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# Hantaviruses: an emerging public health threat in India? A review

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The emerging viral diseases haemorrhagic fever with renal syndrome (HFRS) and hantavirus cardiopulmonary syndrome (HCPS) are a cause of global concern as they are increasingly reported from newer regions of the world. The hantavirus species causing HFRS include Hantaan virus, Seoul virus, Puumala virus, and Dobrava-Belgrade virus while Sin Nombre virus was responsible for the 1993 outbreak of HCPS in the Four Corners Region of the US. Humans are accidental hosts and get infected by aerosols generated from contaminated urine, feces and saliva of infected rodents. Rodents are the natural hosts of these viruses and develop persistent infection. Human to human infections are rare and the evolution of the virus depends largely on that of the rodent host. The first hantavirus isolate to be cultured, Thottapalayam virus, is the only indigenous isolate from India, isolated from an insectivore in 1964 in Vellore, South India. Research on hantaviruses in India has been slow but steady since 2005. Serological investigation of patients with pyrexial illness revealed presence of anti-hantavirus IgM antibodies in 14.7% of them. The seropositivity of hantavirus infections in the general population is about 4% and people who live and work in close proximity with rodents have a greater risk of acquiring hantavirus infections. Molecular and serological evidence of hantavirus infections in rodents and man has also been documented in this country. The present review on hantaviruses is to increase awareness of these emerging pathogens and the threats they pose to the public health system.

[Chandy S, Abraham P and Sridharan G 2008 Hantaviruses: an emerging public health threat in India? A review; *J. Biosci.* 33 495–504]

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## 1. Introduction

Hantaviruses are described as emerging pathogens as newer serotypes are being discovered in many areas non endemic to hantaviruses (Morse and Schluenderberg 1990). Increased globalization and trade, evolution of viral pathogens to adapt to new hosts and increased habitat modification are a few factors responsible for their emergence (Ulrich *et al* 2002).

Hantaviruses are the most widely distributed zoonotic rodent-borne viruses (Johnson 2001) and can cause two important clinical syndromes: haemorrhagic fever with renal syndrome (HFRS) and hantavirus pulmonary syndrome (HPS) in Asia and the Americas respectively (Krüger *et al* 2001). HPS is also referred to as hantavirus cardiopulmonary

syndrome (HCPS) as deaths have been attributed to cardiac failure rather than pulmonary edema (Tager *et al* 2003). Currently up to 21 species and more than 30 genotypes of hantaviruses have been described (van Regenmortel *et al* 2000). The important species include Hantaan virus (HTNV), Seoul virus (SEOV), Puumala virus (PUUV), Sin Nombre virus (SNV) and Dobrava-Belgrade virus (DOBV) (Lednicky 2003).

## 2. Structure and morphology of hantaviruses

Hantaviruses are enveloped RNA viruses (family *Bunyaviridae*, genus *Hantavirus*) that have a negative-sense,

**Keywords.** Cardiopulmonary syndrome; hantaviruses; renal syndrome

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Abbreviations used: ANDV, Andes virus; DOBV, Dobrava-Belgrade virus; ELISA, enzyme-linker immunosorbent assay; GPC, glycoprotein precursor; HFRS, haemorrhagic fever with renal syndrome; HCPS, hantavirus cardiopulmonary syndrome; HPS, hantavirus pulmonary syndrome; HTNV, Hantaan virus; IFA, immunofluorescence assays; IgM, immunoglobulin M; NCR, non-coding region; NE, nephropathia epidemica; nt, nucleotides; ORF, open reading frame; PUUV, Puumala virus; RdRp, RNA-dependent RNA polymerase; SEOV, Seoul virus; SNV, Sin Nombre virus; TPMV, Thottapalayam virus

tri-segmented genome (Schmaljohn and Dalrymple 1983). The large (L) segment codes for the viral RNA-dependent RNA polymerase (RdRp) and the medium (M) segment for the glycoprotein precursor (GPC) which is processed into the two envelope glycoproteins (G1 and G2). The small (S) segment codes for the nucleocapsid (N) protein (Schmaljohn *et al* 1986; Schmaljohn 1990). The hantavirus particle is spherical with a diameter ranging from 80-120 nm and consists of three circular nucleocapsids, each contains one RNA segment complexing with N and RdRp proteins (Lee and Cho 1981; Severson *et al* 2005)

The 3' and 5' termini of all the three RNA segments are conserved and complementary thus forming pan-handle structures, this being an important feature of the family *Bunyaviridae* (Elliot *et al* 1991). The pan-handle structures are about 17 base pairs long and may regulate viral transcription and replication (Flick and Pettersson 2001; Blakqori *et al* 2003). The L segment is approximately 6500 nucleotides (nt) long with a single open reading frame (ORF) coding for about 2150 amino acids. The M segment is approximately 3700 nt long and codes for about 1140 amino acids while the S segment is about 1700 nt long coding for about 430 amino acids (Plyusnin *et al* 1996). In the S segment of hantavirus species carried by rodents of the sub-families, *Arvicolinae* and *Sigmodontinae*, there is an additional ORF coding for a non-structural protein, this is missing in serotypes hosted by the *Murinae* rodents. NS proteins have not been detected in hantavirus-infected cells (Parrington and Kang 1990; Stohwasser *et al* 1990; Spiropoulou *et al* 1994). The 3' non-coding region (NCR) of the hantavirus S segment varies in length from 300-700 nucleotides among the different serotypes (Plyusnin 2002).

Hantavirus N protein is the most abundant viral protein in the virion and infected cells where it is found in the cytoplasm, forming inclusion bodies and filamentous structures (Vapalahti *et al* 1995; Ravkov *et al* 1998). It plays a central role in replication and is expressed in large quantities in infected cells (Flick and Pettersson 2001; Blakqori *et al* 2003). The N protein protects the RNA genome by encapsidation. It is a multifunctional protein with additional functions other than viral RNA encapsidation, protection, replication and virus assembly. It also seems to interact with cellular macromolecules to inhibit important cellular regulatory pathways (Kaukinen *et al* 2005). The N protein is highly antigenic and antibodies are produced early in infection as there is a strong and rapid immune response (Elgh *et al* 1996). The N-terminal 100 amino acids of the N protein are highly antigenic and practically all sera positive for hantavirus antibodies recognize this region. This portion of the N protein is used in diagnostic assays to diagnose hantavirus infections. The middle part of this protein (210-310) is highly variable within different hantavirus species. The C terminus is also highly conserved and is known to

bind RNA. B-cell epitopes are seen in the N terminal region while T-cell epitopes are distributed randomly (Jenison *et al* 1994; Lundkvist *et al* 1995; Vapalahti *et al* 1995; Elgh *et al* 1996). Within a given hantavirus serotype, the primary structure of the N protein is generally conserved (Kaukinen *et al* 2005). Recombinant N protein is currently being commercially expressed in *Escherichia coli*, baculovirus, insect and yeast systems for use in diagnostic assays (Schmaljohn *et al* 1990).

The GPC (1132-1148aa) is not found in infected cells indicating that it is cleaved into Gn and Gc proteins (formerly called G1 and G2). GPC is synthesized on the endoplasmic reticulum membrane where it is cleaved, glycosylated and forms heterodimers which are transported to the Golgi complex (Schmaljohn *et al* 1987; Löber *et al* 2001). Accumulation of Gn and Gc proteins on the Golgi complex provides the budding site for hantaviruses (Schmaljohn *et al* 1986). These glycoproteins mediate cell attachment and fusion (Arikawa *et al* 1985). The L protein is a RNA transcriptase and replicase seen in viruses that have to transcribe mRNA and replicate genomic RNA from antigenomic RNA. So it should have endonuclease, transcriptase and replicase activities. The L protein has a single ORF. The L and N proteins are required for RNA synthesis (Kukkonen *et al* 2005).

### 3. Diversity of hantaviruses

The N protein between hantavirus serotypes shows greater degree of cross reactivity than the G1 and G2 proteins (Jenison *et al* 1994). There is a high degree of antigenic cross reactivity between members belonging to the three groups of hantaviruses namely:

- (i) HTNV-like viruses (HTNV, SEOV, DOBV, Thailand virus [THAIV]) carried by *Murinae* rodents (Old world rats and mice).
- (ii) PUUV-like viruses (PUUV, Tula virus [TULV]) carried by *Arvicolinae* rodents (voles and lemmings).
- (iii) SNV-like viruses (SNV, Andes virus [ANDV]) carried by *Sigmodontinae* rodents (Vapalahti *et al* 2001).

There is a great degree of cross reactivity between SNV and PUUV group of viruses. The amino acid sequences of the N protein terminal regions show 83.7% to 90.7% homology among the HTNV-like viruses and 74.4% homology for SNV and PUUV. The overall amino acid homologies between the HTNV-like viruses and the other two groups are from 44.2% to 46.5% (Elgh *et al* 1997). This antigenic cross reactivity was thought to be sufficient for assays with two antigens of HTNV and PUUV and one SNV antigen for serological diagnosis of hantavirus infections in Eurasia and America respectively. However, later studies have shown that 7.1% of DOBV positive acute phase samples and 12.5%

of DOBV positive convalescent samples were negative with heterologous antigen based assays. This emphasizes the usefulness of homologous antigens in serological assays (Kallio-Kokko *et al* 2000).

The phylogenetic analysis of the N protein also groups hantaviruses in the same way as given above. The Phylogenetic trees show two major lineages of hantaviruses, one branching to HTNV, SEOV, THAIV and DOBV and the other branch leading to PUUV, SNV and other New World hantaviruses. Thottapalayam virus (TPMV), the most divergent member of this genus shows greater genetic relatedness to HTNV-like virus group (A Toney, B Meyer and C Schmaljohn, unpublished data). Phylogenetic trees using the L and M segment sequences also show identical branching suggesting that similar evolutionary events have occurred for all genome segments (Xiao *et al* 1994; Plyusnin *et al* 1996).

The plaque-reduction neutralization method is the most reliable assay for serotyping (Chu *et al* 1994). The M segment gene products (surface proteins) are more prone to mutations and its analysis at the nucleotide and amino acid level would be a more sensitive approach to classification of hantaviruses (Xiao *et al* 1994). Since humans are accidental hosts of hantaviruses, human epidemics of hantavirus disease do not contribute to the virus evolution (Avsic-Zupanc *et al* 1995).

Of all the hantaviruses known, SEOV is genetically the most homogenous. Regardless of the geographical origin, the deduced M segment amino acid sequences of SEOV isolates show 99% homology (Xiao *et al* 1994). HTNV is known to be stable and isolates are known to show M segment amino acid homology of 97% (Schmaljohn *et al* 1988). PUUV isolates are the most variable and amino acid homology of the M segment may range from 83%-94% (Jay *et al* 1997). Persistent infections of the rodent host provide opportunity for two mechanisms responsible for virus evolution: genetic drift (Spiropoulou *et al* 1994) and genetic shift (Henderson *et al* 1995).

#### 4. Old World and New World hantaviruses

Hantavirus are classified into two main groups: Old World and New World hantaviruses. The Old World hantaviruses include species which cause HFRS in Asia and Europe while the New World hantaviruses cause HCPS in the Americas (Mertz *et al* 2006; Muranyi *et al* 2005). The first New World hantavirus was identified during the outbreak of HCPS in the Four Corners Region of southwestern USA in 1993. The etiological agent was SNV; since then many pathogenic New World hantavirus species have been identified and characterized (Khaiboullina *et al* 2005). The New World hantaviruses are associated with rodents belonging to the *Sigmodontinae* subfamily (Montgomery *et al* 2007) while the Old World hantaviruses are associated with rodents

of the subfamilies *Murinae* and *Arvicolinae* (Peters and Khan 2002). The distribution and known rodent hosts of hantaviruses are shown in table 1.

### 5. Clinical features of hantaviruses

The clinical picture and severity of HFRS and HCPS depends on the infecting species.

#### 5.1 HFRS

The incubation period is 1-5 weeks and the onset of the disease is with fever and influenza-like symptoms (Schmaljohn and Hjelle 1997; Muranyi *et al* 2005). Hemorrhagic manifestations if present are seen as flushing of the face, injection of the conjunctiva and mucous membranes (Kruger *et al* 2001). The disease is conveniently described as having five phases: a febrile phase lasting 3-5 days followed by a hypotensive (shock) phase lasting from a few hours to a few days, a subsequent oliguric phase lasting 3-7 days and finally a diuretic phase leading to the convalescent phase (McCaughey and Hart 2000).

The febrile phase is characterized by development of an acute influenza-like illness. Nausea, vomiting, back and abdominal pain are additional findings. Proteinuria suddenly appears on the third to fifth day. In severe HFRS which is often seen in endemic areas, on the 4th day there may be onset of albuminuria. Towards the end of the febrile phase flushing of the face and conjunctival suffusion may be seen. These symptoms may mark the onset of the hypotensive phase characterized by thrombocytopenia. One-third of deaths occurring during this phase are due to shock. Proteinuria may persist. Almost half the fatalities occur during the subsequent oliguric phase due to renal failure. Survivors progress to the diuretic phase which may last from few days to few weeks and is associated with improvement of renal functions: then to a final convalescent phase during which the patient recovers completely (Peters *et al* 1999; Krüger *et al* 2001; Lednicky 2003). During evaluation of patients with suspected hantavirus infections, a physician may encounter mainly three kinds of clinical presentations; fever with shock and multi-organ failure, fever with oliguric acute renal failure and febrile illness without any renal failure (Bruno *et al* 1990).

In patients with severe HFRS the blood picture shows haemoconcentration, leukocytosis and thrombocytopenia. Urine analysis shows proteinuria, hematuria and pyuria. Significant elevations of alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase and creatine kinase enzymes are frequently noticed. Marked polymorphonuclear leukocytosis with a left shift and CD8+ activated cells appear as atypical lymphocytes on a peripheral blood smear

**Table 1.** Hantaviruses: geographical distribution and their natural rodent hosts (adapted from Muranyi *et al* 2005)

Category	Genotype/serotype of hantaviruses	Clinical syndrome	Natural rodent reservoir	Regional distribution
Old World Hantaviruses	Amur	HFRS	<i>Apodemus peninsulae</i>	South east Siberia, China, Japan
	DOBV Af	HFRS	<i>Apodemus flavicollis</i>	Europe, Balkans, Syria,
	DOBV Aa	HFRS	<i>Apodemus agrarius</i>	Central Europe, China, Russia, Korea
	HTNV			
	PUUV	NE	<i>Clethrionomys glareolus</i>	Europe, Russia, Scandinavia
	SEOV	HFRS	<i>Rattus rattus</i> , <i>Rattus norvegicus</i>	Worldwide
	Tula (TULV)	HFRS	<i>Microtus arvalis</i>	Europe
	Thailand (THAIV)	HFRS	<i>Bandicota indica</i>	Thailand
New World Hantaviruses	Thottapalayam (TPMV)	ND	<i>Suncus murinus</i>	South India
	SNV	HCPS	<i>Peromyscus maniculatus</i>	North America
	New York	HCPS	<i>Peromyscus leucopus</i>	North America
	Black Creek Canal (BCCV)	HCPS	<i>Sigmodon hispidus</i>	North America
	Bayou (BAYV)	HCPS	<i>Oryzomys palustris</i>	North America
	Andes (ANDV)	HCPS	<i>Oligoryzomys longicaudatus</i>	South America
	Leguna Negra	HCPS	<i>Calomys laucha</i>	South America
	Oran	HCPS	<i>Oligoryzomys longicaudatus</i>	South America
	Choclo	HCPS	<i>Oligoryzomys fulvescens</i>	South America
	Juquitiba	HCPS	<i>Oligoryzomys nigripes</i>	South America
Lechiguanas	HCPS	<i>Oligoryzomys flavescens</i>	South America	
Araraquara	HCPS	<i>Bolomys lasiurus</i>	South America	

ND, Not documented; NE, Nephropathia epidemica.

(Peters *et al*, 1999). In patients with acute renal failure: fever, abdominal pain, azotemia and thrombocytopenia were common clinical findings. Urinalysis may show proteinuria and hematuria. Elevations in serum aspartate and alanine aminotransferase are moderate and common. Oliguric renal failure is common in most of the patients. In patients presenting with undifferentiated febrile illness, thrombocytopenia is commonly seen; most have increased serum aspartate and alanine aminotransferase values. Urine analysis of some may show proteinuria, hematuria and pyuria. Recovery is complete and uncomplicated. These cases can be mistaken for influenza, viral hepatitis or streptococcal pharyngitis (Bruno *et al* 1990; Mertz 2002).

The clinical picture and severity of HFRS may vary for different hantavirus species. HFRS caused by HTNV and DOBV may show a 5%-15% mortality; SEOV infections

are milder with greater liver involvement (Kim *et al* 1995). PUUV causes nephropathia epidemica (NE), the mildest form of HFRS (Nichol 2001).

Fever and thrombocytopenia are common clinical findings and important clues to diagnosis of HFRS. Other signs that may help in the initial diagnosis of HFRS would be conjunctival hemorrhage, facial flushing and petechiae. Jaundice is noticeably absent and helps to differentiate hantavirus infections from leptospirosis, viral hepatitis or bacterial sepsis. However there has been a report of hantavirus infection in patients presenting with febrile illness and jaundice (Gloriani-Bargaza *et al* 1999). Maculopapular rash is absent and helps differentiate between hantavirus infection, leptospirosis, dengue fever or scrub typhus (Markotic *et al* 2001). It has been reported that *Apodemus agrarius*, *Cricetulus triton* and *Rattus norvegicus* are the

common rodent hosts of both scrub typhus and HFRS in Northern China. Therefore the possibility exists for dual infections of HFRS and scrub typhus (Houck *et al* 2001; Heung-Chul *et al* 2007; Liu *et al* 2007).

## 5.2 HCPS

HCPS can be described to occur in two phases, prodromal and cardiopulmonary phase. The prodromal stage is characterized by fever, headache, chills and myalgia. Like HFRS the clinical picture at this phase may be confused with other viral infections.

The onset of the cardiopulmonary phase is with pulmonary edema, dyspnea and hypoxemia. Patients with severe illness may progress to cardiac depression, respiratory failure and acidosis leading to fatal arrhythmias (Nichol 2001). Common laboratory indicators of HCPS include thrombocytopenia and hemoconcentration; presence of atypical lymphocytes is also a common finding (Peters and Khan 2002). Different hantaviruses can cause HCPS with different clinical presentations. Renal involvement in SNV infection is rare but renal insufficiency has been reported in infections with ANDV, Bayou virus (BAYV) and Black Creek Canal virus (BCCV) (Duchin *et al* 1994; Hjelle *et al* 1996; Khan *et al* 1996). Table 2 highlights differentiating features between HFRS and HCPS.

HFRS and HCPS are uncommon in children. However there have been occasional reports of NE and HCPS in children. The clinical picture of pediatric HCPS cases closely mimics that of adults with fatality rate close to 33% (Overturf 2005). The diagnosis of hantavirus infections in newer geographical areas can be improved if clinicians are aware of the protean manifestations of hantavirus disease.

**Table 2.** Differentiating features of HFRS and HCPS ( adapted from Mertz 2002)

Symptoms/clinical and laboratory findings	HFRS	HCPS
Fever and myalgia at onset	Present	Present
Facial flushing	Present	Seen in ANDV infection
Injection of conjunctiva	Present	Absent
Pulmonary symptoms	Uncommon	Present
Renal symptoms	Common	Uncommon
Hemorrhage	Common	Seen in ANDV infection
Thrombocytopenia	Common	Common
Hemoconcentration	Uncommon	Common
Shock	Uncommon	Present
Hypotension	Common	Common

## 6. Laboratory diagnosis of hantavirus infections

It is difficult to diagnose hantavirus infections clinically as the early signs and symptoms of the disease are non-specific (Nichol 2001). Serology is the mainstay of diagnosis of hantavirus infections as the viremia in HFRS patients is short-lived (Papa *et al* 1998). Since there is considerable cross-reactivity between related hantaviruses, antigens used for serological assays help in identifying hantaviruses but not always the infecting serotype (Wichman *et al* 2001). However a combination of clinical and serological findings is generally used (Muranyi *et al* 2005). There is an early and strong humoral response against the N antigen, hence is the antigen of choice for enzyme linked immunoassays (ELISA)(Zoller *et al* 1993).The use of native N antigen has given way to recombinant entire and truncated N antigens produced in prokaryotic and eukaryotic vector systems (Sjolander *et al* 1997). However homologous antigens are far more sensitive than heterologous antigens and are advisable in areas where circulating serotypes are known (Sjolander and Lundkvist 1999). Immunofluorescence assays (IFA) are also commonly used but have lower specificity. These problems with IFA make them generally unsuitable for serological surveys (Groen *et al* 1991).

Detection of virus-specific IgM is advocated for diagnosis of acute hantavirus infections. Preferably the  $\mu$ -capture ELISA should be used as it has a higher specificity than IFA and indirect antibody detection ELISA (Krüger *et al* 2001). In non-endemic areas presence of virus specific IgM and IgG could be useful for diagnosis; however IgG response may sometimes be delayed (Lundkvist *et al* 1995, 1997). Positive results on single serum samples should be correlated with clinical information (Wichman *et al* 2001). Nested reverse transcriptase-polymerase chain reaction (RT-PCR) using genus and species-specific primers are employed for diagnosis of hantavirus infections (McCaughy and Hart 2000). Hantaviruses are routinely cultured in Vero E6 cell line (African green monkey kidney cell line) in which it does not readily cause any cytopathic effect. The virus is detected in cell culture by IFA. Isolation of hantaviruses from clinical specimens is difficult and hazardous as it should be performed in biosafety level-3 laboratories. In general rodent isolates are commoner than human isolates.

## 7. Epidemiology of hantavirus infections

The epidemiology and geographical distribution of hantavirus species closely reflects that of their rodent reservoirs (Khaiboullina *et al* 2005). Hantavirus infections of the rodent cause an asymptomatic and persistent infection. These viral agents may then spill over to other animal hosts like man resulting in serious disease but with clearance of virus in survivors (Nichol 2001). It is known that in humans,

asymptomatic or non-specific mild infections may occur more frequently than symptomatic infections (McCaughey and Hart 2000). However, since humans are not the natural host reservoir for hantaviruses and infection is accidental, man is a dead-end host for the virus (Muranyi *et al* 2005). Therefore the entire amplification and perpetuation of the virus relies on efficient transmission cycles between rodents.

Transmission of infection is via the aerosols generated from virus-contaminated rodent feces, urine or saliva (Lundkvist and Niklasson 1994). Hantavirus transmission among rodents occurs through bites and may also result in human infection (Glass *et al* 1988; Dournon *et al* 1984). Transmission of infection may also probably occur via food or hands contaminated by rodent excreta or via rodent bites or scratches. Human to human transmission of hantaviruses was considered unlikely until reports of an outbreak of ANDV from Argentina changed this perception (Wells *et al* 1997). This outbreak report from Argentina was also the sole example of a nosocomial transmission of hantaviruses.

There is an occupational risk of transmission of hantavirus infections with animal trappers, mammalogists, forest workers, farmers and military personnel at greater risk (Goren *et al* 1995, Schmaljohn and Hjelle 1997). Pediatric infections are uncommon and men are more often infected than women as an occupational risk (McCaughey and Hart 2000). Laboratory and animal facility-acquired hantavirus infections due to contact with infected animals and infected cell lines has been reported in laboratory personnel (Lee and Johnson 1982; Lloyd *et al* 1984).

HFRS and HPS are basically rural diseases (Young *et al* 1998; Mertz 2002); SEOV is cosmopolitan in nature and known to cause urban cases of HFRS (Kruger *et al* 2001). In Asia, the incidence of hantavirus infections increase during summer and spring and peak during fall because of greater contact between rodents and man during these planting and harvesting months. However in Sweden, the peak incidence of the disease occurs during the first frost in winter when rodents may take shelter in human dwellings (van Ypersele 1991).

In the Old World, the majority of hantavirus cases have been reported from Europe and Eastern Russia (China, Korea and Far East Russia). The prototype, HTNV is vectored by the mouse species *Apodemus agrarius*, a mouse found in the fields. About 10,000 cases of HTNV related HFRS cases are seen in China every year, while in Korea about 300-900 cases occur annually. HTNV related HFRS cases occur during the fall when there is an increased farming activity and there is rodent movement into human dwellings to escape the cold. Most SEOV circulates in the domestic rats and causes urban cases of HFRS. It is worldwide in distribution with the distribution of the hosts through international shipping routes. The majority of SEOV-related HFRS occurs during spring and

early summer. DOBV causes serious HFRS in the Balkans and in southern parts of Europe. The primary reservoir is *Apodemus flavicollis*. DOBV-associated HFRS occur in the late spring and summer months and in rural areas.

NE is a mild form of HFRS and is caused by PUUV. The virus is found throughout Scandinavia and in parts of Europe west of the Ural mountains. The host of this species is the bank vole (subfamily *Arvicolinae*), *Clethrionomys glareolus*. The HCPS in the Four Corners Region of the US in 1993 and the subsequent discovery of the etiological agent, the SNV marked the beginning in the search for hantavirus species. SNV is vectored by the deer mouse, *Peromyscus maniculatus* which belongs to the subfamily *Sigmodontinae*. The 1993 outbreak of HCPS was as a result of increase of deer mice populations owing to the prolonged to the El Niño effect. The increased rain promoted the increase of deer mice populations. The peak of HPS cases occur in late spring and summer and about equal number of males and females are infected. As in other hantavirus infections, pediatric cases are rare. Although initially regarded as new disease, retrospective studies show that HCPS cases have gone unnoticed since 1959 in USA. (Krüger *et al* 2001; Lednicky 2003).

## 8. Hantaviruses as agents of biological warfare

The outbreak of HCPS in the Four Corners Region in 1993 raised many rumors that the etiological agent was a deadly virus that had escaped from a military laboratory involved in bio-weapons research. Retrospective studies showed that the disease was around since 1959. In the list of pathogens listed as biowarfare agents, hantaviruses are included in list C which has the lowest potential for use as a bioterrorist weapon. In man, viremia is short-lived and hantavirus isolates from rodents are commoner than those from humans. HTNV viremia occurs during the prodromal stage and recovery of virus from human samples is poor. The host-related cellular immune response rather than the pathogenic capacity of the virus *per se* are responsible for development of the disease. The aerosol route is the only efficient way of transmission and the survival of the free virus in the environment is doubtful. Human to human transmission has been documented only in one case from Argentina. Some hantavirus infections are treatable and formalin-inactivated vaccines have been in use for more than a decade in Korea. The above mentioned features of hantavirus make it unsuitable for use as a biowarfare agent (Clement 2003).

## 9. Hantavirus infections in rodents

Unlike other members of its genus *Bunyaviridae* which are arboviruses, hantaviruses are maintained in nature in specific

rodent hosts (roboviruses). The geographical distribution of hantavirus species closely reflect that of the reservoir rodent host and hantavirus species in a particular geographical region are closely related (Meyer and Schmaljohn 2000). The phylogenetic trees for hantavirus species and their hosts show amazing congruence thus proving that there has been co-evolution and co-speciation of hantavirus species and their hosts (Plyusnin *et al* 1996; Vapalahti *et al* 2001). The natural reservoir of hantaviruses are murid rodents (order *Rodentia*; family *Muridae*; subfamilies *Murinae*, *Arvicolinae* and *Sigmodontinae*). We do not know yet whether these non-rodent hosts merely represent spill-over hosts which might not have much role in transmission of hantaviruses (Young *et al* 1998). Experiments in laboratory animals have shown that young susceptible rodents develop life long infections. In the adult animal, the infection is transient and may get cleared naturally (Nakamura *et al* 1985; Kim *et al* 1995).

The absence of an arthropod vector is an important reason for the rigid association of hantavirus species with specific rodent hosts which are persistently infected. It is the reason also for the slow geographical movement of hantavirus species as there is only a moderate efficiency in the natural horizontal rodent-rodent transmission of hantaviruses. It also limits movement of hantavirus to other host species.

## 10. Treatment and prevention

There are no effective anti-viral drugs for the treatment of all hantavirus infections. Ribavirin (1- $\beta$ -D-ribofuranosyl-1, 2, 4-triazole-3-carboxamide) has been used in clinical trials for treatment of HFRS patients in the People's Republic of China and has shown reduction in fatality. However, it remains ineffective for treatment of HPS. Supportive therapy is the best to control progression towards life threatening symptoms (Krüger *et al* 2001; Nichol 2001).

Prevention of exposure to rodent excreta is the best way to avoid infection. Simple preventive steps are: decontamination of human dwelling having signs of rodent activity, maintaining rodents as pets should be discouraged and proper storage of food should be practiced. There are a few inactivated vaccines (Hantavax) licensed for use in Korea but the protective response is short lived. Baculovirus and vaccinia-expressed hantavirus glycoproteins confer protection in animal models. There is ongoing research on nucleic acid vaccines (Krüger *et al* 2001; Nichol 2001).

## 11. Hantaviruses research in India with special reference to the Thottapalayam virus

It was in 1966 that Thottapalayam virus (TPMV), the first indigenous hantavirus species was isolated from the spleen of a shrew (insectivore), *Suncus murinus*, captured in South

India during field studies of Japanese encephalitis (Carey *et al* 1971). Initially believed to be an arbovirus, this isolate was later proved to be a member of the family *Bunyaviridae* and genus *Hantavirus*, based on electron microscopic and serological studies (Zeller *et al* 1989). However, TPMV is one of the few hantavirus isolates which has been isolated in a non-rodent host.

Chandy *et al* (2005) in a study of 152 serum samples found 23 (14.7%) individuals with febrile illness positive for anti-hantavirus IgM and 5.7% of healthy blood donor samples tested were positive. These findings suggested the presence of hantavirus infections in the Indian population, presenting as symptomatic or asymptomatic infections.

Evidence exists for SEOV-like infection in 12% and a PUUV-like infection in 5% of Indians presenting with a leptospirosis-like clinical picture from Cochin and Chennai area of India (Clement *et al* 2006). In 2007 there were reports from Western India of hantavirus infections presenting with ocular involvement (Mehta and Jiandani 2007).

TPMV is phylogenetically and antigenically quite distinct from the other hantaviruses and it has probably co-evolved with its non-rodent host (Yadav *et al* 2007). The pathogenicity of TPMV was doubtful as the host insectivore was believed to be a spillover host. Anti-TPMV antibodies in sera from shrews in Indonesia and in a patient presenting with acute febrile illness of unknown etiology may be proof of *Suncus murinus* being the natural host of TPMV and of causing human infections (Okumura *et al* 2007).

Sero-epidemiological studies have indicated a 4% seropositivity of hantavirus infections in India. It has been proved that tribes (Irulas) living in close proximity with rodents show significantly higher frequency of antibody positive status. Patients with chronic renal disease appear to have a higher rate of hantavirus seropositivity compared to the healthy blood donor control group. Warehouse workers (godown workers) showed a low seropositivity reflecting a lower risk of hantavirus infections (Chandy *et al* 2008).

Our own experience with studies on hantaviruses show that THAIV-like, HTNV-like /SEOV-like species are circulating in India (our unpublished data). Partial S gene segment sequences recovered from patients with acute febrile illness show 93%–97% homology with HTNV.

In our laboratory, 54 rodent sera were tested by IFA using HTNV antigen. Of the 54 tested, 9 were seropositive by IFA; 6 of the 9 were sero reactive by WB using THAIV antigens. The partial S segment from a seropositive animal was amplified from the lung tissue and it showed 93% identity to HTNV S segment (our unpublished data).

Considerable research still needs to be done to characterize the circulating species, to extensively study rodent reservoirs in India and to develop of better diagnostic tools (serological and molecular) for rapid diagnosis of hantavirus infections which will further our knowledge of these emerging and reemerging viral agents.

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ePublication: 15 October 2008