Review

Epidemiology and Epizootiology of Hantavirus Infection in Japan

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SUMMARY: Hantaviruses cause two severe human diseases: hemorrhagic fever with renal syndrome (HFRS) and hantavirus pulmonary syndrome (HPS). Various rodent species act as animal reservoirs for hantavirus. In Japan, urban rat- (*Rattus norvegicus*) and laboratory rat-derived human infections were reported during the 1960s and 1970s-1984, respectively. Although no human cases of infection have been reported since 1984, infected urban rats have been found throughout Japan, and infected grey red-backed voles (*Clethrionomys rufocanus*) have been identified in Hokkaido. These carriers can be considered to be potential sources of human infection. This review examines the epidemiology and epizootiology of this important zoonosis in Japan.

Introduction

Hantaviruses are members of the *Hantavirus* genus of the *Bunyaviridae* family (1). Hantaviruses are associated with rodents and other small mammals and are the causative agents of hemorrhagic fever with renal syndrome (HFRS) (2) and hantavirus pulmonary syndrome (HPS) (3) in humans. Transmission of the virus to humans occurs either via the inhalation of infectious aerosols generated from hantavirus-containing animal secretions (4-6) or via contaminated saliva in animal bites (7). Thus, HFRS and HPS are regarded as important rodent-borne viral zoonoses (8).

Between 150,000 and 200,000 HFRS cases are reported annually throughout the world (9). The majority of these cases occur in Asia and Europe, particularly in China, where 50,000 to 100,000 cases have been registered annually since 1985 (10). In Japan, there have been two recent outbreaks of HFRS, one in the 1960s and one in the 1970s-1984. The former outbreak was traced to brown rats (*Rattus norvegicus*) in Osaka City (11,12), and the latter to laboratory rats (13). Although no human HFRS cases have been reported in Japan since 1984, brown rats in several port areas (14-17) and field grey red-backed voles (*Clethrionomys rufocanus*) in Hokkaido (18,19) have been found to be hantavirus-positive. Therefore, the re-emergence of HFRS as a human infectious disease in Japan remains possible.

HPS was first reported in the Southwestern United States (US) in 1993 as an acute respiratory distress syndrome with greater than 40% mortality (20). The causative virus of HPS is transmitted from *Peromyscus maniculatus* and several other rodent species, all of which are members of the subfamily *Sigmodontinae* (21). Since these rodent species inhabit the American continent only, no HPS cases have been reported outside the Americas. However, the introduction of infected rodents into other countries represents a potential public health problem.

In 1998, a new law aimed at controlling infectious diseases was introduced in Japan. Under the new law, HFRS and HPS are graded as group 4 diseases, and afflicted patients must be reported to the government. In spite of these new regulations, information on these diseases is still quite limited.

In this report, we review hantavirus epidemiology and epizootiology in Japan, and emphasize the necessity for caution in dealing with unfamiliar diseases.

Clinical manifestations of HFRS (22,23) and HPS (23,24)

The premonitory symptoms common to both HFRS and HPS, including fever, myalgia, and headache, are seen in more than 90% of infections. However, the later-stage clinical symptoms differ between HFRS and HPS. In HFRS, severe cases usually show four different phases: febrile, hypotensive, oliguric, and diuretic. However, the severity of infection varies, primarily according to the type of infecting virus, but also in

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cases involving viruses of the same type. Therefore, disease confirmation is based not only on clinical signs and laboratory findings, but also on the demonstration of specific IgM antibodies by ELISA or a fourfold or greater rise in anti-hantavirus antibody titer in paired sera, as measured by serological testing. Moreover, renal failure, as evidenced by proteinuria, is observed in 100% of cases (Table. 1). In addition, mild cases of HFRS occasionally show hepatic dysfunction (25). It is important to differentiate HFRS from other acute infectious diseases such as influenza, tsutsugamushi disease, and leptospirosis.

HPS, on the other hand, is characterized by a respiratory syndrome such as tachypnea caused by pulmonary edema and a high mortality rate (30 to 40%) due to pulmonary edema and the rapid onset of shock.

Diagnostic protocols for HFRS and HPS have previously been published (26,27) and released as an information leaflet by the Ministry of Health and Welfare of Japan in 1999 (28).

Viral agents of HFRS and HPS

To date, at least 22 hantaviruses have been identified by based on comparisons of nucleotide-sequence similarity and evolutionary classifications of viral genomes (29). All hantaviruses have specific rodent reservoirs. Phylogenetic analysis of the rodent-associated hantaviruses has revealed three primary lineages: the *Murinae*, *Arvicolinae*, and *Sigmodontinae* subfamilies (30,31). Since the evolutionary trees of the hantavirus and rodent genomes are superimposable (32), hantavirus-rodent coevolution has been hypothesized. Among the known hantaviruses, the Hantaan, (HTN), Seoul (SEO), Dobrava (DOB), and Puumala (PUU) viruses are known to cause HFRS, and the Sin Nombre (SN), New York (NY), Black Creek Canal (BCC), Bayou (BAY), Lagna Negra (LN), and Andes (AND) viruses cause HPS (22, 29) (Table 2).

Distribution of HFRS and HPS

Due to the close relationship between hantavirus type and rodent species, the distribution of HFRS and HPS cases has been confined to areas inhabited by the specific rodent reservoir (Fig. 1). Since HPS-reservoir rodents live in North and South America, HPS has only been reported in these regions. HFRS cases caused by HTN, PUU, and DOB viruses have been reported primarily in Eastern Asia, Northern and Eastern Europe, and Central Europe, respectively. Since brown rats infected with SEO virus are distributed worldwide, infections with this virus might be expected in many countries. However,

Table 1. Clinical manifestations of hemorrhagic fever with renal syndrome (HFRS) and hantavirus pulmonary syndrome (HPS)

	HFRS	HPS
Incubation period (week)	2-3	1-2
Prodrome	fever, myalgia and headache (common to both HFRS and HPS patients)	cough
Symptoms	[severe case; caused by HTN, DOB, SEO] 1) febrile phase 2) hypotension phase (hemorrhage) 3) oliguria phase (proteinuria) 4) diuretic phase (recovery) [mild case; caused by PUU] fever and proteinuria	tachypnea, tachycardia, hypotension, pulmonary edema, bilateral interstitial pulmonary infiltrates, shock
Target organ	kidney	lung
Hematology	elevated white -cell count, thrombocytopenia, hemoconcentration (common to both HFRS and HPS)	
Death rate	1-15% (HTN, SEO, DOB) <1% (PUU)	30-40%

Table 2. Viruses of the causative agent of HFRS and HPS

| Viruses	(Abbreviation)	Principal species	Original isolation in	Distribution of reservoir	Disease
Murinae subfamily-associated viruses					
Hantaan	HTN	*Apodemus agrarius*	Korea	Asia, Europe	HFRS
Dobrava-Belgrade	DOB	*Apodemus flavicollis*	Slovenia	Europe, Middle East	HFRS
Seoul	SEO	*Rattus norvegicus, R. rattus*	Korea	Asia, Europe, the Americas	HFRS
Arvicolinae subfamily-associated viruses					
Puumala	PUU	*Clethrionomys glareolus*	Finland	Europe, Asia	HFRS
Sigmodontinae subfamily-associated viruses					
Sin Nombre	SN	*Peromyscus maniculatus*	New Mexico	North America	HPS
New York	NY	*Peromyscus leucopus*	New York	North America	HPS
Black Creek Canal	BCC	*Sigmodon hispidus*	Florida	The Americas	HPS
Bayou	BAY	*Oryzomys palustris*	Louisiana	Southeastern US	HPS
Lagna Negra	LN	*Calomys laucha*	Paraguay	South America	HPS
Andes	AND	*Oligoryzomys*	Argentina	South America	HPS
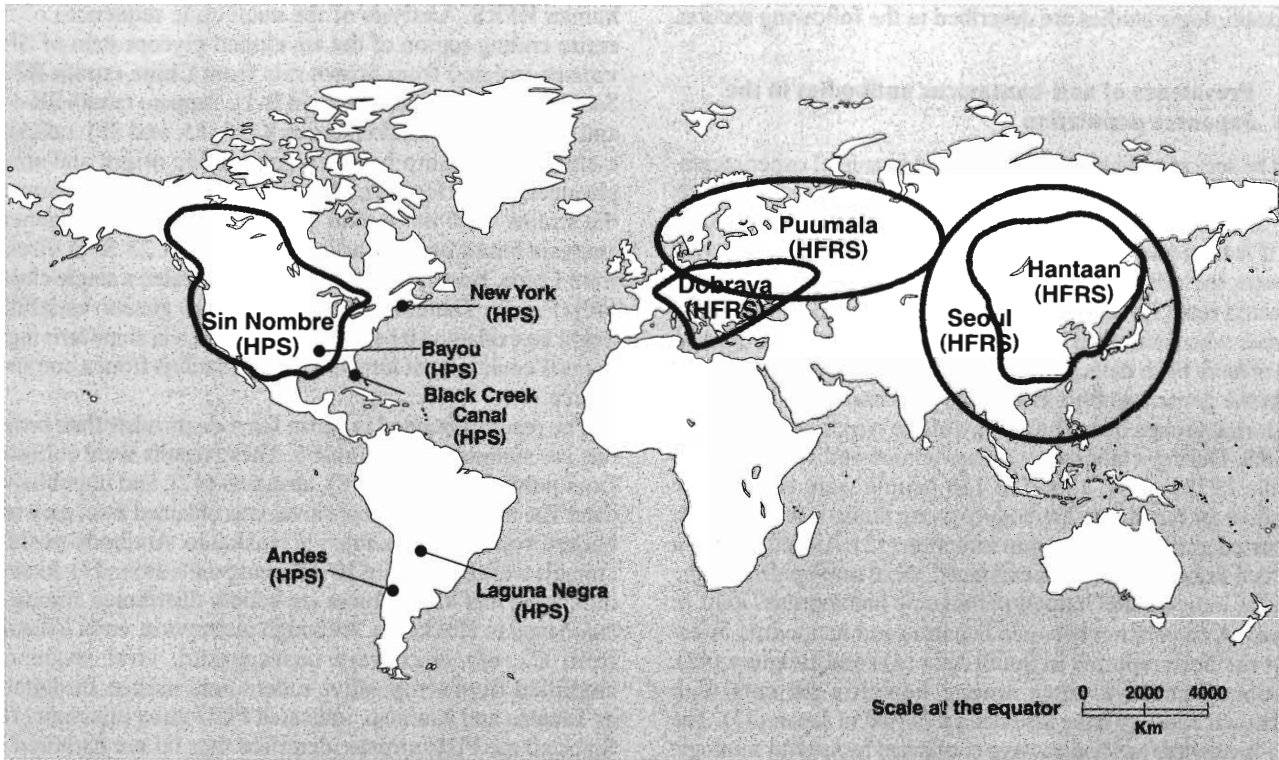
Fig. 1. Distribution of hantaviruses and hantaviral diseases.

HFRS cases due to SEO virus have been confined, thus far, to Asian countries.

Historical background of HFRS in Japan (Table 3)

Russian and Japanese physicians encountered severe febrile disease among troops in Far Eastern Russia and North Eastern China between 1930 and 1940, respectively. The disease was referred to as "epidemic nephrosonephritis" in Russia and "epidemic hemorrhagic fever" in Japan. These physicians identified the agent of disease as a virus and *Apodemus agrarius* as the rodent reservoir. They also identified the gamasid mite (*Laelaps jettmari*) as an arthropod vector of the hantavirus (33). Recent reports by Chinese researchers have demonstrated hantavirus multiplication in gamasid and chigger mites as well as transovarial and transstadial transmission of the virus (10). However, no reports of hantavirus transmission via arthropods have been forthcoming from other

endemic countries.

In Japan, both brown rat- and laboratory rat-associated HFRS cases were reported in the 1960s (11) and 1970s-1984 (13), respectively. SEO-type hantavirus strain SR-11 was first isolated from infected rat-lung tissues in 1982 (34). Subsequently, SEO viruses closely related to strain SR-11 were isolated from both laboratory rats (35) and brown rats in Japan (14, 36). Isolation of the viruses allowed for the establishment of serological diagnostic procedures (37) and facilitated epidemiologic and epizootiologic investigations. Due to extensive surveillance of laboratory rat populations, no laboratory-rat-related HFRS cases have been reported since 1984. However, infected brown rats have been detected throughout Japan (38), and infected grey red-backed voles have been identified in Hokkaido (18,36). SEO and PUU viruses have been isolated from both brown rats and voles, respectively. Therefore, these animals might be considered potential sources of human infection. The results of the epidemiologic and

Table 3. Historical background of hemorrhagic fever with renal syndrome in Japan

Year	Place	Reservoir rodent	No. patient	No. died
1940th	China (Manchuria)	*Apodemus agrarius*	10,000	3,000
1960th	Umeda (Osaka)	*Rattus norvegicus*	119	2
1970 -1984	Laboratory for animal experimentation (21 Institutions throughout Japan)	Laboratory rat (*Rattus norvegicus*)	126	1
1984 -present	Port areas (more than 13 port areas)	*Rattus norvegicus*	No patient has been reported	
1992 -present	Hokkaido (more than 10 areas)	*Clethrionomys rufocanus*	No patient has been reported	

epizootiologic studies are described in the following section.

Prevalence of anti-hantavirus antibodies in the Japanese population

The sera of individuals not involved in animal experimentation were examined for hantavirus antibody (Table 4). Thus far, only five positive sera with low antibody titers (1:16, 32 by IFA test) have been identified (39). In contrast, high-risk groups, including workers at dumping grounds inhabited by infected rats (39) and members of the Japanese Self-Defense Forces who trained on lands where infected grey red-backed voles have been detected (40), showed higher antibody titers than the general public. However, no members of these two high-risk groups have shown any of the typical symptoms of HFRS. During a laboratory rat-associated outbreak of HFRS in the 1970s-1984, a total of 126 people were found to be positive for hantavirus antibody. Among these, at least 18 were reported as cases of apparent infection (13). Although only a limited amount of sera was examined, these sero-epidemiologic results indicate that human-pathogenic hantaviruses exist in Japan. A correlation between hepatitis and hantavirus infection has been reported in South Asia (41) and Belgium (42). Antibody-positive cases among hepatitis patients with unknown etiology have also been reported in Japan (43). The anti-hantavirus antibodies were confirmed by several serologic procedures, including IFA, ELISA, Western blotting, and neutralization tests. However, since all of the positive sera were obtained from patients with chronic rather than acute hepatic disease, no virus or viral genomic samples were isolated from the patients. Therefore, further study is needed to elucidate whether hantavirus causes hepatitis in Japan.

Epizootiologic study of hantavirus infection among rodents in Japan

Hantavirus-infected brown rats have been reported, primarily in the port areas of Otaru, Kamiiso, Tokyo, Yokohama, Nagoya, Kobe, Tokuyama, Moji, Hakata, Nagasaki, Niigata, Osaka, and Shimizu, and at Kansai Airport (38). These results suggest that brown-rat-associated SEO virus can be readily distributed worldwide through transportation systems. In Nagoya City, SEO-virus-infected rats were captured in a residential area adjoining a pier in the port (44), indicating that the brown-rat-borne SEO virus is a possible source of

human HFRS. Analysis of the nucleotide sequences of the entire coding region of the enveloped glycoprotein of SEO viruses isolated from brown rats from China (strain R22), Seoul (strain R22), Osaka (strain B-1), Sapporo (strain SR-11), and Kamiiso-Hokkaido (strains K-83, 85, and 88) indicated a close relationship between geographic origin and strain phylogeny (45). However, nucleotide-sequence identities among the strains were more than 93%. In addition, phylogenetic analysis based on the partial sequences of 23 SEO viruses from China, Korea, Japan, and the US revealed a single cluster (46) (Fig. 2). Therefore, the relatively low genetic variability might be explained by a recent expansion, via ships arriving at various countries, of infected rat populations from a common source.

The results obtained in Japan for rodents other than brown rats are summarized in Table 5. These results were collected from published papers (18), abstracts (47), and unpublished data. The majority of seropositives was obtained from grey red-backed voles (*C. rufocanus*) in Hokkaido. Antibody-positive animals were captured at 10 different points around Hokkaido, indicating that hantaviruses are widely distributed among *C. rufocanus* in Hokkaido. Although attempts at virus isolation from *C. rufocanus* were unsuccessful, viral sequences amplified from seropositive rodent lung tissues, designated as Tobetsu and Kamiiso, indicated PUU virus infection (18). Since all the PUU viruses identified thus far are harbored by either *Clethrionomys* spp. or *Eothenomys regulus* (formerly classified as *Clethrionomys regulus*) (48), a close relationship between hantavirus type and rodent reservoir was confirmed. Phylogenetic analysis indicated that the Japanese PUU viruses form a lineage distinct from that of the European PUU viruses. Therefore, it is possible that the PUU virus was introduced by infected *Clethrionomys* spp. brought from the Eurasian continent through Sakhalin during glacial era when Hokkaido was connected with the continent. Two seropositives were detected; one from an *Apodemus speciosus* in Okushiri Island, Hokkaido, and the other from an *A. speciosus* in Hirosaki City in Aomori Prefecture (unpublished observations). However, since no information relating to the virus or viral genomic sequences is available, further study is necessary to confirm the source of infection.

Phylogenetic analysis based on 300 base pairs of a nucleotide sequence from the M genome segments of 38 HTN viruses (34 from China, 4 from Korea) and 24 SEO viruses (19 from China, 2 from Japan, 2 from US, 1 from Korea) isolated from

Table 4. Seroepidemiologic study of hantavirus infection among human

	Prefecture	Year of collection	Number of sera	Number of positive	(%)
General public	Tokyo	1983	530	5	(0.94)
	Akita, Iwate, Miyagi, Niigata, Gunma, Nagano, Saitama, Fukuoka	1991	550	0	(0.0)
	Hokkaido	1993	1,000	0	(0.0)
		Total	2,080	5	(0.24)
High risk group (Positive group)	Workers at dumping ground in Tokyo Bay	1983	732	33	(4.5)
	Members of Japanese Self-Diffence Forces (Hokkaido)	1999	207	2	(1.0)
	Hepatitis patient with unknown etiology				
	(Tokyo)	1990th	105	3	(2.9)
	(Hokkaido)	1990th	60	1	(1.7)
		Total	1,104	39	(3.5)

Table 5. Seroepizootiologic study of hantavirus infection among rodents in Japan

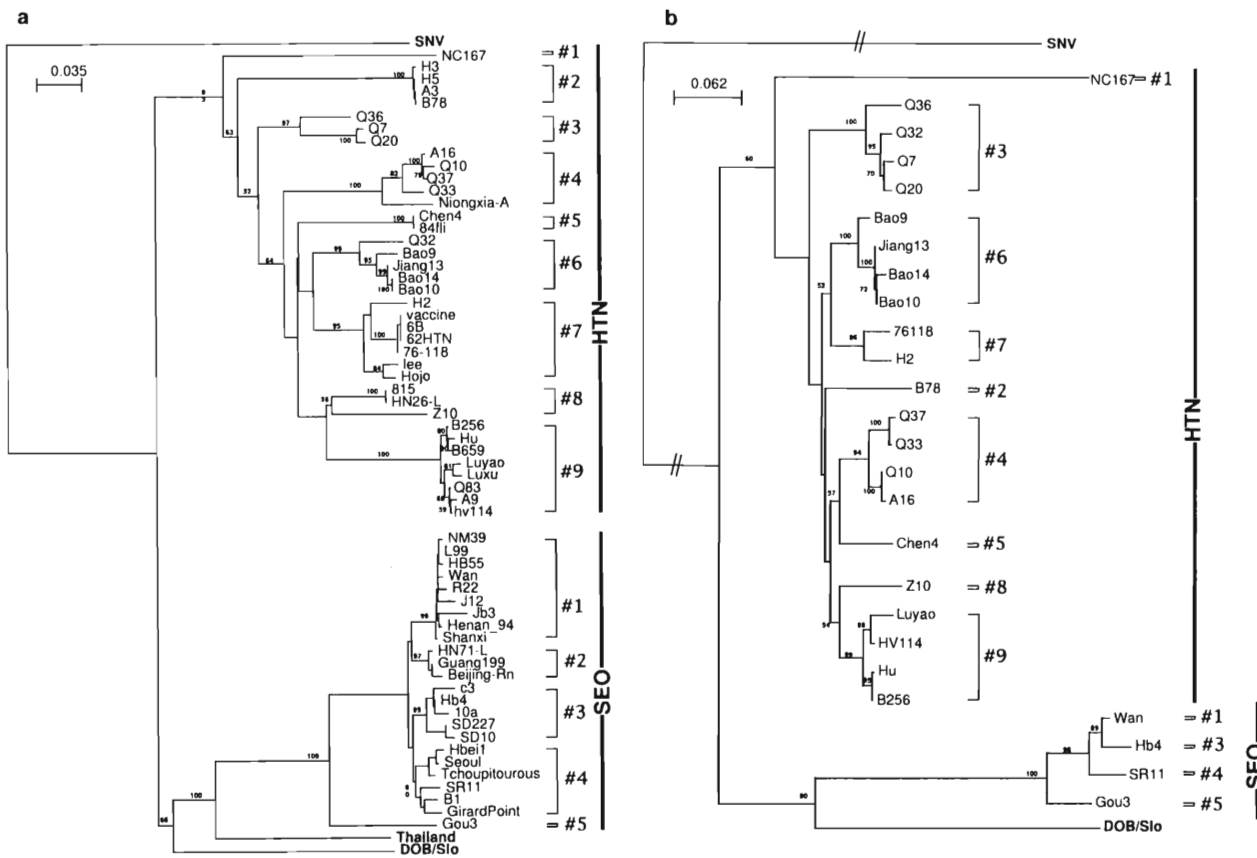| Prefecture	Rodent species	Number of sera examined	(Number of area surveyed)	Number of positive sera	(Number of area)
Hokkaido 1985-2000	*Clethrionomys rufocanus*	385	(13)	36	(10)
	Clethrionomys rutilus	5	(2)	0	(0)
	Apodemus speciosus	274	(13)	4	(2)
	Apodemus argenteus	223	(12)	0	(0)
	Sorex sp.	48	(6)	0	(0)
	Total	935		40	
Rest of the parts of Japan 1988-2000	*Eothenomys smithii*	35	(4)	0	(0)
	Eothenomys andersoni	4	(1)	0	(0)
	Apodemus speciosus	163	(8)	1	(1)
	Apodemus argenteus	102	(7)	0	(0)
	Urotrichus talpoides	7	(2)	0	(0)
	Crocidura dsinezumi	3	(2)	0	(0)
	Microtus monteberi	43	(1)	0	(0)
	Suncus murinus	4	(1)	0	(0)
	Total	361		1	

Fig. 2. Phylogenetic trees for hantaviruses based on partial sequences of (a) the M (nucleotides 2001-2301) and (b) S (nucleotides 1211-terminus) segments, excluding the primer sequences. The numbers at the nodes are bootstrap confidence levels for 100 replicates. The numbers on the right side of the figure indicate the subgroup numbers of HTN and SEO viruses. The reference viruses (Sin Nombre, Thailand, and Dobrava/Belgrade) are indicated in boldface type.   (ref. 46)

either humans or rodents indicates the existence of 9 HTN and 5 SEO genetic subtypes (46) (Fig. 2). Interestingly, one HTN virus isolated from *Niviventer confucianus* (strain NC167) captured in the Anhui Province of China, and one SEO virus isolated from *Rattus rattus* (strain Gou3) captured in the Zhejiang Province of China showed the highest nucleotide divergency among all the HTN or SEO viruses examined. Moreover, examples of *Microtus fortis* captured in Khabarovsk (49)

and Vladivostok (19) bore hantaviruses distinguishable from the PUU virus (Fig. 3). In Korea, Muju virus was identified from *Eothenomys regulus* (47). Phylogenetic analysis of full-length S genome segments suggested that Muju virus was evolutionarily distinct from other *Clethrionomys*- and *Microtus*-borne hantaviruses (48). These results indicate that a variety of rodents carrying different hantaviruses exist in Far-East Asia (Fig. 4).
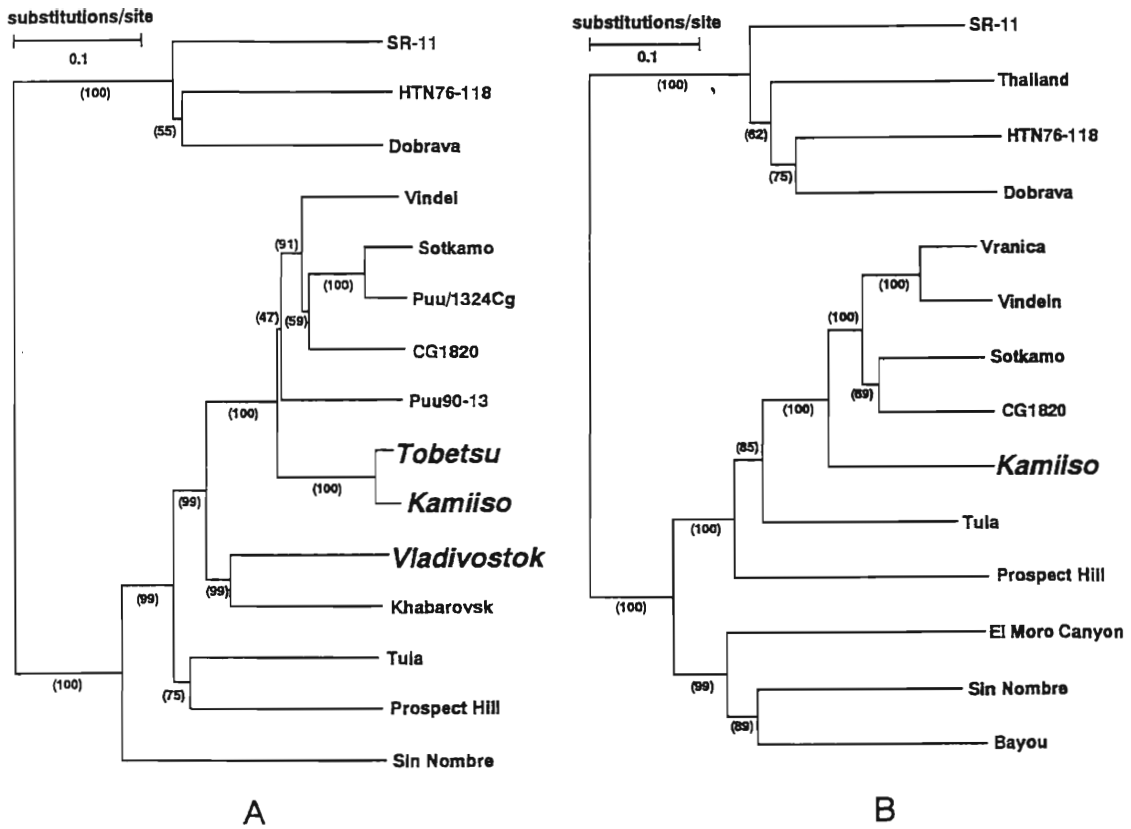
A

B

Fig. 3. Phylogenetic analyses of hantaviruses. Hantavirus sequences were analyzed by neighbor-joining methods using Phylip. Bootstrap confidence limits were calculated from 100 replicates and are shown in parentheses. (A) Phylogenetic dendrogram of the S genome sequences from nucleotides 1 to 1251 in the PUU sequence. (B) Phylogenetic dendrogram of the M genome sequences from nucleotides 2673 to 3652 in the PUU sequence. (ref. 19)
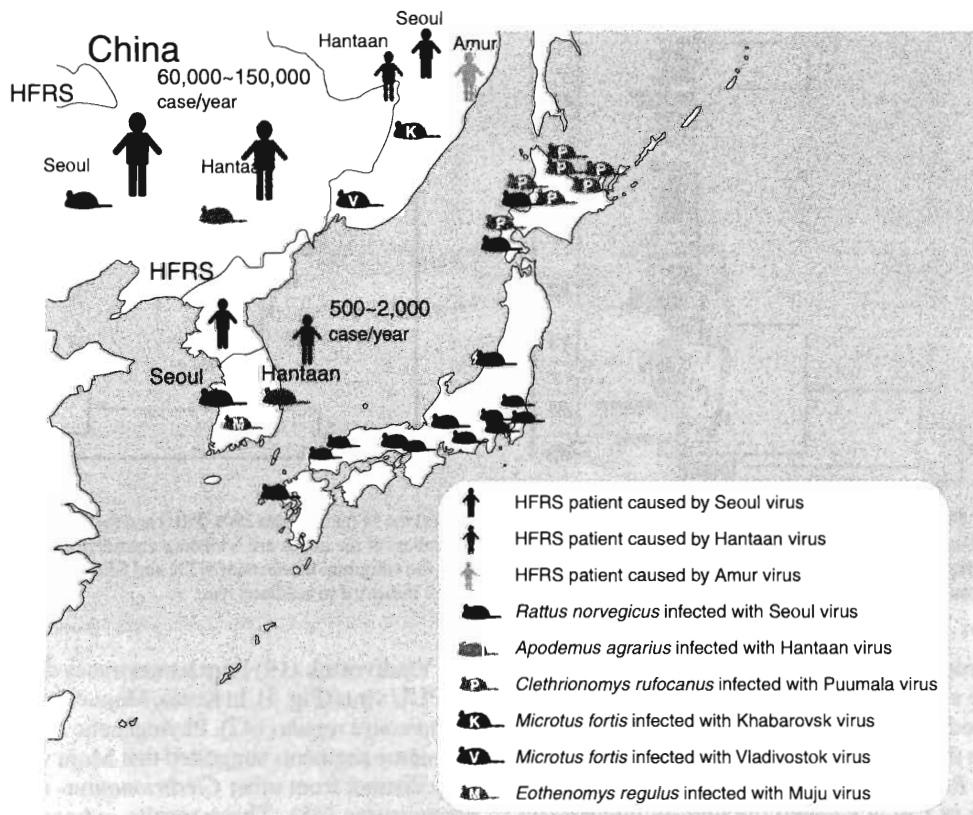

Fig. 4. Distribution of HFRS and hantaviruses in Japan and Far-East Asia.

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Conclusion

Although no recent cases of HFRS have been reported in Japan, infected brown rats are distributed throughout Japan. In addition, grey red-backed voles in Hokkaido are heavily infected with PUU virus. There may therefore be many cases of undiagnosed HFRS in Japan.

HFRS is still prevalent in Far-East Asia, as are the several rodent varieties carrying different hantaviruses (Fig. 4). Therefore, steps must be taken to prevent the introduction of infected rodents via increased international transport. In addition, the epizootiologic investigations among wild rodents, particularly in Honshu, Shikoku and Kyushu, have been quite limited. A program of serological surveillance should therefore be carried out among wild rodents throughout the country.

In addition to HFRS and HPS, various zoonotic diseases have been registered as category 4 diseases, i.e., disease cases that must be reported to the government by a physician in accordance with the new law on infectious disease control. Nevertheless, since many category 4 diseases are nonexistent or occur rarely in Japan, many physicians are unfamiliar with them. As such zoonotic disease information, including geographical distribution of enzootic foci and reservoir animals, may assist physicians and personnel in related fields in diagnosis and control of these unfamiliar infections.

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