Review Article

Hantavirus Infection: a review and global update

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Abstract

Hantaviruses have the potential to cause two different types of diseases in human: hemorrhagic fever with renal syndrome (HFRS) and hantavirus pulmonary syndrome (HPS). HFRS, initially described clinically at the turn of the 20th century, occurs endemically in the Asian and European continents, while HPS, recognized as a clinical entity since 1993, represents the prototype of emerging diseases occurring in the Western hemisphere. Approximately 150,000 to 200,000 cases of HFRS are hospitalized each year world wide, with most of the cases occurring in the developing countries. The case fatality rate of HFRS varies from <1% to 12% depending on the viruses. Although HPS is much smaller in number than HFRS, with approximately 200 HPS cases per year in the Americas, the average case fatality rate is 40%. The reported cases of hantaviral infection is increasing in many countries and new hantavirus strains have been increasingly identified worldwide, which constitutes a public health problem of increasing global concern. Hantaviral infection might be underestimated due to its asymptomatic and non-specific mild infection, and the lack of simple standardized laboratory diagnostics in hospitals, especially in the developing countries. This review summarizes the current knowledge on virology, epidemiology, clinical manifestation, laboratory diagnostics, treatment and prevention of hantaviruses and hantaviral infections.

Key Words: hantavirus, hemorrhagic fever with renal syndrome, HFRS, hantavirus pulmonary syndrome, HPS, rodent control, vaccine.

Introduction

Since the first hantavirus, Hantaan virus (HTNV), was isolated in 1976 [1], many other hantaviruses have been identified [2], with at least 22 being pathogenic to humans. Hantaviruses have the potential to cause two different types of diseases in humans: hemorrhagic fever with renal syndrome (HFRS) and hantavirus pulmonary syndrome (HPS). HFRS, which includes diseases formerly known as Korean hemorrhagic fever (KHF), epidemic hemorrhagic fever (EHF) and nephropathia epidemica (NE), denotes a group of clinically similar illnesses that occur throughout the Eurasian landmass and adjoining areas [3]. After about 30 years of its first modern description in the Russia Federation [4], HFRS came to the attention of the world when approximately 3,200 cases were reported from 1951 to 1954 among American soldiers deployed in the Republic of Korea [5]. Hantavirus once again attracted the attention of the world in 1993, when it was identified to be the etiologic agent of HPS outbreak in the Four Corners region of the United States [6]. Since most

HPS deaths are caused by myocardial dysfunction and hypoperfusion rather than hypoxia, some investigators have recently begun to use the term *hantavirus cardiopulmonary syndrome* (HCPS) [7]. We will use HPS instead of HCPS in the context of the review. Herein, we provide a global update of hantaviral infections focusing on virology, global prevalence, the hantaviruses causing human infections, clinical features and treatment, laboratory diagnostics and control and prevention.

Virology

Hantaviruses, negative-sense single-strained RNA viruses, represent a separate genus in the Bunyaviridae family. However, in contrast to other genera of the Bunyaviridae, hantavirus is transmitted to human not by arthropod but from contact with persistently infected rodents and their excreta [2]. The genus consists of different species, which are also called "serotype", "genotype" or simply "hantavirus". Hantavirus generally grows slowly even inoculated in the most susceptible vero cell E6 clone, and usually results

in little or no cytopathic effect (CPE). Electron microscopic studies of thin sections of postmortem tissue samples show the hantaviral particles to have a morphology fairly typical of members of the Bunyaviridae family, forming predominantly spherical or irregular particles 80 to 120 nm in diameter. Elongated particles averaging about 170 nm in length have also been observed, which is atypical of viruses of the Bunyaviridae family [2,3]. The Virions have surface structures in an unusual square grid-like pattern with each morphologic unit being about 8 nm in diameter when viewed by negative staining. Like other enveloped viruses, hantaviruses are readily inactivated by heat, detergents, UV irradiation, organic solvents and hypochlorite solutions [8].

As all members of the Bunyaviridae family, the consensus terminal nucleotide sequences of the L, M and S genome segments of Hantavirus are AUCAUCAUCUG… at the 3'-end [9, 10] and UAGUAGUA… at the 5'-end (http://www.ncbi.nlm.nih.gov/ICTVdb/Ictv/ index.htm). The Hantavirus coding strategy is the simplest of the five genera of the Bunyaviridae, with all the three segments encoding only one protein in the virus complementary sense. The genome consists of a large [6530-6550 nucleotide (nt)] segment (L) encoding for the protein or viral RNA-dependent RNA polymerase; a medium (3613-3707 nt) segment (M) encoding for a polyprotein cleaved by co-translational cleavage to form two viral glycoproteins, Gn and Gc; and a small (1696-2083 nt) segment (S) encoding for the nucleocapsid (N) protein.

Hantavirus produces chronic persistent infection in the host rodent [11,12]. Transmission of these viruses across a species barrier results in human infections. Virus type correlates closely with disease severity. The pathogenicity of Hantavirus remains incompletely understood. It has been demonstrated that some pathogenic Hantavirus enters cells via beta-3 integrins, which are present on the surfaces of endothelial cells, macrophages and platelets [13,14]; however, a recent study showed that beta-3 integrins did not play a critical role for respiratory epithelial cell monolayer integrity [15]. The hallmark feature of hantaviral infections is capillary leak. Although Hantavirus has been shown to replicate in cultured human endothelial cells and is present in endothelial cells in HFRS and HPS patients

[16,17], there is considerable evidence that immunopathology, especially T-cell responses rather than direct viral cytopathology, is responsible for its pathogenesis [18,19]. Cytokines such as tumor necrosis factor-α (TNF-α), interleukin (IL)-6, IL-10, and γ-interferon may also play some roles in pathogenesis of hantaviral infection [20,21].

Global Prevalence of Hantavirus Infections

Hantavirus causes a significant number of human illnesses, making it a global public health threat (Figure 1). Approximately 150,000 to 200,000 patients with HFRS are hospitalized each year throughout the world [22]. On average, approximately 200 cases of HPS per year are reported in the Americas, and although the number of cases is much smaller in number than that of HFRS, its average case fatality is about 40% [2].

Figure 1. Global geographic distribution of hantavirus pulmonary syndrome and hemorrhagic fever with renal syndrome.
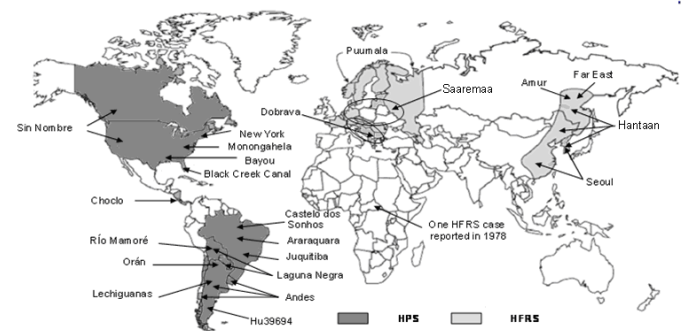
Asia

In Asia, clinical cases of HFRS caused by HTNV and Seoul Virus (SEOV) have been identified mainly in China, the Republic of Korea, and the Far East Region of the Russia Federation (Table 1). In China, more than 1,400,000 clinical cases, with about 45,000 deaths, were reported over the period 1950 to 2001 [23], which makes China the most endemic country of HFRS with 40,000 to 60,000 cases annually reported in recent years, accounting for 70% to 90% of the total HFRS cases reported in the world [24]. In the Republic of Korea, a total of 14,309 HFRS patients were hospitalized from 1951 to 1986, with one third being soldiers [25]. In a recent study [26], it was noted that the yearly number of HFRS patients has decreased from 1,234 cases in 1991

to 750 cases in 1998 since a vaccination campaign began in 1991. The number of hospitalized HFRS patients has declined to 100 to 300 per year in recent years in the Republic of Korea [27]. In the Asian region of the Russia Federation, approximately 100 to 200 HFRS cases are reported each year in recent years [28], which only account for 3% of the total number of HFRS cases in the country [29]. In Japan, although there have been no HFRS cases reported since 1985, HFRS outbreaks were reported from the 1960s to the 1970s, and seropositive *R. norvegicus* have been identified in ports and reclaimed areas in different locations through the country [30].

Table 1. Hantavirus infection (HFRS) in selected countries in Asia.

Countries/districts	Reported Cases	Seroprevalence
China	40000-60000/year	1%-12%
Hong Kong SAR	1 in 1987	4%
Province of Taiwan	14 as of 2005	6.2% (2.5%-1.6%)
Republic of Korea	300-400/year	2.7%-12.5%**
Far East Russia Federation	100-300/year	
Japan	None since 1985	0.48%
India	2 fatal in 2000	5.50%
Indonesia	11 cases in 2002	
Malaysia	3 as of 2001	2.52%
Singapore	3 as of 1996	2%-8%
Thailand	1 in 2005	5.3%-33.3%
Sri Lanka	14 in1988	5.60%
Cambodia		8.20%#
Israel		2%-12.3%*
Kuwait		7% (6%-11%)
Laos		10%
Philippines		6.1%(5.1%-7.6)
Viet Nam		5.40%

*The seroprevalence among hemodialysis patients, mild to moderate renal failure patients, and health population were 12.3%, 9% and 2%, respectively
**Seroprevalence among civilians in endemic areas. The seroprevalence rate in Korea military personnel is 2.1 to 16.4
seroprevalence in rodents.

Clinical cases of HFRS have also been reported in other countries and districts in Asia [31-36] (Table 1). Serological investigation indicated that there were strong evidences of hantaviral infections in humans in Israeli, Kuwait, Laos, Malaysia, Philippines, Viet Nam and the China Hong Kong Special Administrative Region [37-42]. Hantaviral infection was also demonstrated in rodents in Cambodia, though there has been no report of human infections [43] (Table 1).

Europe

NE, a mild form of HFRS described in Sweden since 1934, remains the most prevalent hantaviral disease in Western and Central Europe (Table 2). The causative agent of NE, Puumala virus (PUUV), was first isolated in bank voles (*Clethrionomys glareolus*) in Puumala, Finland, in the early 1980s [44]. Nowadays, more than 9,000 cases per year are reported in Europe (Table 2), with an increasing tendency [45-48].

In Finland, a total of 8,184 laboratory confirmed cases were reported from March 1995 to February 2002 [45]. Recently, peak years have been at 3-year intervals, with 2,300 cases, 2,603 cases and 2526 cases recorded in the years1999, 2002 and 2005 respectively (Markus Brummer-Korvenkontio, Anti Vaheri and Olli Vapalahti, personal communication). With an average PUUV seroprevalence of 5% in humans, it was estimated that about 5,000 infections occurred in Finland on a yearly basis [49]. In Sweden, it has been estimated that at least 4,500 human infections occurred there in 1998, but only one eighth were diagnosed and reported [50]. In Norway, about 100 cases of HFRS are reported each year [3].

In Belgium, two major HFRS outbreaks were reported in 1995-1996 and 1999, with 217 and 124 cases respectively [51], and an increase was observed in recent years [48]. In France, 320 cases were diagnosed from the first recognition of HFRS in 1982 to the end of 1992. A sharp increase has been observed since 2003, with 128 cases reported in that year, and 115 cases were reported in 2005 [46,47]. In Germany, an annual number of about 200 clinical hantavirus infections were reported from 2001 to 2003 [52], and an increase in hantavirus infections was observed in 2005, with at least 258 cases reported in the first half of the year [47].

In Austria, approximately 15 HFRS cases have been diagnosed per year, with a maximum of 72 cases in 2004 [53]. In Hungary, 235 clinical cases of hantaviral infection were confirmed between 1992 and 2000, and the overall seroprevalence was 10% in the general population [54]. In Bulgaria, 399 HFRS cases were diagnosed between 1954 and 1988 with a fatality of 15.8%, and a significant rise in the incidence and mortality was observed in 1987-1988 when 36.7% of the patients died [55]. However, the etiology of HFRS in Bulgaria still needs to be further characterized.

In Czech Republic, HFRS cases including a fatal case have been reported since 1992, and Dobrava virus (DOBV), PUUV and Tula virus (TULV) have been co-circulating, with seroprevalence of antibodies against HTNV and PUUV being 1% and 1.4% respectively [56]. In Estonia, only a few HFRS cases are officially reported each year; however, the overall hantaviral seroprevalence rate is as high as 9.1%, with those for PUUV, Saaremaa/Dobrava virus (SAAV/DOBV) and un-typed viruses being 5.1%, 3.4% and 0.6% respectively [57].

In the Russia Federation, around 123,000 HFRS cases were reported from 1990 to 2006, with an average yearly incidence of around 7,200 cases [58].

In 1997, a large-scale outbreak of HFRS caused by PUUV occurred in the Republic of Bashkortostan, resulting in 10,057 reported cases including 503 children, with an attack rate of 2.87% [59]. The highest prevalence of 58/100,000 was reported in Bashkortostan [3], where 2,723 cases were recorded in 2006, with a 40% increase over the previous year (http://depts.washington.edu/ einet/newsbrief230.html? article=2848#2848).

In the Balkans, and particularly the Federal Republic of Yugoslavia, HFRS outbreaks have been recorded since the early 1950s with a case fatality rate of 5% to 10%, with Dobrava virus (DOBV) being the predominant pathogenic virus [60]. An epidemic with more than 2,000 severe cases was reported in the Federal Republic of Yugoslavia from 1995 to 1996 [61]. In Croatia, 235 HFRS cases, of which 62.6% were soldiers, were reported from 1987 to 2001 [62], whereas 317 HFRS cases were diagnosed during an epidemic in 2002 [63]. In Serbia and Montenegro, a large epidemic with 128 laboratory-confirmed cases occurred in 2002, and since then, more than 30 cases have been serologically confirmed each year [64]. In Greece, most human infections are sporadic, but outbreaks were also reported. From 1982, when the first case of HFRS was described, to May 2001, there were 210 cases diagnosed in the country with a case fatality of 9% [65,66].

There have been reports of clinical hantaviral infections in Albania [67], Denmark [68], Luxembourg [48], Poland [69], Romania [70], Slovakia [71], Switzerland [72], the Netherlands [73] and the United Kingdom [74] (Table 2).

Table 2. Human hantavirus infections in Europe.

Region	PUUV[1]	DOBV[2]	SAAV[3]	Cases/year	Seroprevalence (%)
Europe Russia	+		+	7000	6
Finland	+			2000	5
Sweden	+			300	8.0 in Northern part
Germany	+		+	100	1-3
France	+			100	2.5
Belgium	+			100	1.5
Norway	+			100	24**
Serbia/ Montenegro	+	+		30	
Hungary	+	+		30	10
Austria	+			15	1.2 (0.02-1.8)
Croatia	+	+		15	1.6
Slovenia	+	+	+	15	1.7
Netherlands	+			10	0.7 in blood donor
Bulgaria				10	
Denmark	+		+	10	1 in some areas
Slovakia	+		+	10	
Bosnia-Herzegovina	+	+		10	5
Greece	+	+		10	4
Luxembourg	+			5	
Switzerland				1▲	0-1.9▲▲
Poland				1▲▲▲	
Estonia	+		+		9.1
Latvia	+		+		4
Lithuania	+	+			0.7 in blood donors
Czech Republic	+	+			1-2
Portugal					1
Italy					0-10.7 in high-risks #
Albania		+			
Moldova	+				7.8
Spain					0.06-4.54

1 PUUV=Puumala virus; 2 DOBV=Dobrava virus; 3 SAAV= Saaremaa virus
*In foresters in Ile-de-France;
**In patients without symptoms of NE in Hattfjelldal, an endemic area
▲Only one HFRS case possibly related to Tula virus was reported in Switzerland.
▲▲ 0% in forestry workers, 0.5% in blood donors, 0.8% in farmers, 1.1% in hunters and 1.9% in soldiers.
▲▲▲only one serologically confirmed case reported.
#Hantaan-like virus infection, with a rate of 2.3% in "healthy" population.

Sero-epidemiological surveys have demonstrated human hantaviral infections in Italy [75], Latvia [76], Lithuania [77], Portugal [3], the

Republic of Moldova [78], and Spain [79], though no clinical cases have been reported in these countries (Table 2). Recently, Puumala virus infection was serologically demonstrated for the first time by using immunofluorescence assays in Turkish Microtus voles [80].

Americas

HPS constitutes a public health problem, especially in South America, where an increasing number of HPS cases are reported each year. Since HPS was first recognized as a hantaviral disease in the Four Corner areas of the United States in 1993 [6], clinical cases have also been confirmed in the Americas in Argentina, Bolivia, Brazil, Canada, Chile, Panama, Paraguay, United States and Uruguay [81-83], with more than 2,000 cases of HPS recorded in the Region of Americas from 1993 to 2004.

In Argentina, the first case of HPS was confirmed by virus detection in 1995 [84]. Three clusters involving 29 cases and a severe outbreak with 18 HPS cases were later reported in 1995 and 1996 respectively [85]. By the end of 2006, a total of 841 cases were reported in the country [86]. In Bolivia, through 2002, at least 10 HPS cases were reported with 6 deaths [87]. By the end of 2004, 36 cases had been reported in the country (http://www.paho.org). In Brazil, The first case of HPS was reported in a family cluster in 1993 [88], and 855 HPS cases were reported between 1993 and 2006 with a 39.3% case fatality [89]. In Chile, since the first identification of HPS in 1995 [90], 352 cases of HPS had been reported by August 4, 2006, with a case fatality rate of 33% (http://epi.minsal.cl/epi/html/bolets/reportes/Hantav irus/Hantavirus.pdf). In Uruguay, the first evidence of the circulation of these viruses came from a study of serum specimens collected from blood donors between 1985 and 1987 [91]. Since then, more than 60 cases of HPS have been confirmed [92]

The first cluster of HPS in Central America occurred from late December 1999 to February 2000 in Los Santos Province in Panama. Through 2006, there were 85 cases of HPS reported in Panama with a CFR of 17.6% [93] In Paraguay, the first outbreak of HPS occurred in 1995 [87], and through 2004, there had been 99 cases of HPS in that country (http://www.paho.org). The

overall seroprevalence of hantaviral infections in the Chaco area of Panama was 43% [95].

In the Caribbean region, a single case of HPS was serologically confirmed in eastern Venezuela recently, and a low prevalence (1.7%) but wide distribution of hantaviral infections was demonstrated in the country [96]. Human infections in Colombia [90] and rodent infection with Sin Nombre-like hantaviruses in Costa Rica, Mexico and Peru have been reported [98-100].

In Canada, cases of HPS are rare, fewer than 8 being reported per year, with the first Canadian case of HPS identified retrospectively back to 1989 [83]. A 26% case fatality of HPS was reported in Northern Alberta, Canada [101]. In the United States of America, HPS was retrospectively traced back to as early as 1975 [102], but HPS was first recognized in May 1993 [6]. As of 10 May 2006, CDC-USA has confirmed 438 cases of HPS reported from 30 states; 35% of these cases were fatal [103].

The HFRS-causing Old World hantaviruses are widely distributed in Asian and European countries. However, the Old World hantaviruses, especially the SEOV, have also been detected in the United States, Canada, and South American countries, although few clinical HFRS cases have been reported on the American continent [104,105]. Recently, Seoul- or Puumala-like hantavirus infections were reported in humans and rodents in the Caribbean country, Barbados [106].

Africa

There had been no data available on hantavirus infections in Africa until 1984 when Gonzalez *et al.* demonstrated serological evidence of hantaviral infections in human and rodents in Benin, Burkino Faso, the Central African Republic and Gabon [107]. Since then, human hantavirus infections have also been demonstrated in Senegal, Nigeria, Djibouti, and Egypt through serological survey [108-111]. Recently, the first African hantavirus, Sangassou virus (SANGV), was identified in Guinea [112]. To our best knowledge, only one case of HFRS has been reported in Africa [113]; however, the potential pathogenicity of SANGV or other African hantaviruses cannot be ignored. HFRS may be confused with other severe diseases (leptospirosis, rickettsiosis, other viral hemorrhagic fevers, plague, severe pneumonia, sepsis) or may

be unrecognized because it is difficult to access laboratories for diagnosis in African countries.

Hantaviruses causing Human Infections

HFRS-associated Hantaviruses

Presently, there are seven hantaviruses associated with HFRS (Table 3). The most severe form of HFRS is caused by HTNV in Asia and DOBV in the Federal Republic of Yugoslavia region and other parts of Europe [2,3], with a mortality rate from 3% to12%. Saaremaa virus (SAAV), with *Apodemus agrarius* as the rodent reservoir in Europe, was recently separated from DOBV and recognized as a distinct causative agent of a mild form of HFRS [114]. PUUV, the most variable hantavirus, causes the mild form of HFR through central and northern Europe, the Russia Federation and the Balkans with a mortality of 0.1-0.4%.

SEOV infections are responsible for the moderate form of HFRS, with a CFR of 1-2% [25]. Though SEOV is distributed worldwide in *Rattus norvegicus* and *R. rattus*, and SEOV antibody has been detected in rats and people in Asia, Europe, the Americas and Africa, HFRS caused by SEOV is confined mainly to Asia. The few human HFRS cases in Africa [113] and America [115] were not demonstrated to be associated with SEOV, and no clear evidence of SEOV-related HFRS is available in Europe except from laboratory infections [116]. Amur and Far East viruses were recently identified in severe HFRS cases in the far eastern region of the Russia Federation [117,118], and need to be further characterized.

HPS-associated Hantaviruses

Since Sin Nombre virus (SNV) was first identified as the causative agent of HPS in the US [6], at least 15 hantaviruses have been associated with HPS (Table 3).

The HPS-related New World hantaviruses are mainly confined to the Americas (Figure 1). SNV is the most common cause of HPS in Canada and United States, while New York virus (NYV), Monongahela (MONV), Bayou (BAYV) and Black Creek Canal (BCCV) cause HPS only in the United States [83,119]. This reflects the geographical distribution of Peromyscus in contrast to the reservoirs for these other viruses.

Table 3. Hantaviruses associated with human infections.

Rodent reservoir subfamily, virus	Associated diseases	Reservoir species	Geographical distribution of virus
Murinae			
Hantaan	HFRS	*Apodemus agrarius*	China, Korea, Russia
Dobrava	HFRS	*Apodemus flavicollis*	Balkans
Saaremaa	HFRS	*Apodemus agrarius*	Europe
Seoul	HFRS	*Rattus norvegicus*	World wide
Amur	HFRS	*Apodemus peninsulae*	Far East Russia
Arvicolinae			
Puumala	HFRS	*Clethrionomys glareolus*	Europe
Sigmodontinae			
Sin Nombre	HPS	*Peromyscus maniculatus*	USA, Canada
New York	HPS	*Peromyscus leucopus*	USA
Monongahela	HPS	*Peromyscus maniculatus nubiterrae*	Eastern USA
Bayou	HPS	*Oryzomys palustris*	Southeastern USA
Black Creek Canal	HPS	*Sigmodon hispidus*	USA (Florida)
Laguna Negra	HPS	*Calomys laucha*	Paraguay, Bolivia
Andes	HPS	*Oligoryzomys longicaudatus*	Argentina, Chile, Uruguay
Orán	HPS	*Oligoryzomys longicaudatus*	Northern Argentina
Choclo	HPS	*Oligoryzomys fulvescens*	Panama
Río Mamoré	HPS	*Neacomys spinosus*	Bolivia
Lechiguanas	HPS	*Oligoryzomys flavescens*	Argentina
Araraquara	HPS	*Bolomys lasiurus*	Brazil
Juquitiba	HPS	*Oligoryzomys nigripes*	Brazil
Unknown			
Far East	HFRS	-	Far East Russia
Castelo dos Sonhos	HPS	-	Brazil
Hu39694	HPS	-	Argentina

Andes virus (ANDV), characterized in Argentina in 1995 on the basis of specimens from a patient who died of HPS [81], has been responsible for most HPS cases recorded in Argentina, Chile, and Uruguay. Languna Negra virus (LNV) causes HPS in Bolivia and Paraguay. Oran, Lechiguanas and Hu39694 were found only in Argentina, while Araaquara, Castelo dos Sonhos and Juquitiba are all Brazilian isolates

[81]. Recently, Andes and Juquitiba were detected in Northeastern Argentina and Eastern Paraguay [120]. Choclo virus, identified in Panama, was the first isolate of hantavirus causing HPS in Central America [121].

Hantaviruses with Disease Potentials
Tula virus (TULV) is widely spread in rodents from central and eastern European, in Austria, Belgium, Croatia, Poland, the Russia Federation, Serbia, and Slovakia [122-128]. TULV has been linked to human infections in the Czech Republic, Switzerland and Germany [129-131]. However, association of TULV with human diseases has not been unequivocally demonstrated. The discovery of Topografov virus (TOPV) in Siberian lemming suggested that the historic disease "Lemming fever" may be hantavirus-mediated and may account for an outbreak of disease in German troops in 1942 [132]. Nevertheless, there is no current evidence linking TOPV with human diseases [133]. The Thottapalayam virus (TPMV) was isolated from an insectivore, *Suncus murinus*, in India in 1964 [134], and hantaan-like virus infections were reported in the country [31]. However, the fundamental biology of TMPV, including its true natural host and pathogenicity to humans, is unclear [135]. The Thailand virus (THAIV) was originally isolated from greater bandicoot rats (*Bandicota indica*) in 1985 [136]. Recently, the first clinical case of infection with THAIV (or at least a hantavirus closely related antigentically to THAIV), with symptoms consistent with HFRS, was reported in Thailand, suggesting that THAIV may represent an additional causative agent of HFRS [137]. The newly identified SOOV from Apodemus peninsulae was believed to be responsible for part of the remaining HFRS cases unrelated to HTN and SEOV viruses in Korea [27], but the confirmed HFRS cases caused by SOOV need to be further investigated. Recently, the presence of the hantavirus SANGV was convincingly demonstrated in African wood mouse [112], but its association with human infections remains unclear.

Epidemiology and Transmission
Reservoir hosts
Hantaviruses have been identified in rodents of the subfamilies Murinae, Arvicolinae, Sigmodontinae and at least one Insectivore

(*Suncus murinus*) [2]. Murinae comprise the largest number of Old World rodents and are the reservoirs for HNTV, DOBV, SAAV, SEOV and Amur virus, which cause HFRS and other hantaviruses that are not associated with human disease. Arvicolinae are voles and the reservoirs for PUUV, which has been associated with mild HFRS in Europe, and for Prospect Hill virus and related viruses in the United States, which have not been demonstrated to cause human infection. Sigmodontinae are the largest group of New World rats and mice that are the hosts of SNV and numerous other New World viruses. Each rodent subfamily carries phyelogenetically distinct viruses, some of which are human pathogens but some others are not human pathogens.

Each hantavirus appears to have a single predominant natural reservoir (Table 3). With rare exception, the phylogenetic interrelationships among the viruses and those of their predominant host show remarkable concordance [2,3]. All known hantaviruses, except TPMV [5] and the several newly identified viruses including Tangganya virus (TGNV) [138], Seewis virus (SWSV) [139], Ripley virus (RPLV) [140] and the Cao Bang virus (CBNV) [141], have their own murid rodents host. However, hantaviruses other than these viruses have been detected in insectivores such as *Suncus murinus*, in bats, cats and birds [142-145]. Serological evidence of hantavirus infection was also demonstrated in dogs and pigs [146-147]. It is not clear whether these species are persistently infected or just spillover hosts, i.e., a secondary host infected through contact with the primary host [5].

Transmissions
Transmission of Hantavirus is thought to occur mainly through contact with infected animal excreta, i.e. saliva, urine and feces. Though the aerosol route of infection is undoubtedly the most common means of transmission among rodents and to humans [2,3,5], virus transmission by bite occurs among rodents [148,149] and may also result in human infection. Mites (gamasid mites and chigger mites) have been found PCR positive for HTNV in China [150] and for Bayou virus in USA [151], indicating that they may also play some roles in transmission of both the Old World and New World hantaviruses. There are no cases suggesting transmission of SNV from infected

mother to infants in uterus or via breast feeding [152-153], and no vertical SNV infection was shown in deer mouse [154]. However, it was demonstrated in cotton rats that BCCV, an HPS associated virus, could be vertically transmitted [155]. Recent studies showed that HFRS virus could cause intrauterine infection and lead to fetal death [156], but no post natal deformity in babies naturally born from infected mothers was observed [157]. Hantaviral infection associated with animal manipulation was well recognized through the world [2,3,5]. In a recent study, prolonged survival of PUUV was observed and indirect transmission of PUUV among rodents was demonstrated, providing evidence for hantavirus transmission via environment [158].

Person-to-person transmission of hantaviruses had not been documented until 1996, when possible inter-human transmission was demonstrated in an Andes-virus-associated HPS outbreak in Argentina [159]. The evidence supporting inter-human transmission of ANDV is increasing, although there are also contrary reports [160,161]. Pinna *et al.* reported inter-human transmission in a cluster of three HPS cases caused by AND South lineage [162]. Person-to-person transmission was demonstrated for HPS caused by AND Cent BsAs, another lineage of the virus [163]. Biological evidence for person-to-person transmission of Andes virus was demonstrated in an HPS outbreak [164]. Recently, the analyses of the clusters of hantavirus infection in Southern Argentina [165] and a prospective study in Chile [166] provided further evidence of interpersonal transmission. However, it seems that inter-human transmission is confined to ANDV, and further investigation is needed to explore whether such a transmission mechanism exists among other hantaviruses.

Epidemiological features

Hantaviral infections are predominant in rural areas, though HFRS caused by SEOV occurs in urban areas [2]. Asymptomatic or non-specific mild infections result in underestimation of the number of hantavirus infections. The ratio of sub-clinical to clinical infection is 5:1 to 10:1 in Europe, and the ratio could be as high as 14:1 to 20:1 for some hantaviruses [5]. An eight-year study in Finland demonstrated that the estimated ratio of diagnosed HFRS cases was only 13% (4% to 30% for

different areas), leaving at least 70% of the PUUV infection undiagnosed because they were sub-clinical or showed only minimal or atypical symptoms [49]. A study in China showed a ratio of clinical to sub-clinical infection of 1:5.4 in some rural areas [167]. Previously published studies found no antibodies against SNV, the first HPS-causing hantavirus identified in the US, in a high-risk population [168,169]. However, recent studies found 0.5% to 40.4% seroprevalence rates of antibody SNV [170,171], and a serological survey in Brazil demonstrated 14.3% seroprevalence rate for antibody against ANDV [172], another HPS-causing hantavirus in the southern Americas. High prevalence of antibodies against other HPS-causing hantavirus were also reported by different investigators despite rare clinical cases of HSP in the populations [95,173]. It is therefore suggested that these viruses, like HFRS-causing viruses, may cause unrecognized infections, either asymptomatic or subclinical infection, in addition to HPS.

Occupation is a dominant factor, with animal trappers, forestry workers, farmers and military personnel at highest risk [174]. Epidemiological investigations have linked viral exposure to activities such as heavy farm work, threshing, sleeping on the ground, military exercises, and lower socioeconomic status [5]. For both HFRS and HPS, infection is more common in males than in females, with a M:F ratio of 2:1 to 3:1, with most of the cases occurring within the 20-40 age group [5], although infections can occasionally occur in children [152]. The time- and space-distribution of hantavirus infection mirrors the distribution and fluctuation of their rodent hosts [5,175]. In Finland, the bank vole population follows a 3 to 4 year cycle, often with two consecutive high density years, which is believed to have led to the patterns of PUU infection in human in the country [49]. In Sweden, the years of highest incidence of HFRS show a period pattern coincident with that of bank vole population dynamics with approximately a 3-year interval between peaks [50]. Such human infection-rodent relationships have been observed in China [19].

Clinical Features and Management
Hemorrhagic Fever with Renal Syndrome

Hemorrhagic Fever with Renal Syndrome (HFRS) manifests as mild, moderate, or severe

disease, depending in part on the causative virus [3,165]. In general, after infection with HTNV or DOBV , there is a 2- to 3-week incubation period followed by a typical five-period clinical course, namely, febrile period, hypotensive period, oliguric period, diuretic period and convalescent period (Figure 2). HFRS due to HTNV and SEOV presents clinical features involving multiple organs in the neurological, gastrointestinal, and cardiovascular systems, giving rise to a wide range of symptoms and signs [2]. It was recently observed that DOBV infection could cause unusually extended pulmonary involvement [176].Though HFRS caused by HTNV and DOBV has a relatively high case fatality from 3% to12%, it did not increase mortality rate among survivors in later life, as demonstrated in a case control study in Korean War veterans [177]. However, there is still some impact on selected morbidity outcomes, such as hypertension and renal dysfunctions.

NE is a mild form of HFRS caused by PUUV with a CFR of 0.1% to 0.4% [178]. NE patients, after 1 to 8 weeks of incubation period, typically have an acute onset of disease, with hallmarks of fever, abdominal pain and/or back pain and/or headache, and signs of renal involvement, but they do not necessarily have the five distinct clinical phases of HFRS caused by HTNV and DOBV. NE usually have a favorable prognosis. However, PUUV infection could lead to a severe disease, including disseminated encephalomyelitis, and hypopituitarism [179,180]. Respiratory manifestations and chest X-ray abnormalities were shown in 30% and 50% of PUUV patients respectively [181]. HPS-like severe pulmonary impairment has also been observed in HFRS patients caused by PUUV [182]. In addition, PUUV infection might cause long-term mild to moderate impairment of renal functions [183].

Hantavirus Pulmonary Syndrome
HPS is a more severe disease than HFRS, with a mortality rate of about 40% [2]. The clinical course of HPS is divided into three periods: the febrile prodrome, cardiopulmonary stage and convalescence (Figure 3). There is a 14- to 17-day incubation period after exposure followed by the prodrome phase typically lasting 3-6 days with myalgia, malaise, and fever of abrupt onset in the absence of cough and coryza. Other early

symptoms include gastrointestinal disturbance, headache and chills.

Figure 2. Clinical course and symptoms of hemorrhagic fever with renal syndrome.
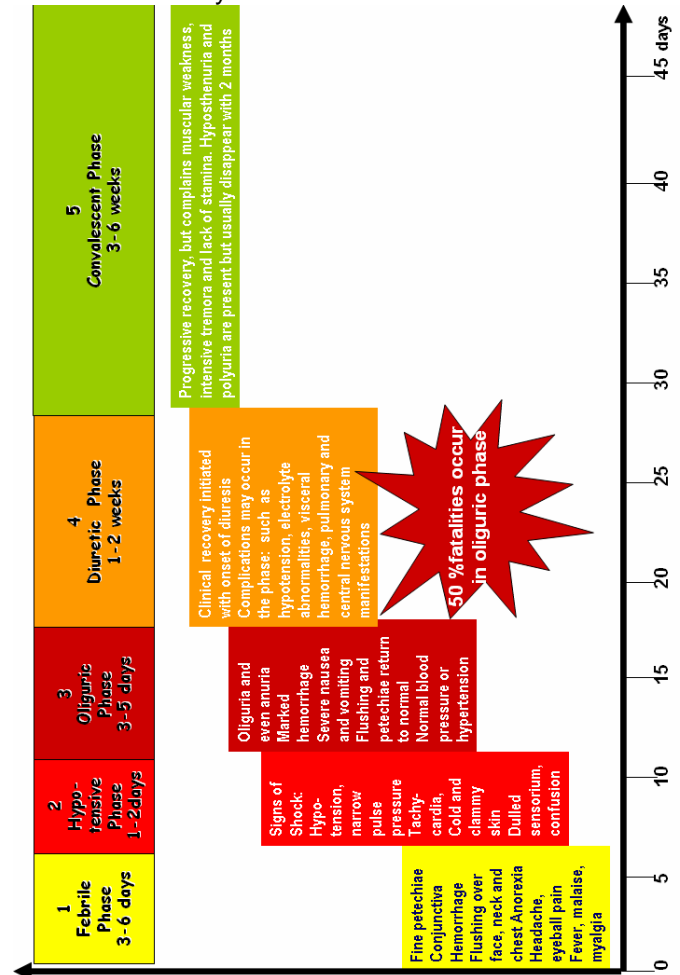
The febrile phase of SNV-induced HPS is followed by a cardiopulmonary phase characterized by acute onset of pulmonary edema [184]. At this stage, cough is generally present, and gastrointestinal manifestations may dominate the clinical presentations.

Tachypnea, tachycardia, and postural hypotension are typical, whereas chest examination is not impressive. Like HFRS, the most common hematologic abnormalities at the late phase of HPS are thrombocytopenia and leukocytosis [185].

Figure 3. Clinical course of hantavirus pulmonary syndrome.
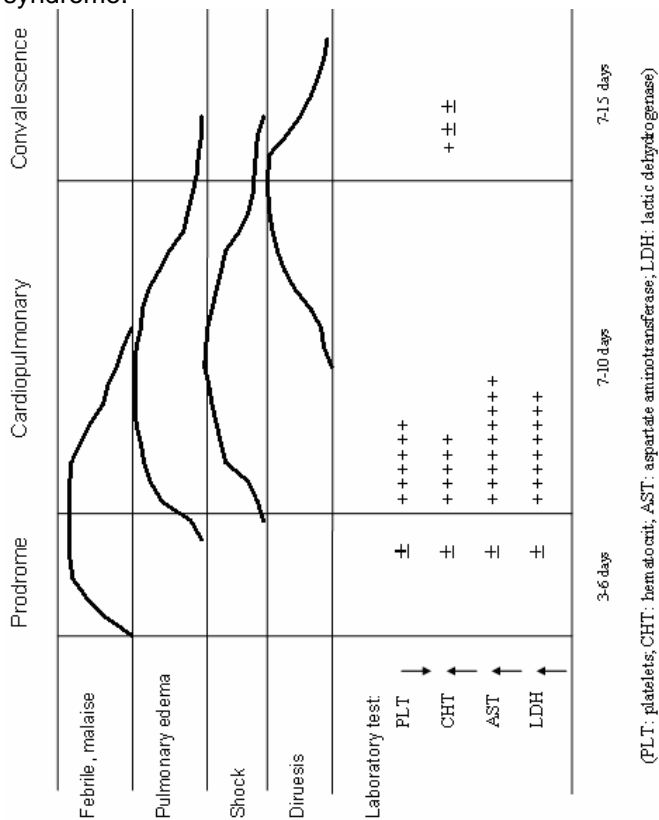
In severe cases, significant myocardial depression occurs, resulting in low cardiac output and hypotension [185]. Pulmonary evaluation will be distinctly abnormal, with low PAO_2 level or low pulse oximetry findings [2]. Like HFRS, symptoms of HPS vary somewhat depending on the causative agents. Renal disease and myositis appear to be more common in cases with Bayou virus and Black Creek virus infection in the United States [186]. Neuropsychological impairments were also observed in some survivors of HPS [187]. There have been confirmed cases of SNV infections without cardiopulmonary involvement [188], indicating the diversity of HPS clinical presentations.

Clinical Management

Currently, there is no specific therapy available for both HFRS and HPS; therefore, the cornerstone of treatment remains supportive measures. The management must include early admission to an intensive care unit where blood and tissue oxygenation, cardiac output, central blood pressure and cerebral pressure can be monitored [165]. Maintaining fluids balance is very important; it must be carefully monitored according to the patient's fluid status, amount of diuresis, and kidney function. Usually one or two haemodialysis sessions are needed for HFRS treatment, while mechanical ventilation when indicated and appropriate use of pressures are crucial to HPS patients [3]. Extracorporeal membrane oxygenation has been found useful as a rescue therapy in patients with severe HPS [189]. Although corticosteroids are not standard of care in the treatment of hantaviral infection, steroid was used to treat severe HFRS and HPS cases. Recently, two HPS cases caused by PUU virus were successfully treated with corticosteroids combined with continuous veno-venous hemodiafiltration [182]. However, the utility of steroids in treatment of hantavirus infections needs further systematic evaluation. High levels of neutralizing antibodies was detected in people long after recovery from SNV infection [7], and the protective capacity of immune serum against HPS caused by ANDV has been demonstrated in animal experiments [190,191], suggesting the possibility of passive immunotherapy at the early stage of HPS, as it is with other hemorrhagic fever [192].

Ribavirin was demonstrated to have anti-hantaviral effect both *in vitro* and *in vivo* by causing error catastrophe during hantavirus replication [194]. Ribavirin is often used in treatment of HFRS in China and clinical trials there have shown that Ribavirin therapy can significantly reduce the mortality and the risk of entering the oliguric phase and experiencing hemorrhage [194]. Ribavirin is included in the WHO Model List of Essential Medicines for HFRS treatment in 2007 (http://mednet3.who.int/EML/expcom/expcom15/expertcomm15.htm). However, an open-label trial of Ribavirin failed to demonstrate a significant improvement in outcome in HPS patients [195], and the subsequent placebo-controlled, double-blind trial suggested that Ribavirin was probably not effective in the treatment of HPS in the cardiopulmonary stage [196]. It seems that Ribavirin should not be recommended for routine therapy of HPS until further evidence is documented. Recently, synergistic antiviral effectiveness of the combined use of amixine, an interferon inducer, and Ribavirin was demonstrated in experimental HFRS in suckling

albino mice [197], and the evidence that hantaviruses are prone to error catastrophe opens the door to the development of new therapeutic strategies.

Laboratory Diagnostics

The diagnosis of hantaviral infections is based on clinical and epidemiological information and laboratory tests. However, it is almost impossible in the individual case with moderate to mild clinical symptoms to diagnose hantavirus infection on clinical grounds only. Laboratory diagnosis of acute hantavirus infection has to be primarily based on serology, since the viraemia of human hantavirus infections is short-termed and viral RNA cannot be regularly detected in the blood or urine of patients in hospitals [198], although the virus is readily detectable by rt-PCR during acute illness in research laboratories [199]. However, high levels of virus-specific antibody are usually detected at the onset of hantavirus diseases (Figure 4), and the serological assay is readily accessible to most hospitals.

A wide array of technologies have been used to detect antibodies to hantaviruses, using cultured and/or purified native-virus preparations or recombinant proteins expressed in bacteria, yeast or insect cells. Both indirect fluorescent assay (IFA) and enzyme immunoassay (EIA) are widely used for detection of specific IgM or low-avidity IgG antibodies [200]. IgM detecting methods are important tools for diagnosis of acute infections, especially in endemic areas with a high prevalence of virus-specific IgG due to previous infections. The μ-captured ELISA to detect IgM antibodies, using viral native or recombinant N antigens, should be preferred because it is superior to IFA and solid phase ELISA in terms of sensitivity [201]. Western blot assays can be used, which are generally in agreement with those of the IgM-capture format for acute infections. In addition, the immunochromatographic 5-min IgM-antibody test has been developed for rapid diagnosis [202].

The IFA test remains popular in Europe and Asia, perhaps in part because it is so easily performed, but such tests are intrinsically limited by problems with specificity, especially with inexperienced users. Although ELISA is optimal for a highly specific serological confirmation of hantaviral infections, the antibody responses usually cross-react strongly between different

hantaviruses [203], indicating that ELISA or other serological tests such as IFA or immunoblotting cannot be used for serotyping. The plaque reduction neutralization test (PRNT) is considered to be the gold standard serological test and, it can be used to discriminate between different species of Hantavirus [204]. However, the PRNT test with infectious hantavirus should be done in a biosafety level-three laboratory, which is a serious limitation for many investigators. For post-mortem confirmations, detection of hantavirus antigens can be done by immunohistochemistry testing of formalin-fixed tissues with appropriately specific monoclonal or polyclonal antibodies [205]. Nucleic acid tests and reverse transcriptional-polymerase chain reaction (RT-PCR) can detect hantaviral RNA in fresh-frozen lung tissues, blood clots or nucleated blood cells, and can be used for hantavirus confirmation and genotyping [206]. Recently, one-step assays for detecting hantaviruses based on real-time RT-PCR were developed and proved to be of high levels of sensitivity, specificity and reproducibility [207]. Virus isolation is extremely rare from human sources and thus is not considered an option for diagnostic purpose of hantavirus infections.

Control and Prevention

The most effective way of controlling hantaviral diseases is to reduce human exposure to infected rodents and their excrement. Monitoring of hantavirus prevalence in rodent populations may give some warning of expected increase in the numbers of human cases [208]. CDC recommendations call for rodent-proofing of homes, reduction of rodent cover around houses, minimization of food available for rodents, trapping in and around dwellings, and the careful disposal of dead rodents [209]. Removal of rodents from a non-rodent-proofed ranch building did not reduce rodent infestation, while the application of simple rodent-proofing measures to dwellings can decrease the frequency and intensity of rodent intrusion, thereby reducing the risk of HPS among rural residents [210,211]. Similarly, workplaces and conditions in agriculture, forestry and military activities should be modified when possible to reduce human-rodent exposure. In China, a comprehensive preventive strategy against hantavirus infection, including health education and promotion, rodent control, surveillance, and

vaccination, has been implemented in the most endemic areas [24]; however, the contributions of these measures to control and prevent hantavirus disease remains to be evaluated.

Figure 4. Viremia and antibody response in human hantavirus infection.
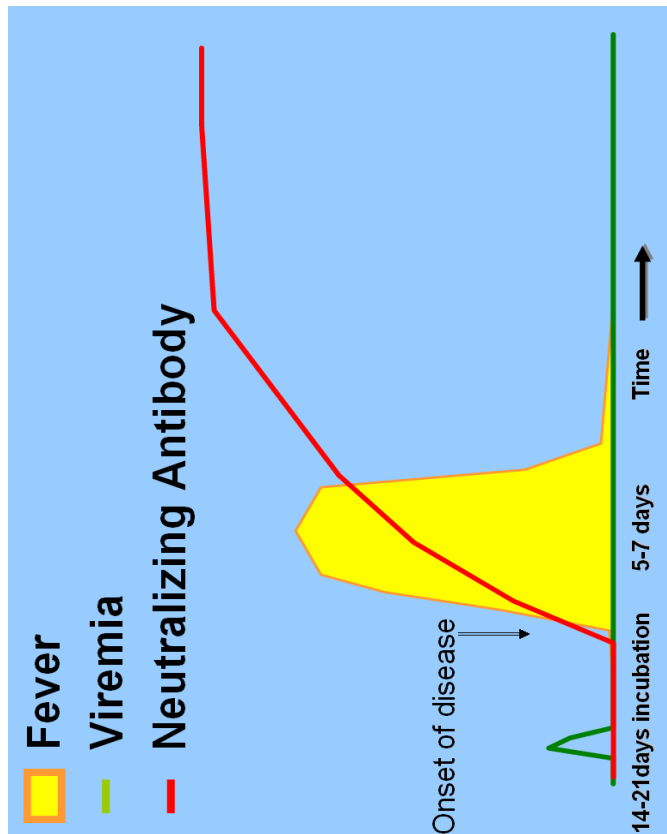
In laboratory animal facilities, all laboratory work involving the propagation of hantaviruses in cell culture or animals should be conducted in biosafety level-four conditions. Even in work with animals of unknown hantaviral infection status, protocols should minimize potential contact with secretions [209].

Vaccines against hantaviral infections have been used for years in China and the Republic of Korea (Table 4). Four kinds of hantavirus vaccines based on inactivated HTN and SEO viruses have been widely used and have been demonstrated safe and effective in China [212]. A new purified bivalent vaccine for HTNV and SEOV is also under development [213]. In the Republic of Korea, an inactivated vaccine purified from suckling mouse brain (Hantavax) against HTNV was approved in 1990 and started to be used in 1991 [26]. A recent

case-control study demonstrated dose-dependent protective effectiveness of the vaccine [214]. More recently, a cell culture-derived inactivated vaccine against Hantaan virus was developed in Korea, and was demonstrated to be more protective than Hantavax [215].

Table 4. Inactivated hantavirus vaccines used in China and Korea.

Virus strains	Generated in	Vaccination Programme	Protection	Country
HTNV	MGKC[+]	3 basic doses + 1 booster	>90%	China
SEOV	GHKC[++]	2 basic doses + 1 booster	>95%	China
HTNV	SMB[+++]	3 basic doses + 1 booster	>90%	China
HTN/SEO	MGKC	2 basic doses + 1 booster	100%	China
HTNV	SMB	2 basic doses + 1 booster	75-100%	Korea

+ MGKC: Mongolian gerbil kidney cell;
++ GHKC: Gold hamster kidney cell;
+++SMB: suckling mouse brain.

Recombinant candidate hantavirus vaccines have been generated on the basis of replication-competent vaccinia viruses (VACV) or recombinant bacteria encoding single or various viral proteins [216]. A VACV recombinant HTNV vaccine carrying the S and M segment was demonstrated to be immunogenic and safe in human volunteers. A recent double-blinded, placebo controlled clinical trial revealed the induction of neutralizing antibodies in 72% of VACV-naive volunteers after two immunizations [217]. A virus-like particle (VPLs) vaccine against PUUV was developed in Europe [218]. VLPs, such as hepatitis B virus (HBV) core antigen, are highly-structured, repetitive protein complexes that have many desirable properties as immunogens. The 120 aa region of PUUV N-protein presented on the HBV core particle provided complete protection in the bank vole [219]. The VLP approach, while still at an early stage, shows some promise because of the unusually intense immune responses that VLPs often provoke against foreign antigens.

DNA vaccine is based on the introduction of an antigen-encoding plasmid into the organism directing the *de novo* synthesis *in vivo*. DNA vaccination with SEOV M segment elicits neutralizing antibodies and protects against SEOV infection in Hamsters [220], and vaccination with HTNV M segment protects against several HFRS-causing hantaviruses and elicits a high-titer

neutralizing antibody response in Rhesus monkey [221]. DNA vaccines against SNV and ANDV have also been shown to be effective in mice models [222,223]. Recently, a bivalent HTN/AND viral DNA vaccine was constructed and has been shown to elicit a potent memory response, and to elicit antibody responses that neutralize viruses causing both HFRS and HPS [224].

The high yield of stable and highly pure nucleocapsid proteins of HTNV, PUUV and DOBV in yeast *Saccharomyces cerevisiae* represents a useful tool for vaccine development against hantavirus infection [225]. Hantaviral recombinant proteins, which could also be obtained from transgenic plants, were able to elicit specific immune responses [226]. In addition, through the development of reverse genetics for negative-stranded RNA viruses [227], it should be possible in the future to generate attenuated hantavirus vaccine with defined alterations/deletions in pathogenicity-related regions.

Concluding Remarks

Over the past few decades, the understanding and recognition of hantaviral infections through the world has greatly improved. The number of recognized viruses continues to increase, as does the spectrum of hantaviral infections. Though newly detected, Hantavirus is an old disease. Environmental changes may affect the geographic distribution, abundance, and dynamics of the rodent carrier, and hence the epidemiology of hantavirus infections. It is generally accepted that hantaviruses are distributed worldwide, but the distribution of specific virus remains to be further investigated. With the development of more rapid and sensitive tests, and increased clinician awareness, human hantaviral infections will presumably be detected in new areas, and new rodent species might be found to carry yet unknown viruses. There is still a long way to go to find an effective treatment for hantavirus infections, and the long-term prognosis of hantaviral infections and the pathogenicity of certain virus species remain to be established. Prevention can be partially achieved by rodent avoidance, but real protection will require a safe and effective multivalent vaccine or a vaccine adapted to local conditions.

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Conflict of interest: No conflict of interest is declared.