Chapter 4
Hantaviruses

Thomas M. Yuill and James N. Mills

Abstract This chapter focuses on hantaviruses of known human health importance. In humans, New World hantaviruses cause hantavirus pulmonary syndrome (HPS) and Old World hantaviruses cause hemorrhagic fever with renal syndrome (HFRS). Hantaviruses are distributed world-wide and are maintained primarily in rodent hosts.

Rodent hosts are persistently infected, transmitting the viruses among themselves, through fighting or contamination of their surroundings, the latter being the most frequent source of human infection. A variety of ecological factors influence the population dynamics of these rodent hosts and, in turn, the dynamics of transmission among them with corresponding risk of human infection.

Keywords Diagnosis • Disease • Hantaviruses • Prevention • Rodents • Transmission

4.1 Background

Hantaviruses and their diseases have interesting histories. These viruses are distributed nearly world-wide and are maintained primarily in rodent hosts (Fig. 4.1). An increasing number of hantaviruses have recently been discovered in association with insectivore (order Soricomorpha) species, but none have been associated with human disease and they will not be discussed here. The hantaviruses of the Old World cause hemorrhagic fever with renal syndrome (HFRS) (Tables 4.1). Hantaviruses are a cause of HFRS throughout much of Europe and Asia (Vapalahti et al. 2003). In 1934, a mild form of HFRS, much later found to be due to Puumala virus (PUUV), was reported in Finland. During World War II, Japanese troops in

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Fig. 4.1 Named hantavirus genotypes that have been associated with human disease

Manchuria succumbed to a more severe disease. Hantaan virus (HTNV) infections causing HFRS with a 10 % case fatality rate were first recognized in 1951 in United Nations troops in Korea, when the disease was termed Korean hemorrhagic fever (KHF). The disease doubtless occurred in Asia perhaps for centuries. From 1951 to 1954, approximately 3,200 troops developed KHF (Schmaljohn and Hjelle 1997). Fatality rates declined gradually, from 4.9 % in 1982 to 2.7 % in 1991, then to 1 % in 1995 through 2007 (Zhang et al. 2010). Many years after the clinical syndrome was recognized, HTNV was first isolated by Lee et al. (1982) and later propagated in cell culture (French et al. 1981).

The isolation of Dobrava virus from a yellow-necked mouse (*Apodemus flavicollis*) was reported in 1992 (Avsic-Zupanc et al. 1992). The isolation of Belgrade virus from a severe human case of HFRS was reported that same year (Gligic et al. 1992). Subsequently, these viruses were shown to be identical and the International Committee for Taxonomy of Viruses (ICTV 2013) designated the name as Dobrava-Belgrade virus (DOBV). Following the isolation of the virus, DOBV was shown to be widely distributed in Europe and eastward in Russia (Tables 4.1), with *A. flavicollis* as the main rodent host. DOBV was isolated from a sibling rodent species, Black Sea field mice (*A. ponticus*), in the Black sea region of European Russia (cited in Klempa et al. 2013). The Saarema isolate of DOBV was found in striped field mice (*A. agrarius*) in two Estonian islands (Plyusnin et al. 1997). A Central European DOBV also was isolated from a striped field mouse (Klempa et al. 2005) Other molecularly distinct DOBV isolates were made from striped field mice from the Kurkino region of Russia (Plyusnin et al. 1999) and from Slovakia (Sibold et al. 1999, 2001). Interestingly, in several European countries where both striped and yellow-necked mice are present in the same areas, their viruses in each are from distinct genetic lineages. Because of the difference in lineages, Klempa et al. (2013) proposed that DOBV be subdivided into four

Table 4.1 Named hantavirus genotypes, their putative rodent host, approximate recognized distribution, and disease for those hantaviruses known or suspected to be pathogenic for humans

Virus	Host scientific name[a]	Host common name[a]	Host family: subfamily	Known distribution of virus	Disease	References
Europe						
Dobrava-Belgrade[b] (DOBV)	*Apodemus flavicollis*	Yellow-necked field mouse	Muridae: Murinae	Balkans N to Slovakia, Czech Republic, Turkey	Moderate/severe HFRS	Avsic-Zupanc et al. (1992), Olsson et al. (2010)
Saaremaa[b] (SAAV)	*Apodemus agrarius* (*agrarius*)	Striped field mouse	Muridae: Murinae	Saaremaa Island, Estonia	Subclinical?[b]	Olsson et al. (2010), Plyusnin (2002)
Kurkino[b]	*Apodemus agrarius* (*agrarius*)	Striped field mouse	Muridae: Murinae	Germany, Balkans, N to Estonia, Russia	Mild/moderate HFRS	Klempa et al. (2013)
Sochi[b]	*Apodemus ponticus*	Caucasus field mouse	Muridae: Murinae	SE Russia	Moderate/severe HFRS	Klempa et al. (2008, 2013)
Puumala (PUUV)	*Myodes* [*Clethrionomys*] *glareolus*	Bank vole	Cricetidae: Arvicolinae	Europe, Scandinavia, Russia, Balkans,	Mild HFRS (Nephropathia epidemica)	Brummer-Korvenkontio et al. (1980), Olsson et al. (2010)
Asia						
Hantaan (HTNV)	*Apodemus agrarius* (*mantchuricus*)	Striped field mouse	Muridae: Murinae	Far Eastern Russia, N Asia, Balkans	Severe HFRS	Lee et al. (1978a, b)
Amur[c] (AMRV)	*Apodemus peninsulae*	Korean field mouse	Muridae: Murinae	Far Eastern Russia, Korea[c], China[c]	HFRS	Lokugamage et al. (2004)
Thailand (THAIV)	*Bandicota indica*	Greater bandicoot rat	Muridae: Murinae	Thailand	HFRS	Elwell et al. (1985), Hugot et al. (2006), Pattamadilok et al. (2006)

(continued)

Table 4.1 (continued)

Virus	Host scientific name[a]	Host common name[a]	Host family: subfamily	Known distribution of virus	Disease	References
Seoul[d] (SEOV)	*Rattus norvegicus*[d]	Brown rat	Muridae: Murinae	Nearly Worldwide	Mild/Moderate HFRS	Lee et al. (1982)
Muju (MUJV)	*Myodes regulus*	Korean red-backed vole	Cricetidae: Arvicolinae	South Korea	HFRS	Song et al. (2007)
Africa						
Sangassou (SANGV)	*Hylomyscus alleni* [*simus*]	Allen's hylomyscus	Muridae: Murinae	Guinea	Febrile syndrome	Klempa et al. (2010)
North America						
Sin Nombre (SNV)	*Peromyscus maniculatus*	North American deermouse	Cricetidae: Neotominae	North America	HPS	Childs et al. (1994)
Monongahela[e] (MGLV)	*Peromyscus maniculatus* (*nubiterrae*)	North American deermouse	Cricetidae: Neotominae	E USA and Canada	HPS	Song et al. (1996)
New York[f] (NYV)	*Peromyscus leucopus*[e]	White-footed deermouse	Cricetidae: Neotominae	NE USA	HPS	Hjelle et al. (1995)
Bayou (BAYV)	*Oryzomys palustris*	Marsh oryzomys	Cricetidae: Sigmodontinae	SE USA	HPS	Ksiazek et al. (1997)
Black Creek Canal (BCCV)	*Sigmodon hispidus* (*spadicipygus*)	Hispid cotton rat	Cricetidae: Sigmodontinae	S Florida, USA	HPS	Rollin et al. (1995)
Latin America (*Americas South of USA*)						
Río Mamoré[g] (RIOMV)	*Oligoryzomys microtis*	Small-eared colilargo	Cricetidae: Sigmodontinae	Bolivia, Peru	None recognized[g]	Hjelle et al. (1996)
Maripa[g]	Unknown		Unknown	French Guiana	HPS	Matheus et al. (2010)

Anajatuba[g] (ANAJV)	*Oligoryzomys fornesi*	Fornes' colilargo	Cricetidae: Sigmodontinae	NE Brazil	HPS	Travassos Da Rosa et al. (2005)
Andes[h] (ANDV)	*Oligoryzomys longicaudatus*	Long-tailed colilargo	Cricetidae: Sigmodontinae	SW Argentina & Chile	HPS	Levis et al. (1998)
Bermejo[h] (BMJV)	*Oligoryzomys flavescens*[i]	Flavescent colilargo	Cricetidae: Sigmodontinae	NW Argentina, S Bolivia, Paraguay	HPS	Levis et al. (1998), Padula et al. (2002)
Lechiguanas[h] (LECV)	*Oligoryzomys flavescens*[i]	Flavescent colilargo	Cricetidae: Sigmodontinae	C Argentina SW Uruguay	HPS	Levis et al. (1998)
Central Plata[h] (none)	*Oligoryzomys flavescens*[i]	Flavescent colilargo	Cricetidae: Sigmodontinae	S Uruguay	HPS	Delfraro et al. (2003)
Hu39694[h]	*Oligoryzomys flavescens*? [i]	Flavescent colilargo	Cricetidae: Sigmodontinae	C Argentina	HPS	Levis et al. (1998)
Orán[h] (ORNV)	*Oligoryzomys chacoensis*	Chacoan colilargo	Cricetidae: Sigmodontinae	NW Argentina, S Bolivia	HPS	Levis et al. (1998), Rivera et al. (2007)
Castelo dos Sonhos[h] (CASV)	*Oligoryzomys eliurus* [*utiaritensis*][j]	Brazilian colilargo	Cricetidae: Sigmodontinae	N Brazil	HPS	Firth et al. (2012), Johnson et al. (1999), Travassos Da Rosa et al. (2011)
Tunari[h] (TUNV)	Unknown			Central Bolivia	HPS	Cruz et al. (2012), Firth et al. (2012)
Araraquara[h] (ARAV)	*Necromys* [*Bolomys*] *lasiurus*	Hairy-tailed akodont	Cricetidae: Sigmodontinae	SE and C W Brazil	HPS	Firth et al. (2012), Suzuki et al. (2004)
Juquitiba[h] (JUQV)	*Oligoryzomys nigripes*	Black-footed colilargo	Cricetidae: Sigmodontinae	S Brazil, N Argentina, S Uruguay	HPS	Delfraro et al. (2008), Levis et al. (1998)
	Oxymycterus nasutus	Long-nosed hocicudo				
Laguna Negra[k] (LANV)	*Calomys laucha*	Little laucha	Cricetidae: Sigmodontinae	W Paraguay, Bolivia, W Brazil	HPS	Firth et al. (2012), Johnson et al. (1997), Levis et al. (1998)
	C. callosus	Big laucha				
	C. callidus	Reclusive laucha				

(continued)

Table 4.1 (continued)

Virus	Host scientific name[a]	Host common name[a]	Host family: subfamily	Known distribution of virus	Disease	References
Choclo (CHOV)	*Oligoryzomys fulvescens* (*costaricensis*)	Fulvous colilargo	Cricetidae: Sigmodontinae	SW Panama	HPS	Vincent et al. (2000)

Only underlined viruses are currently recognized by the International Committee on Taxonomy of viruses to be viral species. If no abbreviation is provided, the virus does not have a widely accepted abbreviation. *N, S, E, W* North, South, East, West

[a]Nomenclature follows Wilson and Reeder (Wilson and Reeder 2005); subspecies are provided in parentheses for some species; taxonomic references in brackets are synonyms and are provided because of their presence in the literature

[b]Although SAAV was recently recognized as a virus species (Ictv 2013), Klempa et al. (2013), concluded that Saaremaa, Kurkino, and Sochi genotypes are all subtypes of DOBV. Those authors also suggest that the HFRS cases on mainland Estonia formerly attributed to Saaremaa virus were caused by Kurkino virus, leaving the pathogenicity of Saaremaa virus for humans questionable

[c]Includes Soochong strain isolated from *A. peninsulae* South Korea (Baek et al. 2006) and H5 and B78 strains from human patients in China (Liang et al. 1994)

[d]Includes GOU3 strain isolated from *Rattus rattus* in eastern China (Wang et al. 2000)

[e]Considered by ICTV as a subtype of SNV

[f]NYV is probably associated with a geographically restricted coastal population of *P. leucopus*

[g]Maripa and Anajatuba are likely subtypes of Río Mamoré virus, implying that Río Mamoré virus should be considered a human pathogen (Firth et al. 2012; Matheus et al. 2010)

[h]Bermejo, Lechiguanas, Central Plata, Hu39694, and Oran are all considered as subtypes of ANDV by ICTV; recent analyses (Firth et al. 2012) also group Castelo dos Sonhos, Tunari, Araraquara, and Juquitiba viruses with Andes virus

[i]Recent phylogenetic analysis suggests that *O. flavescens* is a complex of geographic species or subspecies (Rivera et al. 2007)

[j]Validity of this host-virus association has been questioned (Firth et al. 2012)

[k]Multiple genotypes of the virus may exist in association with the several named hosts (Firth et al. 2012)

genotypes, Dobrava, Kurkino, Saaremaa and Sochi, based on phylogeny, rodent host reservoir species, geographical distribution and pathogenicity for humans (Tables 4.1). Although Saarema virus has been recognized as a separate species, Klempa et al. (2013) make a strong case for it being a genotype of Dobrava-Belgrade virus. Following the recognition of HFRS due to HTNV, milder cases of HFRS were recognized in Finland due the Saaremaa lineage of DOBV, somewhat more severe cases in central and eastern Europe due to DOBV and HFRS cases of intermediate severity in urban settings in Europe and Asia due to Seoul virus (SEOV).

SEOV was first isolated from urban brown rats (*Rattus norvegicus*) in Seoul, Korea and reported in 1982 (Lee et al. 1982). There was evidence of SEOV infections occurring previously in laboratory rats in medical institutions in Japan (Umenai et al. 1979, Lee et al. 1979, Lee et al. 1980). In China, HFRS caused by SEOV was first identified in humans in 1981 in the neighboring regions of Henan and Shanxi provinces along the Yellow River (Hang et al. 1982). It was subsequently isolated from rats of two other species, *R. losea* and *R. confuscianus* (Liu et al. 1984). SEOV is unusual with its wide geographic distribution because movement of its carrier host, the brown rat through international shipping. The virus occurs in brown rats in Asia, Africa, Europe, and the Americas (Cueto et al. 2008; Leduc et al. 1986). More than 15,000 cases of HFRS are estimated to occur yearly, with more than half of these in China (Song 1999).

New World hantavirus pulmonary syndrome (HPS) is sometimes called hantavirus cardiopulmonary syndrome (HCPS). In 1993, the first recognized cases of HPS occurred in the Four Corners area of the southwestern USA (where the states of Arizona, Colorado, New Mexico, and Utah are contiguous) leading to the identification of a new hantavirus named Sin Nombre virus (SNV) detected in the tissues of patients and in deermice (*Peromyscus maniculatus*) trapped near patient's dwellings (Hjelle et al. 1994; Ksiazek et al. 1995; Nichol et al. 1993).

As of December 31, 2013, 637 cases of HPS had been reported in the United States (CDC 2014). Of these reported cases, 63 % were male, 37 % female with a mean age of 37 years and a range of 6 to 83 years (CDC 2014). The discovery of SNV was followed by studies throughout the Americas, with several viruses identified as etiological agents of HPS, along with their Cricetid rodent reservoir hosts (Tables 4.1).

There are two other hantaviruses in the Americas that cause HPS with some frequency. Andes virus (ANDV) is endemic in the Andean region of Argentina and Chile, where a small number of cases of hantavirus pulmonary syndrome (HPS) occur every year. It was first detected in southwest Argentina, in a family outbreak in 1995 in a rural area near El Bolsón, where two of three individuals who developed HPS died. Hantavirus RNA was extracted from frozen autopsy lung and liver tissues, and was identified as ANDV (Lopez et al. 1996). In early outbreaks in Argentina, ANDV was shown to be transmitted directly from one person to another but only when individuals are in close contact (Enria et al. 1996; Padula et al. 1998; Toro et al. 1998). In Chile, confirmed cases of ANDV HPS have occurred since 1995 with serological surveys having confirmed its presence from 30° 56′S to 53° 37′S (Toro et al. 1998; Torres-Pérez et al. 2004). However, ANDV

has been found in the long-tailed pygmy rice rat, its natural rodent host, throughout the animal's range in Chile and in the Valdivian temperate forests in Argentina (Palma et al. 2012).

Cases of HPS also occur with some frequency in the Azuero Peninsula of Panama. The cases were first diagnosed in 1999. Subsequent studies found that the Costa Rican pygmy rice rat, *Oligoryzomys fulvescens costaricensis*, was the host of a novel hantavirus, Choclo virus, that was related to the cases of human HPS (Vincent et al. 2000). In a study in four western Panama clinics, individuals presenting with a severe febrile prodrome for acute hantavirus infection from 2006 to 2009, at least 21 % of 117 patients diagnosed with acute hantavirus infection had no evidence of pulmonary edema (without respiratory distress or radiographic lung infiltrates), and 44 % of patients had very mild HPS (radiographic pulmonary edema but no respiratory insufficiency). Thus, acute hantavirus infection caused by Choclo virus in Panama often occurs without severe HPS (Armien et al. 2013). However, there have been occasional cases of clinically severe HPS up to the present time.

Other hantaviruses have been shown to cause sporadic cases of HPS in the Americas (Tables 4.1). Studies of HPS cases and their epidemiologies in the Western Hemisphere are continuing.

4.2 Viruses

Hantaviruses are a genus within the family *Bunyaviridae* (Schmaljohn and Dalrymple 1983; Schmaljohn et al. 1983, 1985). The genus *Hantavirus* contains the only bunyaviruses that are not arthropod transmitted. Hantaviruses are enveloped, negative sense, with RNA in three segments designated as L (large, 6,530–6,550 nucleotides), M (medium, 3,613–3,707 nucleotides) and S (small, 1,696–2,083 nucleotides). The L segment codes for RNA-dependent RNA polymerase, the M segment for Gn and Gc envelope glycoproteins and the S segment for the nucleocapsid. The genome segments are encapsidated by the N protein to form ribonucleoproteins enclosed within a lipid envelope with glycoprotein spikes composed of Gn and Gc. The virion morphologically is round or pleomorphic with a diameter of 120–160 nm (Hepojoki et al. 2012). Electron microscopy shows that the virions have a grid like surface pattern unique to this genus (Martin et al. 1985). Unlike other genera of the *Bunyaviridae*, HTNV and SEOV do not have a nonstructural NSs protein (Schmaljohn et al. 1986). The viruses are inactivated by heat, organic solvents, detergents, ultraviolet irradiation, and hypochlorite solutions (Bi et al. 2008; Kraus et al. 2005). Reassortment between HTNV and SEOV tripartite genome segments was found in naturally infected brown rats in Guizhou Province, China (Zou et al. 2008), with S and M segments of two different lineages of DOBV (Klempa et al. 2003), and different lineages of PUUV in Finland (Razzauti et al. 2009), between different lineages of SNV (Rodriguez et al. 1998), which indicates that genetic reassortment can occur naturally between

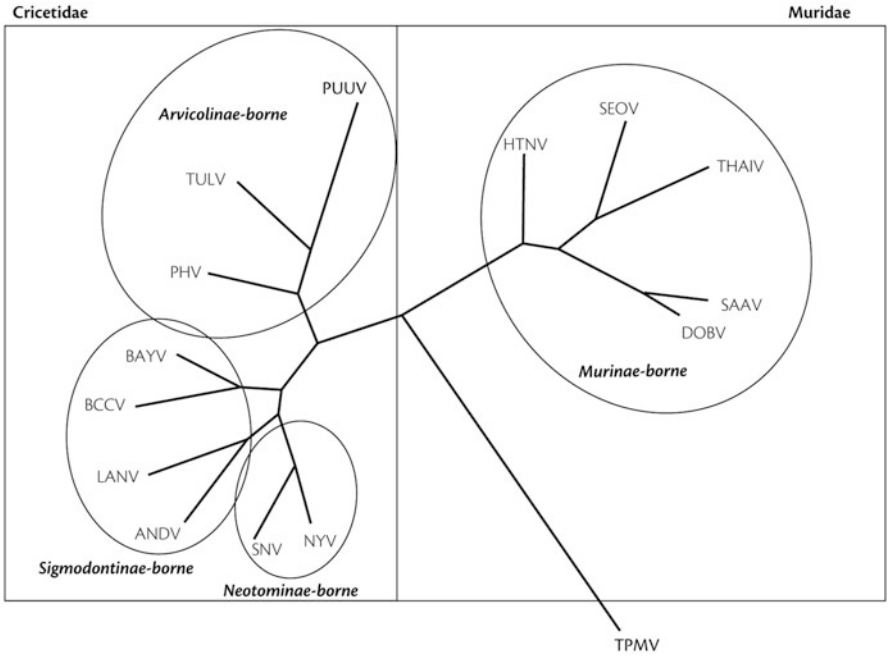

Fig. 4.2 Phylogeny and host relationships of some major hantaviruses. Thottapalayam virus is nonpathogenic for humans and is hosted by an insectivore (order Soricomorpha). All other viruses are hosted by rodents (order Rodentia) of the superfamily Muroidea, families Muridae (Europe and Asia) and Cricetidae. Three subfamilies of Cricetidae host hantaviruses: Sigmodontinae (South America and southern North America) Neotominae (North America), and Arvicolinae (circumboreal). The phylogram is constructed using the complete S segment. *PUUV* Puumala virus, *TULV* Tula virus, *PHV* Prospect Hill virus, *BAYV* Bayou virus, *BCCV* Black Creek Canal virus, *LANV* Laguna Negra virus, *ANDV* Andes virus, *SNV* Sin Nombre virus, *NYV* New York virus, *HTNV* Hantaan virus, *SEOV* Seoul virus, *THAIV* Thai virus, *SAAV* Saaremaa virus, *DOBV* Dobra virus. TULV and PHV are not known to be human pathogens and are not included in Tables 4.1. From: Vaheri et al. (2011)

different hantaviruses or between lineages of the same hantavirus. The evolutionary radiation of selected hantaviruses and association with their rodent hosts is illustrated in Fig. 4.2.

4.3 Pathogenesis in Human Disease

The hantaviruses are responsible for human disease in the Western Hemisphere, Europe, and Asia. Both disease syndromes (HPS and HFRS) involve capillary leakage (Peters et al. 1999). There is evidence that pathogenesis is due to immunopathology, rather than direct cell and tissue damage (Borges et al. 2006;

Kilpatrick et al. 2004; Terajima et al. 2004). It has been proposed (Terajima et al. 2007) that impairment of endothelial cells' defense mechanisms against cytotoxic CD8+ T cells is the mechanism resulting in capillary leakage in HPS and HFRS. Tumor necrosis factor-α, interleukin-6 and -10 and γ-interferon play a role in pathogenesis (Makela et al. 2002; Mori et al. 1999). Studies of 21 HPS patients indicated that IL-6 may have an important role in the pathogenesis of HPS and was associated with fatal outcome. A mixed Th1/Th2 immune response occurred during the course of HPS and the magnitude of Th1 response effector cytokines was correlated to HPS severity. Reduced levels of TGF-beta in HPS patients suggested immunoregulatory damage (Borges et al. 2008).

Clinically, HPS is a severe disease with a case fatality rate of 36 % in the USA. The case definition of HPS (CDC 1997) is a febrile illness characterized by bilateral interstitial pulmonary infiltrates and respiratory compromise usually requiring supplemental oxygen and clinically resembling acute respiratory disease syndrome. Hematological and pulmonary histopathological features were described for a series of fatal HPS cases (Zaki et al. 1995). The incubation period is 1–5 weeks after exposure. Four to ten days after the initial phase of illness, coughing and shortness of breath may occur. The typical prodrome consists of fever, chills, myalgia, headache, and gastrointestinal symptoms with thrombocytopenia progressing rapidly to acute pulmonary edema, hypoxia, respiratory insufficiency, hypotension, and cardiogenic shock. There is hemoconcentration, left shift in the white blood cell count, neutrophilic leukocytosis, thrombocytopenia, and circulating immunoblasts. Because hypoxia induces pulmonary epithelial and endothelial cells to secrete vascular endothelial growth factor it can also increase capillary permeability and edema locally (Duchin et al. 1994; Gavrilovskaya et al. 2012). SNV-specific CD8(+) cells contribute to the severity of HPS disease outcome (Kilpatrick et al. 2004).

In general, HFRS symptoms usually develop 1–2 weeks after infection, but may take up to 8 weeks to appear. Initial symptoms begin suddenly and include intense headaches, back and abdominal pain, fever, chills, nausea, and blurred vision. There may be flushing of the face, inflammation or redness of the eyes, or a rash. Symptoms can progress, including low blood pressure, acute shock, vascular leakage, and acute kidney failure, which can cause severe fluid overload. The severity of the disease varies depending upon the virus causing the infection. Hantaan and Dobrava virus infections usually cause severe symptoms, while Seoul is intermediate, and Saaremaa and Puumala virus infections are usually more moderate (Plyusnin et al. 2006). Complete recovery may take months (CDC 2013b; Muranyi et al. 2005).

Nephropathia epidemica (NE) is a clinically milder form of HFRS. There is sudden onset with high fever, headache, backache, abdominal pain, and transient thrombocytopenia in the early phase of the disease. Three days later, there may be conjunctival hemorrhages and palatine and truncal petechiae. Usually, only 1 % of patients develop severe neurologic signs including seizures or bladder paralysis. Hemorrhages develop with oliguria, azotemia, proteinuria, and hematuria. The rash disappears after the third day and polyuria develops. The convalescent

phase lasts for several weeks, usually without sequelae. Fatality from acute renal failure ranges from 0.1 to 1 % (Beers and Berkow 2005). Patients with neurological disease were seen in a large study of HFRS patients infected by Puumala virus. The common symptoms included headache, blurred vision, and vomiting and some of the patients had all three. Nine patients had severe neurological manifestations: meningism and cerebral hemorrhage during the first week of illness, and epileptiform seizures and urinary bladder paralysis during the second week (Alexeyev and Morozov 1995). Impaired pulmonary function has been documented in some HFRS patients (Linderholm et al. 1997; Mustonen et al. 1996) and more than half of 70 PUUV-infected, hospitalized patients had abnormal cardiac findings (Makela et al. 2009). However, one patient with Puumala virus infection who developed a severe clinical syndrome typical of hantavirus pulmonary syndrome (Gizzi et al. 2013).

Severe HFRS disease occurs in 10–15 % of cases. HFRS involves capillaries and venules, causing hemorrhage circulation disorders. Acute renal failure may result from interstitial hemorrhage and infiltrates (Sirotin and Keiser 2001).

The clinical course of severe HFRS has five phases: febrile, hypotensive, oliguric, diuretic, and convalescent. The onset lasts for 3–4 days with high fever, backache, abdominal pain, chills, myalgia, malaise, and bradycardia. Photophobia, pharynx enanthema, and a diffuse flushing of the face occur. Petechia develop on the palate and conjunctival hemorrhages may appear with temporary vision impairment. There is hematuria with gross proteinuria. Hypotension occurs 3–6 days after onset of fever and there may be shock. Laboratory findings include leukocytosis and thrombocytopenia. Renal damage occurs, including acute tubulointerstitial nephritis, necrotizing glomerulonephritis, and IgA nephropathy (Cosgriff 1991). The oliguric phase starts and hemorrhage may become severe. The diuretic phase usually begins on day 11. Convalescence usually begins 3 weeks to 6 months after the acute phase. Sequelae are unusual, but when they occur may include hypertension and chronic renal failure (Beers and Berkow 2005).

4.4 Zoonotic Hantaviruses and Their Rodent Hosts

Hantaviruses establish persistent infection in their rodent hosts without apparent disease (Botten et al. 2000, 2002). Studies suggest that TGF-β1-expressing regulatory T cells may play an important role in limiting immunopathology in the natural reservoir host, but may interfere with viral clearance (Schountz et al. 2007). This response may have arisen as a mutually beneficial, coadaptive, evolutionary process between hantaviruses and their natural rodent reservoirs, limiting disease from the infection while allowing virus persistence (Schountz et al. 2007). Perhaps there has been historic host switching followed by long-term adaptation (Ramsden et al. 2009), with persistent infections and minimal host damage. However, that

strict concept has been challenged with new information indicating that host switching can occur currently (Lin et al. 2012; Vapalahti et al. 1996).

Natural and human-induced environmental changes can affect the prevalence and transmission of hantaviruses among their rodent hosts and spillover of the viruses to humans. It has been suggested that regulators of hantavirus prevalence and transmission can be categorized into five major classes (Mills 2005). (1) Environmental regulators (weather and food availability) affect transmission rates through their effect on reproductive success and on population densities. (2) Anthropogenic factors, such as ecosystem disturbance, may simplify those systems, decreasing biodiversity and favoring opportunistic species that may be hantavirus reservoirs. (3) Genetic factors may influence susceptibility of mice to infection or for chronic shedding. (4) Behavior, such as fighting, can increase risk of hantavirus transmission, causing different patterns of infection between males and females. In temperate regions, communal nesting may result in overwinter transmission. (5) Physiologic factors can control host response to infection and length of time the host remains infectious. Thus, risk prediction is difficult because these several regulators often interact. The relative importance of each factor varies according to the status of the host species, season, year, and geographic location.

There is evidence that regulators 1 and 2 above may be interacting synergistically to produce counterintuitive effects on the incidence of HPS. Although high biodiversity has been associated with high risk of emergence of infectious diseases (Jones et al. 2008; Wolfe et al. 2005), outbreaks of HPS and of the rodent borne viral hemorrhagic fevers have been associated with areas with severe anthropogenic disturbance and extremely low biodiversity (Mills 2006). There are several possible explanations for this apparent paradox.

Anthropogenic disturbance is known to simplify natural ecosystems, decreasing biodiversity and resulting in local extirpation of some species. As a result of global climate change, which is increasingly blamed on human factors (Stocker and Qin 2013), numerous species, including rodent hosts of zoonotic diseases, are moving their ranges poleward and upward in altitude (Hickling et al. 2006; Jannett et al. 2007; Moritz et al. 2008). Although a similar migration occurred at the end of the last ice age (Wright et al. 1993); migration is now complicated by massive barriers created through mechanized agriculture, massive deforestation, building of towns and cities and highways. Many species, especially nonvolant specialists, will not be able to migrate (Root and Schneider 2002). The Intergovernmental Panel on Climate Change (IPCC IV) predicts that 20–30 % of species are likely to at increased risk of extinction as global average temperature exceeds 1.5–2.5 °C above pre-industrial levels. Species, however, will not go extinct randomly. Specialist species with narrow habitat and diet requirements will disappear quickly, while more adaptable opportunistic species take their place, rapidly reproducing to high population densities in the absence of their specialist competitors (Dahlberg 1992; Peters 1997; Ruedas et al. 2004). Although opportunistic species constitute a minority of total Cricetid species, they form the majority of known hantavirus hosts in the Americas. Thus, climate change and anthropogenic disturbance may be

acting synergistically to create conditions where opportunistic hosts of hantaviruses thrive, increasing risk to humans inhabiting those disturbed habitats.

A phenomenon labeled the "dilution effect" is hypothesized to result in higher risk of vector-borne (Ostfeld and Keesing 2000) and, apparently, directly transmitted zoonotic diseases including HPS (Clay et al. 2009; Mills 2006; Suzan et al. 2009) to humans in ecosystems with lower potential host diversity. Studies of the dilution effect are providing increasing evidence that human perturbation of ecosystems in the form of direct disturbance and indirectly through climate change are resulting in biodiversity loss which leads to greater incidence of HPS and other zoonotic diseases.

4.4.1 The Old World Zoonotic Hantaviruses and Their Rodent Hosts

Three hantaviruses in Europe, Dobrava, Seoul, and Puumala viruses, cause HFRS (Olsson et al. 2010).

4.4.1.1 Hantaan Virus (HTNV)

HTNV and its Asian variants are harbored in mice of the genus *Apodemus* (Lee et al. 1978a, b, 1981a, b). The reservoir of HTNV is *A. agrarius koreae* in eastern Asia including China. In China, the density of *A. agrarius*, the water-level difference in the Huai River and crop production were correlated with the incidence of HFRS (Bi et al. 1998). In another study employing a landscape epidemiologic approach, along with geographic information system and remote sensing techniques, multivariate logistic regression analysis showed that incidence of HFRS from HTNV infection was associated with elevation, a vegetation index, precipitation, annual cumulative air temperature, semihydromorphic soils, timber forests, and orchards (Yan et al. 2007). In farming areas of the Anhui Province of China, where cases of HFRS occurred, there was higher risk of HTNV infection among those who had slept on the ground or had been engaged in heavy farm work (Xu et al. 1985; Chen et al. 1986). HTNV variants Amur and Soochong viruses, both human pathogens, are harbored by *A. peninsulae* (Baek et al. 2006; Zhang et al. 2007). In laboratory studies, laboratory rats (*R. norvegicus*) infected with HTNV shed virus in saliva and feces but longest in urine (Lee et al. 1981a). A study of HFRS related hantaviruses in the Russian Far East has shown the presence of several different genotypes of viruses related to, but with S segments somewhat different from, HTNV (Yashina et al. 2000).

4.4.1.2 Puumala Virus (PUUV)

The bank vole *Myodes glareolus*, the reservoir host of PUUV is widely distributed in northern and central continental Europe (Bernshtein et al. 1999; Brummer-Korvenkontio et al. 1980). As with SNV in deer mice, PUUV infection in adults is associated with wounds in the fall, i.e., at the end of the breeding season, but not in spring. In addition, in a study in southern Belgium, sexually active animals were significantly more often wounded and positive for infection. Wounds resulting from biting or scratching were observed mainly in adult rodents. PUUV infection was associated with higher mobility in juvenile and subadult males (Escutenaire et al. 2002).

HFRS epidemics due to PUUV can be predicted based on the population dynamics of bank voles, the reservoir hosts (Kallio et al. 2009; Olsson et al. 2009). A recently developed model (Sauvage et al. 2007) indicated that only vole populations with multi-annual fluctuations resulted in simultaneously high numbers of infected voles with a high proportion of voles in the acute virus excretion phase as the population increase was ending. This results in a brief peak of exceptionally high virus concentrations in the environment with an increased risk of human exposure. In assessing factors influencing the association of increased PUUV infection in bank voles in a northern Sweden area endemic for the virus, four factors together predicted 80 % of the model outcome: age, body mass index, population abundance (increasing, peak, or declining/low), and sex . Specifically, voles that were in the oldest age class, of higher body mass index, in the peak stage of abundance and of male sex were most likely to be infected (Olsson et al. 2002). In this area in northern Sweden, particular environmental characteristics associated with old-growth moist forests dominated by *Alectoria spp*., *Picea abies*, fallen wood, and *Vaccinium myrtillus* were associated with increased bank vole abundance and, hence, the number of PUUV-infected voles, whereas dry forests did not have this association (Olsson et al. 2005).

Efficient spread and transmission of PUUV depends on high bank vole population densities that increase as food availability becomes abundant during good mast (edible shrub and tree seeds or nuts) years in central Europe (Schwarz et al. 2009; Tersago et al. 2009). Climate change can affect hantavirus occurrence in rodent hosts and risk of human PUUV infection. Climatic conditions favoring increased mast production have resulted in an increase in HFRS cases a year later (Clement et al. 2009). Increased average temperatures in West-Central Europe have been associated with more frequent PUUV outbreaks with increased bank vole population densities due to increased mast production. Warmer climate, perhaps coupled with increased surveillance, have resulted in an increase in documented cases of HFRS from PUUV infections (Heyman et al. 2009; Schwarz et al. 2009). In contrast, warm winters in Scandinavia have led to a decline in vole populations as a result of reduced protective snow cover with increased predation (Klempa 2009). Similar to findings with deermice and SNV discussed below, a study of wild populations of bank voles in Finland showed that PUUV infected voles had

significantly lower overwinter survival (Kallio et al. 2007), slowed maturation, and reduced survival and reproduction compared to uninfected voles (Tersago et al. 2012).

4.4.1.3 Dobrava-Belgrade Virus (DOBV)

DOBV is a genetically distinct hantavirus (Xiao et al. 1993). In Europe, *Apodemus flavicollis*, the yellow-necked forest mouse is the reservoir species of DOBV (Avsic-Zupanc et al. 1992; Taller et al. 1993). Sequence comparison and phylogenetic analysis of the Slovenian wild type DOBV from *A. flavicollis* strains were closely related whereas the strain harbored by *A. agrarius* had a high level of genetic diversity from other Slovenian DOBV strains and clustered together on phylogenetic trees with other DOBV strains harbored by *A. agrarius* from Russia, Estonia, and Slovakia. These findings suggest that the DOBV variants harbored by the two species of *Apodemus* in Europe represent distinct genetic lineages (Avsic-Zupanc et al. 2000). DOBV was recently reported to occur in *A. uralensis* captured on the Black Sea coast of Turkey (Oktem et al. 2014).

4.4.1.4 Seoul Virus (SEOV)

The brown rat (*Rattus norvegicus*) is the main reservoir host of SEOV and is doubtless responsible for moving it around the world. Lin et al. (2012) hypothesized that an ancestor of phylo-group A SEOV variants was first exported from China to Europe and then spread through the New World following the migration of brown rats. Phylogenetic analysis carried out by these authors that included 136 novel Chinese strains, indicated existence of four distinct phylogroups. All non-Chinese SEOV strains and most of the Chinese variants fell into the phylogroup A, while the Chinese strains originating from mountainous areas clustered into three other distinct groups (B, C, and D).

SEOV has also been isolated from wild (Lee et al. 1982) and domestic pet *Rattus rattus* (Jameson et al. 2013). SEOV variants Geo and Serang viruses are associated with *R. rattus* in China and *R. tanezumi* in Indonesia respectively (Leduc 1987; Plyusnin et al. 2009). Transmission between brown rats can occur through exposure to SEOV-containing excrement or by wounds inflicted through fighting (Glass et al. 1988; Hinson et al. 2004). Infection of newborn laboratory *R. norvegicus* resulted in persistent infection, but infection was transitory when adult rats were infected (Kariwa et al. 1996). SEOV was detected in pet rats (*R. norvegicus*) in England (Jameson et al. 2013) and in Sweden (Lundkvist et al. 2013) with a risk of human infection to humans in contact with these pets.

4.4.2 The New World Zoonotic Hantaviruses and Their Rodent Hosts

HPS due to SNV infection was first recognized in 1993 in the Four Corners area of the USA. SNV was shown to be harbored by the North American deermouse, *Peromyscus maniculatus*, a species widely distributed in North America that occurs in a variety of habitats (Childs et al. 1994; Nichol et al. 1993). Subsequently, presence of SNV antibody indicated that deermice were infected throughout their range in the United States, Canada, and Mexico (Mills et al. 1998; Monroe et al. 1999). Studies during the initial outbreak indicated that cases clustered seasonally and temporally by biome type and geographic location. Areas of human exposure and areas of highest prevalence in host populations were most often found in pinyon-juniper woodlands, grasslands, and Great Basin desert scrub lands, at elevations of 1,800–2,500 m (Engelthaler et al. 1999; Mills et al. 1997). Elevation, as well as habitat evaluation accrued from satellite data, showed an association between environmental conditions and HPS risk the following year (Glass et al. 2000). It was hypothesized that the 1991–1992 El Niño-southern oscillation (ENSO) caused increased precipitation, increasing the food supply that led to greater rodent population densities with enhanced risk of transmission to humans. The result of this series of events may have been responsible for the 1993–1994 outbreak of the disease in the Four Corners states. A second strong ENSO occurred in 1997–1998. Researchers who were monitoring rainfall, habitat quality, and deermouse population density in the southwestern US at the time observed increased rainfall, green-up of vegetation, increased food supplies, and an abrupt spike in deermouse population density. The peak in rodent density was followed by a similar peak in HPS cases in the Four Corners states in 1998–1999 (Mills 2005; Yates et al. 2002). Most of the 1998–1999 patients reported indoor exposure to deermice (Hjelle and Glass 2000). Several of the initial (1993) cases in the Four Corners area occurred in Native Americans. Interestingly, the oral history of local American Indian healers describes clusters of similar deaths occurring over three cycles during the twentieth century in association with specific ecological changes (Chapman and Khabbaz 1994).

Subsequent field studies indicated that SNV occurred in an extensive geographic area where *P. maniculatus* is found. However, infections in deermouse populations were focal, being common in some areas and absent in others. Areas of high SNV antibody prevalence in deermouse populations were determined and satellite imagery was used to identify environmental characteristics associated with transmission within its reservoir population. At least 2 years of high-risk conditions were needed for prevalence to increase. Areas with persistently high-risk environmental conditions may serve as maintenance foci for the survival of SNV in local deermouse populations (Glass et al. 2002). Despite very low rodent population densities at some sites, hantavirus infection persisted at a low level, perhaps because of chronic infection and shedding in a few long-lived individuals or by periodic virus reintroduction from neighboring populations. Hantavirus antibody prevalence was

seasonal with multiyear patterns suggesting a delayed density-dependent relationship between prevalence and population density (Mills et al. 1999). SNV infection was more prevalent in males and individuals of larger body mass (Douglass et al. 2001; Mills et al. 1997). In deermice, IgG antibody prevalence was positively associated with delayed population density. Virus transmission among deermice, as indicated by seroconversion, occurred primarily during the breeding season (spring through summer) and primarily affected males (Douglass et al. 2007). In some sites, there was a second peak in the in the winter that affected males and females equally (Calisher et al. 1999). This might be explained in that breeding season transmission may involve male-to-male aggression while mid-winter transmission may be associated with communal huddling that involves both sexes. Serological results suggested that the longer deermice live, the greater the probability they will be infected with SNV (Calisher et al. 1999). At numerous sites in the southwestern US, SNV antibody prevalence in deermice was inversely correlated with rodent species richness (number of species) and diversity (a measure combining richness and proportional representation of species) (Calisher et al. 2002; Clay et al. 2009; Mills 2006).

Higher prevalence of SNV infections in male deermice related to virus transmission from aggression was demonstrated in several studies. In longitudinal studies in Colorado and Montana, there was a positive association between wounds and SNV antibody in adult deermice suggesting that when infected rodents fight with uninfected individuals, virus transmission occurs (Calisher et al. 1999; Douglass et al. 2001). As in other studies, male rodents comprised a larger percentage of the total seropositive mice suggesting that male mice contribute more to the SNV epizootic cycle than female mice.

Antibody prevalence and occurrence of SNV RNA in blood have been used as indications of presence of SNV in deermouse populations. However, the antibody response to SNV infection in naturally infected deermice was shown to be highly variable. Presence of SNV RNA has been used as an indicator of relative risk of transmission. Blood levels of viral RNA varied as much as 100-fold, even in individuals infected with identical strains of virus. Deermice that infected other susceptible individuals tended to have a higher SNV RNA levels than those that did not infect other individuals (Bagamian et al. 2012).

Although hantavirus infections have been considered to have little adverse effect on their natural rodent hosts, a field study in Montana showed that recently infected male deermice gained less weight over the 1-month period following seroconversion than did those that did not acquire antibody, suggesting that SNV infection may have negatively impacted the health of infected individuals (Douglass et al. 2007) and decreased survival time (Luis et al. 2012). SNV infected deermice had smaller movement areas on trapping grids than uninfected individuals (Amman et al. 2013), another effect that can influence population dynamics and the maintenance of the virus in nature.

The ecological setting can influence the prevalence of SNV infections in deer mice populations. Studies of SNV infections in *P. maniculatus* populations in California and Nevada characterized the vegetation type and density, elevation,

slope, and hydrologic features of study sites using remote sensing and geographic information systems data. The data retroactively predicted infection status of deermice with up to 80 % accuracy (Boone et al. 2000), with potential use as a determinant of risk of human infection.

Numerous other rodents of the families Cricetidae, Muridae, and even Sciuridae (squirrels) have been occasionally found with antibody to SNV, or even SNV RNA, as a result of spillover infection, especially during periods of very high deermouse population density (Childs et al. 1994). It is likely that similar spillover occurs for all hantaviruses and such events in the past may have led to host-switching, coadaptation and the evolution of new hantaviral lineages.

Among the New World hantaviruses, SNV epidemiology is the best studied. After its discovery, other hantaviruses that cause HPS were discovered in various areas of North, Central and South America (Tables 4.1). At least 13 named hantavirus genotypes have been described in 12 species of rodent hosts of the family Cricetidae, subfamily Sigmodontinae (New World rats and mice) in the four countries of the Southern Cone of South America (Palma et al. 2012).

Andes virus is endemic in the Andean region of Chile and Argentina. Andes virus HPS in Chile and Argentina occurs where there is contact with the pygmy rice rat (*Oligoryzomys longicaudatus*) and its habitat in rural areas. The habitat is characterized by shrub vegetation, and forest edge with bamboo (colihue cane, *Chusquea quila*) and brushy peridomestic areas. Population irruptions of these rodents can occur when colihue cane flowers, producing seeds that are a preferred source of food for them (Palma et al. 2012). Population densities of these rodents during population irruptions may reach as much as 100 individuals per ha (Jimenez et al. 1992; Gallardo and Mercado 1999). Interestingly, ANDV antibody prevalence in the long-tailed pygmy rice rats was seasonally highest in the spring, when the population was comprised mainly of adults, than in the autumn, when the populations, although of higher densities, consisted mainly of juvenile individuals. The highest relative seroprevalence of *O. longicaudatus* was found in the Mediterranean ecoregion. Torres-Pérez et al. (2010) postulated that spatial features such as landscape structure and habitat fragmentation are major components in differences in ANDV antibody prevalence in this rodent in Chile. This relationship suggests delayed density dependent effects on antibody prevalence (Mills et al. 2007). The peridomestic habitat places them in close juxtaposition with human dwellings.

In Panama, cases of HPS occur in the Azuero Peninsula where contact with the Costa Rican pygmy rice rat (*Oligoryzomys fulvescens costaricensis*), the host of Choclo virus, and its habitat occur. This rodent is found in anthropogenically disturbed habitats characterized by several crops including corn (maze), watermelon, beans, coffee and sugar cane (Salazar-Bravo et al. 2004).

Other hantaviruses associated with human disease in North, Central, and South America are listed in Table 4.1. The rodent hosts for most of these hantaviruses have been identified, although there is incomplete understanding of host and virus taxonomy.

4.5 Transmission to Humans

Risk of transmission to humans usually depends on presence of viable virus in the environment. Several hantaviruses have been shown to be relatively stable under environmental conditions. Transmission of hantaviruses to humans most frequently occurs through breathing of aerosols of virus-contaminated rodent excreta with exposure often occurring when entering or cleaning rodent-infested structures (Armstrong et al. 1995). Large quantities of infectious virus may be excreted in the urine, saliva, and feces of the infected rodents. Voles infected with PUUV have shown that the shed virus is surprisingly stable, and thereby infectious over long periods outside the rodent host (Kallio et al. 2006). In laboratory studies, cell-cultured HTNV on glass or plastic surfaces remained infectious for 1–3 days at room temperature (Schmaljohn et al. 1998). Similar laboratory experiments with dried PUUV from cell culture gave similar results with all virus becoming noninfectious after 24 h. In contrast, naïve bank voles that were exposed to bedding (wood shavings) contaminated by laboratory infected "donor" voles became infected when exposed to the contaminated bedding up to 15 days after the donor voles had been removed (Kallio et al. 2006). In cotton rats (*Sigmodon hispidus*) infected experimentally with Black Creek Canal virus, virus was sporadically isolated from wet bedding and consistently from dried feces, strongly suggesting that the virus was somewhat stable in the environment (Hutchinson et al. 1998).

These experiments were conducted in the laboratory environment. Exposure to sunlight would likely have rendered the virus noninfectious in a few hours, if not minutes. Virus may be shed by infected hosts at least intermittently for the life of the rodent. The quantity of virus shed may be orders of magnitude higher during the first 2–8 weeks following infection (Lee et al. 1981a; Hutchinson et al. 1998). Peak shedding of PUUV occurred at 11–28, 14–21, and 11–28 days postinfection for saliva, urine, and feces, respectively (Hardestam et al. 2008).

4.6 Diagnosis and Treatment of Hantavirus Infections

4.6.1 Diagnosis

Clinically, the patterns of symptoms, the rate of development of signs and symptoms, and specific clinical laboratory parameters discriminated between individuals having SNV infections and developing HPS versus those suspected of having the infections but later were ruled out (Chapman et al. 1999).

Laboratory diagnosis can be made by serology (detection of immunoglobulin M or rising titers of immunoglobulin G or A) (Padula et al. 2000), by demonstration of hantavirus-specific RNA by polymerase chain reaction (PCR) (Giebel et al. 1990) or of hantavirus antigens by immunohistochemistry (CDC 1997). The requirement for a high level of biological containment for infectious hantaviruses has been a

significant constraint in the development of serological diagnostic tests. Use of an expression vector for the nucleocapsid protein gene of provided specific serological reactivity with immune sera (Schmaljohn et al. 1983). The low level of biological containment required for production of this protein offers a significant advantage over live virus antigens for serological diagnosis of hantavirus infections. As a field test, a strip immunoblot assay bearing four immobilized antigens for SNV showed promise for the detection of SNV antibodies early in the course of HPS (Hjelle et al. 1997). Presumptive diagnosis may be made by examination of a peripheral blood smear after the onset of the cardiopulmonary phase of HPS (Mertz et al. 2006). A rapid and easy test for PUUV and ANDV employed an immunochromatographic assay and was useful for the diagnosis of nephrophathy from PUUV infection in Europe. Recently, multiparametric indirect immunofluorescence assays (IFA) based on biochip mosaics were developed to detect serum antibodies against clinically important Old and New World hantaviruses simultaneously. The multiparametric IFA provided highly sensitive and specific serological diagnosis of HTNV, PUUV, SEOV, SAAV, DOBV, SNV or ANDV (Lederer et al. 2013). With both human and animal sera, antibody responses fell into two groups: those that reacted with HTNV, SEOV, and DOBV and those reacting with SNV and PUUV (Elgh et al. 1997).

A real-time reverse transcriptase (RT) PCR method developed for detection of PUUV RNA had a detection threshold for PUUV cDNA of two copies per reaction. A two-step qualitative RT-PCR to detect PUUV RNA showed 100 % agreement with the real-time RT-PCR assay (Evander et al. 2007).

4.6.2 Treatment

Critical care management for HPS includes the avoidance of fluid overload and cardiac output maintained. In severe SNV infections, patients experience extreme pulmonary edema and cardiogenic shock and may require mechanical ventilation and occasionally extracorporeal membrane oxygenation therapy (Koster and Jenison 1997). About 5 % of hospitalized PUUV and 16–48 % of DOBV patients require dialysis and prolonged intensive-care treatment (Vaheri et al. 2013).

Treatment with intravenous ribavirin is probably not effective when initiated during the cardiopulmonary phase of HPS (Mertz et al. 2006). However, ribavirin has been used successfully to reduce mortality and the severity of disease in HFRS patients

4.6.3 Prevention and Control

Vaccines are used to prevent HTNV infections in Asia. To control and prevent HFRS in China, a comprehensive preventive strategy has been implemented and includes public health education and promotion, rodent control, surveillance, and

vaccination (Zhang et al. 2010). Approximately two million doses of inactivated rodent brain- or cell culture-derived HFRS vaccines are given annually in China. Although vaccination, along with public education and rodent control measures, have coincided with a reduction in HFRS cases to less than 20,000 per year, China still has the highest number of HFRS cases and deaths in the world (Zhang et al. 2010). A rodent brain-derived inactivated HFRS vaccine has also been used in the Republic of Korea since the early 1990s and has similarly resulted in reduced numbers of HFRS cases (Cho et al. 2002). This vaccine has been used in Korea for military personnel and high-risk rural residents (Cho and Howard 1999; Lee et al. 1990; Sohn et al. 2001). Schmaljohn et al. (1990) found that passively transferred neutralizing monoclonal antibodies prevented infection, suggesting that an antibody response alone can prevent infection.

There are no commercially available vaccines for New World hantaviruses. In experiments designed as a proof of concept, Rhesus macaques were vaccinated with an expression plasmid that contained HTNV and ANDV M genome segments (Custer et al. 2003). The animals developed high levels of neutralizing antibodies that not only neutralized ANDV but also cross-neutralized other HPS-associated hantaviruses, including SNV (Hooper et al. 2006). However, the high cost of development of commercial vaccines is prohibitive considering the relatively small number of HPS cases in the Americas.

Prevention is the best approach to avoid becoming infected with hantaviruses. Although the CDC recommendations are focused on North American hantaviruses, (CDC 2013a) the same measures apply to avoidance of hantavirus infection in other geographic areas. The CDC preventive measures, as well as those of most national and local health agencies include:

- Eliminate or minimize contact with rodents in the house, workplace, or campsite.
- Seal up holes and gaps in the house and garage.
- Place traps in and around the house to decrease rodent infestation.
- Eliminate available rodent food sources.
- Ventilate closed areas that have been unoccupied for a long period of time that may be inhabited by rodents.
- Avoid making dust. Wet down floors and other surfaces with bleach before sweeping.
- Keep food and garbage in rodent-proof thick plastic or metal containers with tight lids.
- Keep outside cooking areas and grills clean.
- Put pet food away after use and do not leave pet-food out overnight.
- Keep garbage in a rodent-proof thick plastic or metal garbage can with a tight lid.
- Keep bird feeders away from the house and utilize squirrel guards to limit access to the feeder by rodents.
- Keep compost bins as far away from the house as possible (30 m or more).

- Keep grains and animal feed in rodent-proof thick plastic or metal containers with tight lids. In the evening, uneaten animal feed should be returned to containers with lids.
- Eliminate possible rodent nesting sites outside the house. Elevate hay, woodpiles, and garbage cans at least 30 cm off the ground.
- Move woodpiles far away from the house (30 m or more).
- Get rid of old trucks, cars, and old tires that could house mice and rats.
- Keep grass cut short and shrubbery within 30 m of the home well trimmed.

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