.

**Evolution of Hantaviruses**

Phylogenetic trees derived by comparing complete or partial S (Figure), M, or L segment nucleotide sequences (41,52,53) show two major lineages of hantaviruses, one leading to HTN, SEO, Thailand, and DOB viruses, and one leading to PUU, Prospect Hill, SN, and other New World hantaviruses. TPM virus, the first hantavirus isolated in cell culture (54), may be the most antigenically and genetically disparate member of the genus; however, comparison of the complete nucleotide sequence of the TPM S segment (A. Toney, B. Meyer, C. Schmaljohn, unpub. data) suggests that TPM virus is more closely related to HTN, SEO, and DOB viruses.
than to any of the other viruses in the genus. The exchange of gene segments is suggested to be nonrandom, with a higher propensity for M segment swapping, than for S or L. Whether it contributes to the pathogenesis of hantavirus infections for thousands, however, this has not been studied systematically.

Murid rodents have probably harbored inapparent hantavirus infections for thousands, perhaps millions of years. It is likely that the genus Hantavirus evolved in the Old World and that viruses were carried by rodents across the Bering land bridge when they migrated during the Oligocene, and into South America in the Pliocene (71). Humans are incidental hosts, the victims of spillover infections from the natural host rodents. One of the two major forms of hantaviral diseases is endemic in each hemisphere. Both HFRS and HPS can be divided into distinct clinical subtypes, and the viral strain is a key determinant of the severity and nature of the clinical abnormalities. Not covered in this review are clinical studies of HFRS and HPS patients, which suggest that pathogenesis may be immunologic and may be mediated by cytokine responses (72). New outbreaks with novel hantavirus strains are still being uncovered, especially in South America. However, the largest clinical caseload and largest number of deaths occur in Asia and Europe.

Dr. Schmaljohn is chief, Department of Molecular Virology, USAMRDC. Current research interests include the development of molecular vaccines for hantaviruses, filoviruses, and flaviviruses. Dr. Hjelle has been active in studies of the molecular biology, evolution, epidemiology, and clinical aspects of hantavirus disease. His laboratory is a reference diagnostic center for hantavirus infections of humans and animals and has recently received funding to develop innovative vaccine strategies against HPS and other emerging viral diseases.

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