

## Seroepizootiology of Hantavirus Infection in Indigenous Rodents in Korea, During 1995–2000

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**Abstract** To better understand the reservoir host range and distribution of hantaviruses in small mammal populations in Korea, a serological survey was conducted on 1,375 wild rodents and 62 insectivores captured in seven provinces during the six-year period, 1995 to 2000. As determined by the indirect immunofluorescent antibody (IFA) test, 90 (13.1%) of 685 *Apodemus agrarius*, 47 (13.6%) of 345 *Apodemus peninsulae*, and 4 (6.5%) of 62 *Crocidura laciura* were seropositive against the Hantaan virus, while 38 (13.5%) of 282 *Eothenomys regulus* were seropositive against the Puumala virus. Serological evidence for hantavirus infection was not found in 50 *Microtus fortis*, six *Micromys minutus*, six *Mus musculus*, and one *Cricetulus triton*. Our serological data indicate that hemorrhagic fever with renal syndrome (HFRS)-related hantaviruses are widely distributed in indigenous rodents in Korea. Particularly noteworthy was the high seropositivity rates among *Apodemus peninsulae* and *Eothenomys regulus* captured in certain mountainous regions, suggesting that HFRS may be under-reported among nearby residents or among individuals who might visit such areas for recreational or occupational purposes.

**Key words:** Hemorrhagic fever with renal syndrome, hantavirus, rodents

Hantaviruses [8, 12], the etiologic agents of hemorrhagic fever with renal syndrome (HFRS) [10, 11], and hantavirus pulmonary syndrome (HPS) [2, 17, 24], are serologically related viruses of the family *Bunyaviridae*, which are distributed worldwide [13, 16, 22]. They are primarily harbored by rodents, although other small mammals including insectivores

may serve as reservoir hosts [3,6,18,23,26]. To date, more than 20 distinct hantaviruses have been identified that represent unique serotypes or genotypes [27]: *Murinae* rodent-associated viruses - Hantaan (HTN), Seoul (SEO), Dobrava-Belgrade (DOB), Saaremaa (SAA), Thailand (THAI); *Arvicolinae* rodent-associated viruses - Puumala (PUU), Prospect Hill (PH), Tula (TUL), Khabarovsk (KBR), Topografov (TOP), Isla Vista (ISLA), Blood Land Lake (BLL); *Sigmodontinae* rodent-associated viruses - Sin Nombre (SN), New York (NY), Black Creek Canal (BCC), El Moro Canyon (ELMC), Bayou (BAY), Rio Segundo (RIOS), Andes (AND), Cano Delgadito (CAD), Rio Mamore (RIOM), Laguna Negra (LAN), Muleshoe (MUL); insectivore-associated virus - Thottapalayam (TPM).

HFRS is primarily a Eurasian disease, whereas HPS appears to be confined to the Americans. These geographic distinctions correlate with the phylogenies of the rodent hosts and the hantaviruses that have coevolved with them. Accordingly, a close correlation has been found between the host species and the hantavirus genotype. Chronically infected rodents exhibit no evidence of disease [19]. In Far East Asia, the primary rodent reservoir hosts, the striped field mouse (*Apodemus agrarius*) and the common rat (*Rattus norvegicus*), carry HTN and SEO viruses, respectively. In Scandinavia, Europe, and European Russia, the bank vole (*Clethrionomys glareolus*) and the yellow-necked field mouse (*Apodemus flavicollis*) harbor PUU and DOB viruses, respectively. KBR virus has been isolated from the reed vole (*Microtus fortis*) in Far East Russia, but it has not yet been implicated in human disease [4]. Vladivostok virus has been identified in *M. fortis* in this region [5] and a DOB-related virus (now called Saaremaa) has been detected in *A. agrarius* in Europe [20]. Another hantavirus, TOP virus, has recently been identified in the Siberian lemming (*Lemmus sibiricus*) from Arctic

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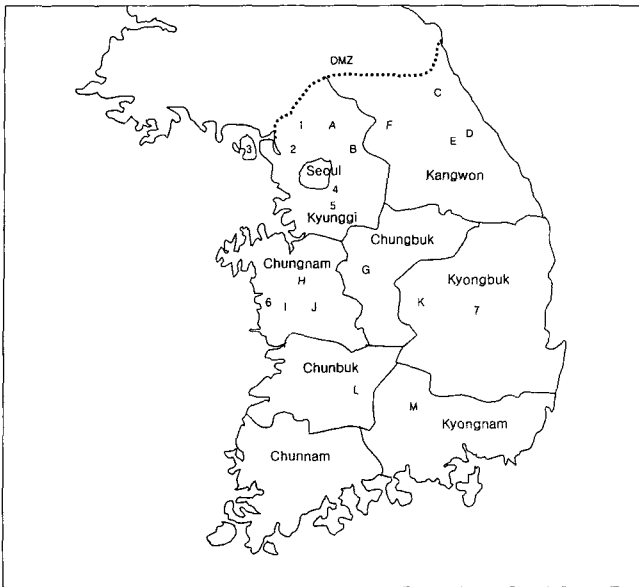
Siberia, but no human pathogenicity has been recognized [28].

HTN and SEO viruses, two *Murinae* rodent-associated hantaviruses, are known to cause HFRS in Korea. However, serological evidence of PUU virus-related (*Arvicolinae* rodent-associated) infection has recently been found in another species of indigenous rodent (*Eothenomys regulus*) in Korea [1]. To better clarify the reservoir host range and distribution of hantaviruses in small mammalian populations in Korea, we conducted serological surveys during a six-year period, 1995 to 2000, in various ecological habitats throughout Korea. Our data indicate that the striped field mouse (*A. agrarius*), the Korean field mouse (*A. peninsulae*), and the Korean red-backed vole (*E. regulus*) are the principal reservoirs of hantaviruses in Korea.

## MATERIALS AND METHODS

### Field Collection of Rodents

Indigenous wild rodents and insectivores were captured using live traps at multiple sites in seven provinces in South Korea during the six-year period, 1995 to 2000 (Fig. 1). Trappings were conducted in 29 widely separated areas, including eight rural farmlands, and 21 mountainous regions with well-developed, undergrowth and herbaceous vegetation. Trapping sites were selected with the consideration of endemic areas and geological locations. Careful consideration



**Fig. 1.** Geographic location of trapping sites in South Korea. Mountainous areas are designated by upper-case letters (A. Pochon; B. Kapyong; C. Inje; D. Pyongchang; E. Hongcheon; F. Whachon; G. Umsong; H. Asan; I. Yesan; J. Kongju; K. Munkyong; L. Muju; M. Sanchong) and farmlands by Arabic numbers (1. Yeonchon; 2. Paju; 3. Kangwha; 4. Shihung; 5. Ansong; 6. Sosan; 7. Bongwha).

was given to the natural habitat of each wild rodent species to maximize the trapping efficiency; for example, traps were set in cultivated fields for *A. peninsulae*; in mountain valleys for *E. regulus*; and reed grass bushes near river banks for *M. fortis*.

Captured rodents were identified and classified, then killed by cardiac puncture in a biosafety level 3 (BSL-3) laboratory. Serum samples from wild animals were diluted 1:16 in phosphate buffered saline (PBS, pH 7.4), and stored at 4°C until testing.

### Viruses

All viruses were propagated in Vero E6 cells (CRL 1586) obtained from the American Type Culture Collection (Rockville, MD, U.S.A.) according to the previously described methods [14]. Suspensions of Vero-E6 cells infected with each of four principal hantaviruses (HTN virus strain 76-118, SEO virus strain HR80-39, PUU virus strain Sotkamo #141247, PH virus strain PH-1) were spotted onto 10-well slides for testing by the indirect immunofluorescent antibody (IFA) technique. Cell preparations were free of reovirus and mycoplasma contamination.

### Serological Tests

Sera, diluted 1:16, were screened for anti-hantaviral antibody by the IFA technique using acetone-fixed hantavirus-infected Vero-E6 cells and fluorescein isothiocyanate-conjugated goat antibodies to mouse IgG (ICN Co., Costa Mesa, CA, U.S.A.) as the secondary antibody [9]. Sera exhibiting characteristic granular fluorescence were titrated, and those having reciprocal IFA titers of 16 or higher were considered positive.

## RESULTS

This seroepizootiologic study was conducted between 1995 to 2000 to estimate the overall prevalence of hantavirus infection among indigenous wild rodents in seven widely separated provinces in Korea. A total of 1,375 wild rodents representing six genera (*Apodemus*, *Mus*, *Eothenomys*, *Microtus*, *Micromys*, *Cricetulus*) and seven species, and 62 insectivores of the family *Soricidae* (representing a single genus and species) were captured (Table 1). *A. agrarius* accounted for 49.8% (685/1375) of all captured rodents and were more frequently captured in farmlands (323/382 or 84.6%) than in mountainous areas (362/993 or 36.5%), where *A. peninsulae* was captured at the same high frequency (345/993 or 34.7%), and *E. regulus* was caught less often (282/993 or 28.3%).

*A. agrarius* and *A. peninsulae* of the subfamily *Murinae*, *E. regulus* of the subfamily *Arvicolinae*, and *C. lacitura* of the family *Soricidae* were seropositive for hantavirus infection by the IFA test. Overall, 90 (13.1%) of 685 *A.*

**Table 1.** Indigenous rodents and insectivore trapped in Korea.

Year	Rodents							Insectivore	Total
	<i>Apodemus agrarius</i>	<i>Apodemus peninsulae</i>	<i>Eothenomy regulus</i>	<i>Microtus fortis</i>	<i>Micromys minutus</i>	<i>Mus musculus</i>	<i>Cricetulus triton</i>	<i>Crocidura laciura</i>	
1995	133	78	100	6	-	1	-	12	330
1996	69	21	8	-	-	-	-	2	100
1997	212	89	43	-	2	-	-	10	356
1998	199	78	33	35	4	4	1	23	377
1999	69	55	76	9	-	1	-	13	223
2000	3	24	22	-	-	-	-	2	51
Total	685	345	282	50	6	6	1	62	1,437

*agrarius*, 47 (13.6%) of 345 *A. peninsulae*, and 4 (6.5%) of 62 *C. laciura* were seropositive against HTN virus, and 38 (13.5%) of 282 *E. regulus* were seropositive against PUU virus (Table 2). By contrast, *Microtus fortis* of the subfamily Arvicolinae, *Micromys minutus* and *Mus musculus* of the subfamily Murinae, and *Cricetulus triton* of the subfamily Cricetinae had no serological evidence of hantavirus infection (Table 2). Among *A. agrarius*, the seropositivity rate was higher in animals captured in farmlands (16.1%) than in mountainous regions (10.5%). Moreover, seropositivity was higher in *A. agrarius* captured in farmlands near the demilitarized zone (18.4%) than in farmlands located further away (7.4%) (Fig. 1 and Table 3).

Although *A. agrarius* is the principal reservoir of HTN virus in Korea, the overall hantavirus seroprevalence (as determined by antibody positivity to HTN virus) for *A. peninsulae* was higher (13.6%) than that for *A. agrarius* (13.1%) (Table 2). All *E. regulus* were also captured in mountainous areas, and showed 13.5% seropositivity to PUU virus, which was also slightly higher than the seropositivity of *A. agrarius* to HTN virus. The seropositivity of *E. regulus* and the antiviral antibody titers to PUU virus were

higher than to the other hantaviruses (HTN, SEO, and PH viruses) (data not shown). The insectivore *C. laciura* of the order Insectivora, trapped only in the highly populated areas of HTN virus-infected *A. agrarius*, were found to be seropositive to HTN and SEO viruses, but not to PUU and PH viruses. However, the antibody titers in *C. laciura* were low and usually less than 256, compared to the titers up to 4,096 in the seropositive rodents (data not shown).

Interestingly, all 71 *A. agrarius* captured in Muju county, Chonbuk province, were found to be antibody-negative against HTN virus, while 18.3% (21/115) of *A. peninsulae* and 16.7% (14/84) of *E. regulus* from the same area were seropositive against HTN virus and PUU virus, respectively. By contrast, in other mountainous areas, such as those in Inje and Hongcheon counties, the seropositivity rates in all three rodent species were somewhat comparable (Table 3).

## DISCUSSION

Hantaviruses, particularly HTN, PUU, SEO, and DOB viruses, cause approximately 150,000 HFRS cases of varying

**Table 2.** Seroprevalence of hantavirus infection in indigenous rodents and insectivore in Korea, 1995–2000.

Species	No. of antibody positive/No. of serum tested (%)			
	HTNV	SEOV	PUUV	PHV
<i>Apodemus agrarius</i>	90/685 (13.1)	47/685 (6.9)	40/685 (5.8)	16/685 (2.3)
<i>Apodemus peninsulae</i>	47/345 (13.6)	31/345 (9.0)	33/345 (9.6)	24/345 (7.0)
<i>Eothenomys regulus</i>	30/282 (10.6)	17/282 (6.0)	38/282 (13.5)	24/282 (8.5)
<i>Microtus fortis</i>	0/50	0/50	0/50	0/50
<i>Micromys minutus</i>	0/6	0/6	0/6	0/6
<i>Mus musculus</i>	0/6	0/6	0/6	0/6
<i>Cricetulus triton</i>	0/1	0/1	0/1	0/1
<i>Crocidura laciura</i> *	4/62 (6.5)	3/62 (4.8)	0/62	0/62
	171/1,437 (11.9)	98/1,437 (6.8)	111/1,437 (7.7)	64/1,437 (4.5)

HTNV: Prototype hantaan virus strain 76-118.

SEOV: Seoul virus strain HR80-39.

PUUV: Puumala virus strain sotkamo #141247.

PHV: Prospect Hill virus strain 405.

\*: Insectivore.

**Table 3.** Serologic evidence for hantavirus infection in indigenous rodents and insectivore in various locations in Korea, 1999 –2000.

Geographic location* (Province, County)		Rodents							Insectivore
		<i>Apodemus agrarius</i>	<i>Apodemus peninsulae</i>	<i>Eothenomys regulus</i> **	<i>Microtus fortis</i>	<i>Micromys minutus</i>	<i>Mus musculus</i>	<i>Cricetulus triton</i>	<i>Crocidura laciura</i>
Kyunggi	Pochon	8/40	-	0/3	-	-	-	-	0/3
	Kapyong	3/39	0/22	0/1	-	0/1	-	0/1	0/2
	Yeonchon	41/211	-	-	0/50	0/1	0/6	-	1/14
	Paju	0/8	-	-	-	-	-	-	-
	Ansong	1/9	-	-	-	0/1	-	-	-
	Shihung	0/16	-	-	-	-	-	-	0/3
	Kangwha	6/36	-	-	-	0/1	-	-	-
Kangwon	Inje	4/72	7/55	3/17	-	-	-	-	0/5
	Hongcheon	13/77	19/119	19/148	-	0/1	-	-	2/13
	Pyongchang	-	0/6	-	-	-	-	-	-
	Whachon	1/21	0/13	1/9	-	0/1	-	-	0/4
Chungbuk	Umsong	2/7	0/1	-	-	-	-	-	-
Chungnam	Kongju	0/3	-	-	-	-	-	-	-
	Yesan	4/22	0/3	0/7	-	-	-	-	1/3
	Asan	2/3	0/3	-	-	-	-	-	0/1
	Sosan	4/42	-	-	-	-	-	-	-
Kyongbuk	Munhyong	0/5	0/8	1/13	-	-	-	-	0/6
	Bongwha	0/1	-	-	-	-	-	-	-
Kyongnam	Sanchong	1/2	-	-	-	-	-	-	-
Chonbuk	Muju	0/71	21/115	14/84	-	-	-	-	0/8
Total (%)		90/685 (13.1)	47/345 (13.6)	38/282 (13.5)	0/50	0/6	0/6	0/1	4/62 (6.5)

\*The geographic location is identified in Fig. 1.

\*\*All of the result is against HTNV, except *E. regulus* against PUUV.

severity annually in Eurasia [7, 13]. In Korea, HTN and SEO viruses, two *Murinae* rodent-associated hantaviruses, cause HFRS, and serological evidence of PUU virus-related infection has been found in *E. regulus* [1]. However, much less was known about the epizootiology of hantavirus infection among wild rodents in South Korea. The aim of the present study was to clarify the reservoir host range and distribution of hantaviruses in small mammal populations in Korea.

Each hantavirus appears to have a single rodent species that serves as a natural reservoir [15, 21, 23, 25, 29]. Rodents comprise about 40% (30 families, 390 genera, 1,703 species) of all mammals. The order *Rodentia* in Korea is represented by 14 genera and 18 species in the families *Muridae*, *Dipodidae*, and *Sciuridae*. Hantavirus infections have not been reported in members of the families *Dipodidae* and *Sciuridae*. Among the seven genera and nine species of rodents reported in South Korea [30], the most dominant species is the striped field mouse, *A. agrarius*, which accounts for three-fourths of the wild rodents, mainly inhabiting cultivated fields, and mountain valleys. *A. peninsulae* and *E. regulus* are the second and third dominant species, respectively, in Korea, and they are often found in mountains with elevations of

about 1,500 feet above sea level with no cultivated fields nearby.

*M. fortis* is known to inhabit reed grass bushes near river banks. *M. minutus*, and *C. triton* are very rare. *R. norvegicus*, *R. rattus* and *M. musculus* are distributed worldwide, and are mainly peridomestic, being found around human habitation.

In Korea, the primary reservoir host of HTN virus, responsible for significant numbers of severe HFRS, is the striped field mouse, *A. agrarius*. In this study, *A. agrarius* was the most dominant species, accounting for nearly 50% of the total captured rodents, even though main capture sites were in the mountain areas. The higher hantavirus seropositivity rate among *A. agrarius* captured in farmlands near the demilitarized zone was consistent with the high frequency of recorded HFRS cases occurring among individuals working in cultivated fields, where contacts between rodents and humans are frequent. Although the hantavirus seropositivity rates for *A. peninsulae* and *E. regulus* were higher than that for *A. agrarius*, most mountainous areas are not known to be endemic for HFRS. This discrepancy may simply be the result of infrequent contacts between rodents and humans in such areas, since most of the trapping sites in the mountains

were not easily accessible by the general population. Therefore, appropriate notice and education should be provided to hikers, local residents, and mushroom pickers to prevent hantavirus infections.

*M. fortis* was only captured in one farmland in Yeonchon county, but all were antibody-negative, despite the fact that the area is known to be highly endemic for HFRS.

Strikingly high hantavirus seropositivity rates were found in *A. peninsulae* and *E. regulus* captured in mountainous areas in Muju county, while *A. agrarius* captured at the same time were uniformly seronegative. Such was not the case in other mountainous regions, as in Inje and Hongcheon counties. None of these areas are known to be endemic for HFRS. Seroepidemiologic surveys in nearby farmlands may provide clues for these differences.

*C. laciura* of the order *Insectivora*, which were trapped inadvertently, showed a seropositivity rate of 6.5%. They were evenly distributed in both farmlands and mountainous areas and accounted for 4.5% of the captured animals. *C. laciura* was not considered a natural host of hantaviruses, because seropositive *C. laciura* was found only in areas populated by HTN virus-infected *A. agrarius*. Moreover, the antibody titers in *C. laciura* were very low, and partial sequencing data of amplified products from seropositive *C. laciura* tissues were identified as HTN virus. Hantavirus seropositivity in *C. laciura*, therefore, may represent spillover from HTN virus-infected *A. agrarius*.

In the present study, we report for the first time the results of a nationwide seroepizootiologic survey of hantavirus infection in *A. peninsulae* and *E. regulus*. These findings are particularly important from the standpoint of further clarifying the epidemiology of HFRS in the mountainous areas of Korea.

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