

Review Article

*“Rodent Biodiversity Human Health and Pest Control
in a Changing Environments”*

Rodent-Borne Zoonotic Viruses in Southeast Asia

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ABSTRACT

Arenaviruses and hantaviruses circulate among the rodent populations of southeast Asia, and can occasionally be transmitted to humans. The latter virus has been identified in human patients in southeast Asia, although the former has not. The case fatality rate due to hemorrhagic fever with renal syndrome (HFRS), caused by hantaviruses and carried by murine rodents, varies between 2–12%, while the case fatality rate due to the arenaviral lymphocytic choriomeningitis virus (LCMV) is lower than 1%. Great care must be taken to avoid infection in pregnant women by LCMV, where serious complications can occur. At present, treatment other than supportive therapy is unavailable for LCMV. A range of vaccines exists in Asia, or are under development for the prevention of hantavirus infection, while ribavirin can help in the early phase of an acute illness.

With changing climates and land use and rapidly increasing globalization, it is likely that the situation regarding these zoonotic viruses will change, resulting in an increase in human infections. Few studies have been carried out in this region, particularly in terms of LCMV. More are needed to establish the rates of infection by these agents (and for other potential rodent-borne zoonoses), both in their rodent hosts and in humans, so that they can be used as a baseline to monitor any changes that may occur.

Key words: arenavirus, hantavirus, rodents, southeast Asia, zoonoses

REVIEW

Although numerous zoonotic diseases have been identified in southeast Asia in recent years, few have been viral with rodents as their primary hosts. Tick-borne encephalitis virus

(TBEV), which is capable of infecting a range of mammalian species including rodents, has been isolated in ticks from at least two foci in China (Cai *et al.* 1995; Hou *et al.*, 1991) and rodents have been suggested as one of the natural reservoirs of hepatitis E virus in Nepal and the

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United States of America, but there is only serological evidence and the virus was never detected in rodent specimens (Favorov *et al.*, 2000; He *et al.*, 2002; He *et al.*, 2006).

Of the virus species known conclusively to have rodents as their primary hosts, evidence for infection in southeast Asia has only been demonstrated for the lymphocytic choriomeningitis virus (LCMV) and for several hantavirus species.

The lymphocytic choriomeningitis virus is from the *Arenaviridae* family and was the first species to be identified in 1933 during investigations into an outbreak of St Louis encephalitis (Armstrong and Lille, 1934). Its primary host, *Mus musculus*, was identified a few years later (Armstrong and Sweet, 1939) and due to this association, LCMV is believed to have a worldwide distribution. The *Arenaviridae* family is split into two groups, the New World group (comprising species from the Americas) and the Old World group (comprising African species and LCMV) (Clegg *et al.*, 2000). With numerous species identified recently in the Americas, there are now over 20 species of arenaviruses recognized (ICTVdB, 2006). Almost all species are believed to have rodent hosts and there is evidence to suggest that at least some of the viruses have co-evolved with their hosts (Bowen *et al.*, 1997; Hugot *et al.*, 2001).

Although the house mouse *Mus musculus* is presumed to be the primary host for LCMV, it has also been detected in several other rodent species. In southeast Asia, serological evidence of LCMV infections in rodents has been found in China, in *Mus musculus* (Morita *et al.*, 1996) and in Thailand, especially in *Bandicota savilei* and *Rattus norvegicus* (Nitapattana *et al.*, 2000), although few other studies have been carried out (see Table 1). The data from Europe on the occurrence of LCMV in several rodent species without any connection to *Mus* suggest that LCMV in fact could be a complex of strains (Laakkonen

et al., 2006; Kallio-Kokko *et al.*, 2006). LCMV seropositivity in several murine rodent species in southeast Asia could also mean that more than one LCMV-type strains may circulate there.

Transmission in house mice occurs through either a horizontal or vertical route. The latter usually results in a life-long, asymptomatic, carrier state, whilst infection through the horizontal route leads to a generalized spread of the virus followed by either death of the animal or virus clearance and immunity (Buchmeier *et al.*, 1980).

At least nine *Arenavirus* species are known to cause human disease and antibodies to a further three species have been detected in humans (Salazar-Bravo *et al.*, 2002). Human LCMV infections occur through direct or indirect exposure to infected rodents or their bodily secretions and are rarely fatal. Infections usually result in a febrile disease with myalgia, headache, photophobia and vomiting, which is often biphasic in nature (Vanzee *et al.*, 1975). Deeper neurological disorders are observed in less than 10% of cases, whilst some infections are asymptomatic (Peters, 1995). More serious consequences occur in pregnant women, where infection may lead to abortion, stillbirth or congenital neurological defects of the fetus, including chorioretinitis and hydrocephalus (Jamieson *et al.*, 2006). With the exception of vertical transmission from mother to fetus and the recent case of transmission through organ transplantation (Fischer *et al.*, 2006; Palacios *et al.*, 2008), human-to-human transmission has not been documented for LCMV. However nosocomial human-to-human transmission has been demonstrated for the African *Arenavirus*, Lassa virus (Fischer-Hoch *et al.*, 1995). No human LCMV clinical cases in southeast Asian countries have been reported to date.

The *Hantavirus* genus belongs to the *Bunyaviridae* family. What were later found to be *Hantavirus* infections were first described in Asia in 1951-1953 when United Nation troops were

deployed during the North-South Korean conflict (Gajdusek, 1956). It took 25 years to identify *Apodemus agrarius* as the rodent reservoir of Hantaan virus (HTNV) (Lee *et al.*, 1978). Seoul virus (SEOV) was first isolated in *Rattus norvegicus* and *R. rattus* in Korea, China and Japan (Lee *et al.*, 1982) and subsequent studies of rats in port cities showed that rats infected with Seoul virus were present throughout the world.

Most hantaviruses are potentially pathogenic for humans and several serologically distinct groups associated with different syndromes have been identified. Yet, most investigations have been conducted where human infections by hantaviruses constitute a real and well identified public health problem, i.e. the holarctic and neotropical areas. However, some hantaviruses have also been described from:

- A shrew in India, Thottapalayam virus (TPMV) was initially discovered in *Suncus murinus* by Carey *et al.*, 1971 and anti-TPMV antibodies have recently been found in a Thai patient (Pattamadilok *et al.*, 2006) as well as in shrews in Indonesia (Okumura *et al.*, 2007).

- A bandicoot rat, *Bandicota indica* in Thailand, described by Xiao *et al.*, 1994.

- Different *Rattus* spp. in Cambodia (Reynes *et al.*, 2003).

- Recently, two new *Hantavirus* species were described, both from Africa (Guinea): Sangassou from a murid rodent *Hylomyscus simus* and Tanganya from a shrew *Crocidura theresae* (Klempa *et al.*, 2006, 2007).

- A new Hantaan-like virus named “Jilin-AP06 virus” was isolated from *Apodemus peninsulae* in northeastern China (Jiang *et al.*, 2007) and another new *Hantavirus* species has been identified from a Chinese mole shrew (*Anourosorex squamipes*) in Vietnam (Song *et al.*, 2007) (Table 1).

- Song *et al.* (2007) have isolated a distinct *Hantavirus* in the Eurasian common shrew, *Sorex araneus*, in Switzerland.

- Finally, Arai *et al.* (2007, 2008) have successively found a new *Hantavirus* in the northern short-tailed shrew, *Blarina brevicauda*, and later two new hantaviruses in *Sorex cinereus* and *Sorex monticolus*, respectively, all in the United States of America.

Worldwide, over 20 species of hantaviruses have now been accepted as separate species (ICTVdB, 2006) and a similar number are awaiting classification. All are associated primarily with a single rodent or insectivore host. The phylogeny of the hantaviruses has been shown to mirror the genealogical relatedness of their rodent host, indicating co-evolution (Plyusnin and Morzunov, 2001; Plyusnin *et al.*, 1996; Hugot *et al.*, 2006; Herbreteau *et al.*, 2007) (Figure 1). Several new species have been identified in recent years, although most studies have concentrated on areas known or suspected to be endemic for the human hantaviral disease.

HTNV and SEOV, or closely related strains are responsible for hemorrhagic fever with renal syndrome (HFRS) in humans in southeast Asia. Of approximately 200,000 HFRS cases reported annually worldwide, about 100,000 are Hantaan-related HFRS from China where the disease occurs mainly in rural areas (Song *et al.*, 1984). SEOV is associated with domestic rats and causes disease predominantly in urban areas. The majority of Seoul virus-related HFRS cases have occurred in China and Korea. However, evidence of *Hantavirus* infections has also been found among humans in: Indonesia (Groen *et al.*, 2002); Laos, Vietnam (Rollin *et al.*, 1986) and Myanmar (Lee, 1999); in humans and in several *Rattus* species in Thailand (Elwell *et al.*, 1985; Nitatpattana *et al.*, 2000; Nitatpattana *et al.*, 2002; Tantivanich *et al.*, 1992); in the Philippines (Quelapio *et al.*, 2000; Lee and van der Groen 1989), in *Rattus rattus*, *R. Norvegicus*; in *Rattus* sp. in Cambodia (Reynes *et al.*, 2003); in *Rattus norvegicus* and humans in Malaysia (Lam *et al.*, 2001; Plyusnina *et al.*, 2004); and in Singapore

(Wong *et al.*, 1989) (Table 1).

Hantaviruses are shed for some weeks after infection in the urine, feces and in the saliva of rodents. The reduction and eventual clearance of the viremia correlates with the induction of hantavirus-specific antibodies, which appear about 14 days after infection and remain detectable for life (Botten *et al.*, 2000). Nevertheless, viremia could still be high at the early phase of the immune

response and organs could stay infected despite the appearance of specific antibodies. Transmission can be direct, but mainly occurs by inhalation of infectious aerosols produced from the rodent excreta (Kallio *et al.*, 2006).

In humans, the incubation period usually lasts two to three weeks (Vial *et al.*, 2006; Young *et al.*, 2000) and is followed by the sudden onset of influenza-like symptoms, associated with

Table 1 *Arenavirus* and *Hantavirus* species identified in southeast Asia by country.

Country	Viruses identified	Human infection	Implicated host species	References
Bangladesh	No data	N/A	N/A	N/A
Bhutan	No data	N/A	N/A	N/A
Brunei	No data	N/A	N/A	N/A
Cambodia	Hantavirus sp. (Seoul?)	?	<i>Rattus</i> spp.	Reynes <i>et al.</i> , 2003
China (SE)	LCMV	No	<i>Mus musculus</i>	Morita <i>et al.</i> , 1996
	Hantaan virus	Yes	<i>Apodemus agrarius</i>	Tang <i>et al.</i> , 1991
	Seoul virus	Yes	<i>Rattus norvegicus</i>	Tang <i>et al.</i> , 1991
East Timor	No data	N/A	N/A	N/A
India	Thottapalayam virus	?	<i>Suncus murinus</i>	Carey <i>et al.</i> , 1971
	Hantavirus sp. (Seoul?)	Yes	Unknown	Chandy <i>et al.</i> , 2005
Indonesia	Thottapalayam virus	?	<i>Suncus murinus</i>	Okumura <i>et al.</i> , 2007
	Hantavirus sp. (Seoul)	Yes	<i>Rattus norvegicus</i>	Groen <i>et al.</i> , 2002
			<i>Rattus rattus</i>	Ibrahim <i>et al.</i> , 1996
			<i>Rattus exulans</i>	Plyusnina <i>et al.</i> , 2004
Laos	Hantavirus sp.	Yes	Rodents	Rollin <i>et al.</i> , 1986
Malaysia	Hantavirus sp. (Seoul?)	Yes	<i>Rattus</i> spp.	Lam <i>et al.</i> , 2001
Myanmar	Hantavirus sp.	Yes	Unknown	Lee, 1999
Nepal	Hantavirus sp.	Yes	Unknown	Rai <i>et al.</i> , 1997
Philippines	Hantavirus sp. (Seoul?)	Yes	<i>Rattus</i> spp.	Quelapio <i>et al.</i> , 2000
Singapore	Hantavirus sp.	Yes	<i>Rattus norvegicus</i>	Wong <i>et al.</i> , 1989
Sri Lanka	Hantavirus sp. (Seoul?)	Yes	<i>Rattus</i> spp.	Vitarana <i>et al.</i> , 1988
Taiwan	Seoul virus	Yes	<i>Rattus</i> spp.	Chin <i>et al.</i> , 2000
Thailand	LCMV	No	<i>Bandicota saveli</i>	Nitatpattana <i>et al.</i> , 2000
			<i>Rattus norvegicus</i>	
	Thailand virus	Yes	<i>Bandicota indica</i>	Xiao <i>et al.</i> , 1994
			<i>Rattus norvegicus</i>	Hugot <i>et al.</i> , 2006
	Thottapalayam virus	Yes	<i>Suncus</i> spp.?	Pattamadilok <i>et al.</i> , 2006
Vietnam	Cao Bang virus	?	<i>Anourosorex squamipes</i>	Song <i>et al.</i> , 2007
	Hantavirus sp. (Seoul?)	Yes	<i>Rattus</i> spp.	Rollin <i>et al.</i> , 1986

nausea, back and abdominal pain, as well as other gastrointestinal symptoms. Traditionally, the febrile phase lasts from three to seven days and is followed by a hypotensive phase lasting several hours to days characterized by marked thrombocytopenia and often conjunctival and petechial hemorrhages. Oliguria may occur and renal failure contributes to half of the deaths (Tai *et al.*, 2005). A common factor for many of the clinical symptoms is increased capillary permeability, which explains the hemorrhagic tendency and the abdominal pain due to retroperitoneal edema (Cosgriff, 1991). The Seoul virus infection tends to be milder than Hantaan virus infections, with a case fatality rate of 1-2%

with SEOV compared to 5-15% with HTNV (Song *et al.*, 1984).

Ribavirin has successfully been used to treat infected patients. This antiviral drug significantly reduces the case fatality rate and the risk of entering the oliguric phase and of experiencing hemorrhage (Huggins *et al.*, 1991). Best results are seen if treatment is applied in the early stages of the disease. Several vaccines have been produced or are in development: killed hantavirus vaccines (e.g. Hantavax® from South Korea, monovalent HTNV and SEOV from China) (Cho and Howard 1999; Song *et al.*, 1992); and recombinant live vaccines, virus-like particle-based vaccines and nucleic acid vaccines

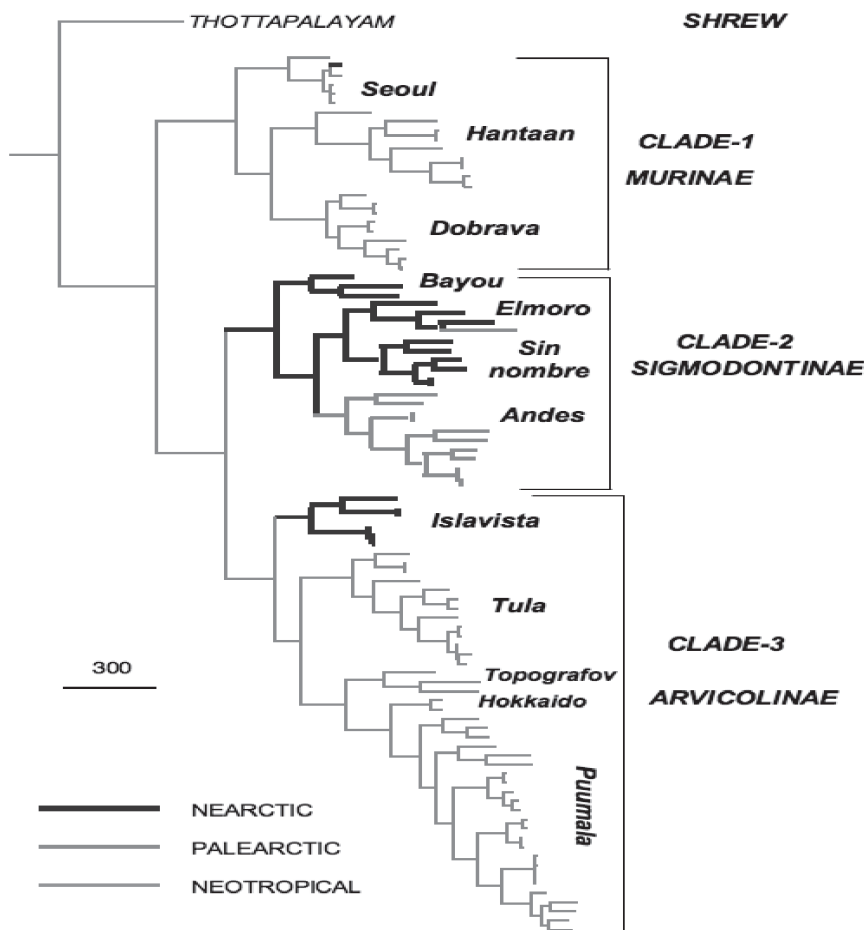


Figure 1 Classification of genus *Hantavirus*, related hosts and geographic distribution (after Herbreteau *et al.*, 2007). Sigmodontinae includes Sigmodontini and Neotomini.

(Geldmacher *et al.*, 2005; Lindkvist *et al.*, 2007). The vaccines developed in eastern countries do not usually meet the international standard requirements and have not been accepted in western countries. Since viremia in HFRS patients is short-term, laboratory diagnosis has to be based on serology (e.g. Immuno-Fluorescence assay, Hemagglutination Inhibition assay, Complement Fixation, IgG avidity test, IgM and IgG ELISA tests) (Koraka *et al.*, 2000). There is a high humoral cross-reactivity in humans (and rodents) between the different Hantavirus serotypes and also in Asia between the HTNV, SEOV (Chu *et al.*, 1994). Hantaviral antibodies are not specific in the acute phase of disease.

Although reports of human infections from these viruses may be rare or even absent at present in some southeast Asian countries, these findings may change in the future. Increasing globalization and the availability of travel may affect the disease dynamics of arenaviral and hantaviral infections in southeast Asia. Studies in Japan demonstrated that LCMV-infected house mice could be found in several marine ports (Tsuda *et al.*, 2007) and several cases of Lassa fever and Hantavirus Pulmonary Syndrome have been exported to non-endemic countries (Hugonnet *et al.*, 2002; Espinoza *et al.*, 1998). Although the risk of acquiring an infection in southeast Asia is generally considered by the traveling community, often little thought is given to the importation of infectious diseases to these countries. Zoonotic viruses have been imported into non-native countries accidentally before (Maskalyk, 2003) and there is a real risk that this could happen again.

New diagnostic techniques, alongside improving healthcare systems in many of these countries, may promote the discovery of new and previously unrecognized infections by these viruses, as well as the potential discovery of new infectious agents. Other factors such as changing climate, habitat destruction and modification and fast-growing human populations are likely to

increase the number of people at risk from infection by these viruses.

This has already happened for the hantaviruses in North America, as demonstrated by the Four-corners outbreak in the early 1990's. Increased rainfall in the previous years caused by El Niño (the warm phase of the El Niño/Southern Oscillation (ENSO)), resulted in a dramatic increase in the number of *Peromyscus maniculatus*, which in turn led to the first recognized outbreak of Sin Nombre virus infection in humans (Engelthaler *et al.*, 1999). A second outbreak has since occurred in the same region, also due to the effect of El Niño (Hjelle and Glass, 2000). As ENSO is linked to fluctuations in rodent populations and therefore to the incidence of rodent-borne disease (Kovat, 2000), it is likely that this natural environmental phenomenon will also affect the incidence of *Arenavirus*-associated disease.

In southeast Asia, changes in land use and agricultural practices have also taken place (Myers *et al.*, 2000), and these are likely to have altered rodent species distribution and diversity. This may eventually have a knock-on effect on virus prevalence in some of these communities, which in some cases could increase exposure risk for the local human population. El Niño (and its counterpart 'La Niña', the cold phase of ENSO) also affects many of the countries of southeast Asia (Anyamba *et al.*, 2006), so similar conditions that led to the Four Corners hantavirus outbreak in the United States of America could also occur there. The only way to truly monitor the situation in southeast Asia is to initiate surveys, both on human (suspect patients) and on rodent and insectivore communities in the region.

CONCLUSIONS

LCMV and most hantaviruses have rodents as their natural hosts, although some hantaviruses have insectivores as primary hosts.

The recent worldwide discoveries of several new hantaviruses in different species of shrews show that a special effort has to be made to investigate insectivorous hosts systematically. The evolutionary relationships between rodent versus shrew hantaviruses are currently poorly understood. Whether hantaviruses carried by insectivores are a danger or not to human health, also has to be investigated.

Hantaviruses and/or antibodies to hantaviruses have been detected in humans and/or rodents in a wide-range of southeast Asian countries, while LCMV has only been detected in Thailand and China. Both hantaviruses and LCMV are capable of causing human disease and are probably under-recognized pathogenic agents in the southeast Asian region. Improving health care and diagnostic techniques should help in the detection of both of these virus groups.

Increasing globalization, changing climates and altered land use in southeast Asia are likely to increase the proportion of the human population at risk of infection by these zoonotic viruses. More extensive and more detailed studies on both hantaviruses and particularly LCMV are needed to establish the epidemiology of these viruses both in their natural hosts and in the human populations of southeast Asia.

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