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Special Article

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Hemorrhagic Fever with Renal Syndrome

Ji Yun Noh [1,*], **Jaehun Jung** [2,*], **and Jin-Won Song** [3]

[1]Division of Infectious Diseases, Department of Internal Medicine, Korea University College of Medicine, Seoul, Korea
[2]Department of Preventive Medicine, Gachon University College of Medicine, Incheon, Korea
[3]Department of Microbiology, Korea University College of Medicine, Seoul, Korea

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Corresponding Author:
Jin-Won Song
Korea University, College of Medicine, Department of Microbiology, 73 Goryoedae-ro, Seongbuk-gu, Seoul 02841, Korea.
Tel: +82-2-2286-1336
E-mail: jwsong@korea.ac.kr

*Ji Yun Noh and Jaehun Jung contributed equally to this study.

ORCID iDs
Ji Yun Noh
https://orcid.org/0000-0001-8541-5704
Jaehun Jung
https://orcid.org/0000-0002-4856-3668

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ABSTRACT

In Korea, hemorrhagic fever with renal syndrome (HFRS) was first reported in a United Nations (UN) soldier stationed in the central front, also known as the "Iron Triangle". In 1976, professor Ho Wang Lee discovered an antigen in the lung and kidney tissues of *Apodemus agrarius.* In 1980, this novel virus was named Hantaan virus after the Hantaan river. The Old World Hantaviruses, which are usually found in East Asia and Europe, are generally transmitted to humans via the respiratory pathway during dry seasons, usually in late spring and fall. Currently, 300 – 600 cases per year are reported in Korea with a mortality rate of 1 – 2%. The typical clinical course of HFRS is classified into five phases: febrile, hypotensive, oliguric, diuretic, and convalescent. And treatment for HFRS is mostly conservative. A vaccine for the Hantaan virus was developed in 1988 and marketed in 1990. Because HFRS outbreaks mostly occur in regions near the truce line in Korea, vaccination is virtually the only protection against the virus among military personnel working in such regions and local residents. Therefore, proving the effectiveness of the HFRS vaccine and devising efficient vaccination plans have been considered a major task for Korea's health authorities.

Keywords: Family hantaviridae; Hemorrhagic fever with renal syndrome; Hantavirus; Epidemiology

1. DISCOVERY AND EPIDEMIOLOGY

A. History

In Korea, hemorrhagic fever with renal syndrome (HFRS) was first reported in a United Nations (UN) soldier stationed in the central front, also known as the "Iron Triangle". It eventually spread to Cheorwon, Gimhwa, and Pyeongyang by June 1951, during the Korean War. Because it was the first acute infectious disease encountered in Western medicine, UN military medical personnel were unaware of the cause and appropriate treatment. Subsequently, 3,200 cases of HFRS were reported with a mortality of 15 – 20%, making HFRS a heated topic of interest in the field of medicine worldwide [1]. Because this disease appeared native to Korea, United States (US) military officers referred to it as Korean hemorrhagic fever. However, a similar disease was reported in a Chinese medical book written in 960 AD [2]. Moreover, the first report of HFRS in the literature was found in a

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Author Contributions

Conceptualization: JWS, JYN. Data curation: JJ. Formal analysis: JJ. Investigation: JYN. Methodology: JYN. Project administration: JWS. Resources: JWS. Supervision: JWS. Writing - original draft: JWS, JYN, JJ. Writing - review & editing: JWS, JYN, JJ.

hospital record in Vladivostok, Russia, in 1913 [3]. During the Second World War, HFRS affected 10,000 Japanese military soldiers stationed in Manchuria, and several hundred Russian soldiers in the Far Eastern region also developed the disease. As a result, Russia and Japan each formed a research team in late 1930s and mid-1940s to investigate the clinical symptoms and epidemiological patterns of HFRS. Blood and urine samples were obtained from infected patients and were injected either intravenously or intramuscularly in volunteers to induce epidemic hemorrhagic fever, but the pathogen could not be isolated. In 1952, American scholars founded an epidemic hemorrhagic fever center in Seoul during the Korean War but the pathogen remained elusive [4].

In 1976, professor Ho Wang Lee and his research team discovered an antigen in the lung and kidney tissues of *Apodemus agrarius* (**Fig. 1**) captured in Songnae-dong, Dongducheon-si, and Gyeonggi-do, regions marked with high incidence of hemorrhagic fever. Using an indirect immunofluorescence technique, the antigen was found to specifically react to sera taken from patients with Korean hemorrhagic fever during the recovery period. The team named it the Korean-type antigen and went on to isolate it from blood samples of hemorrhagic fever patients in 1978 and successfully proliferate the virus in A549 cells [5]. In 1980, this novel virus was named Hantaan virus after the Hantaan river (**Fig. 2**) [6]. With the development of a serologic diagnostic technique using the Hantaan virus as the antigen, it has been confirmed that the Hantaan virus or similar viruses are responsible for the Korean hemorrhagic fever occurring in Korea, the hemorrhagic nephrosonephritis occurring in Russia, epidemic hemorrhagic fever in China and Japan, and nephropathia epidemica in Scandinavia. In the spring of 1982, the World Health Organization (WHO) launched a meeting with the Working Group on Hemorrhagic Fever with Renal Syndrome in Tokyo, Japan. During this meeting, various diseases showing clinical symptoms similar to those of the Korean hemorrhagic fever were collectively termed hemorrhagic fever with renal syndrome. In 1984, a new genus, Hantavirus, was discovered under which all pathogens of HFRS are included.

Figure 1. *Apodemus agrarius*, the host for Hantaan virus.

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Table 1. Major Hantaviruses in Korea

Virus (Serotype)	Year of discovery	Disease	Host	Major affected regions
Hantaan virus	1976	HFRS	*Apodemus agrarius*	Asia and Europe
Seoul virus	1982	HFRS	*Rattus norvegicus*, l aboratory rat	Worldwide
Soocheong virus	2006	HFRS	*Apodemus peninsulae*	Korea, China, and Russia
Muju virus	2007	HFRS	*Tscherskia triton*	Korea and China
Imjin virus	2009	-[a]	*Crocidura lasiura* (Insectivora)	Korea and China
Jeju virus	2012	-[a]	*Crocidura shantungensis* (Insectivora)	Korea

[a]Pathogenicity is yet to be confirmed.
HFRS, hemorrhagic fever with renal syndrome.

2. TYPES OF VIRUS

Hantaviruses are known as rodent-transmitted viruses, and each species of this family is associated with a unique wild rodent as a carrier. These viruses are generally found in East Asia and Europe, but New World Hantaviruses have also been discovered in North and South America. The latter are distinguished from the Old World Hantavirus that causes HFRS by their substantially higher mortality (40 – 50%). Recently, novel Hantaviruses, such as Imjin virus, were discovered in shrews (Insectivora) and bats (Chiroptera) worldwide, including Korea (**Table 1**).

Hantaan virus was first discovered in 1976 by Professor Ho Wang Lee of the School of Medicine at Korea University. With persistent research, six types of hantaviruses have been discovered in Korea: Hantaan virus (1976), Seoul virus (1982), Soocheong virus (2006), Muju virus (2007), Imjin virus (2009), and Jeju virus (2012). Among them, Hantaan, Seoul, Soocheong, and Muju viruses were known to be pathogenic in humans.

The new family *Hantaviridae* is classified into four subfamilies, *Mammantavirinae, Repantavirinae, Actantavirinae* and *Agantavirinae*. The subfamily *Mammantavirinae* is divided into four genera including *Orthohantavirus, Loanvirus, Mobatvirus* and *Thottimvirus*. The four Hantavirus species

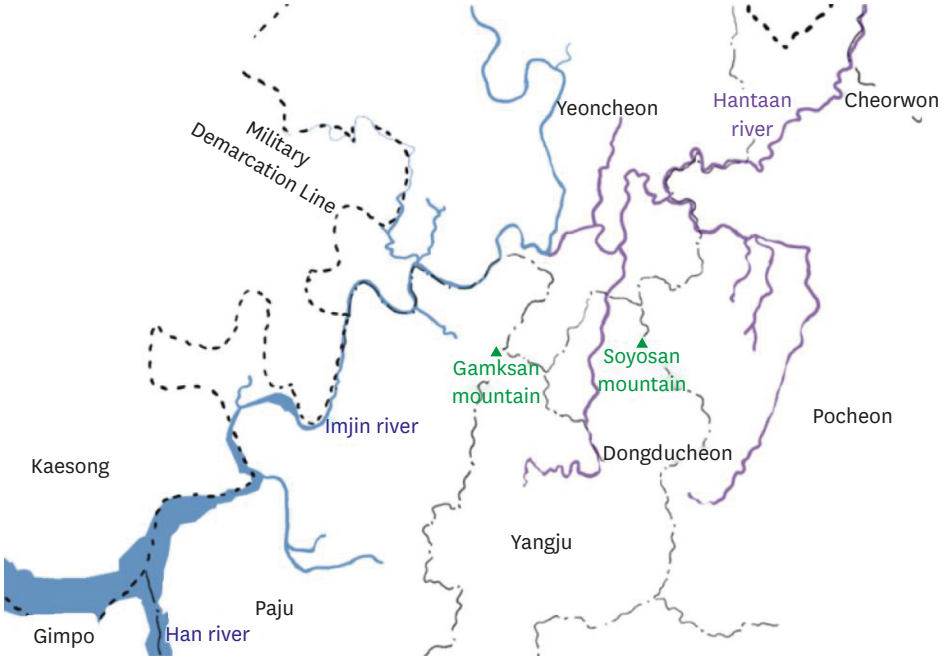

Figure 2. Regions affected by the hemorrhagic fever with renal syndrome epidemic, including Hantaan River.

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have been found in Korea including three Orthohantaviruses (*Hantaan orthohantavirus, Seoul orthohantavirus* and *Jeju orthohantavirus*) and one Thottimvirus (*Imjin thottimvirus*).

3. INCIDENCE AND EPIDEMIOLOGY

The Old World Hantaviruses, which are usually found in East Asia and Europe, are generally transmitted to humans via the respiratory pathway during dry seasons, usually in late spring and fall. However, in recent years, an increased incidence of Hantavirus infection in Korea has been reported in late fall and early winter. During the Korean war, the Hantavirus affected Korean soldiers and civilians in the region along the truce line and subsequently spread to the entire nation with the exception of a few island regions. More than 1,000 infections were reported in one year, with mortality ranging from 5% to 7%. Currently, 12,000 – 20,000 cases of HFRS are reported every year in China, while approximately 300–600 cases per year are reported in Korea (**Fig. 3**) with a mortality rate of 1 – 2% [7].

4. DISEASE CHARACTERISTICS

A. Symptoms

During the Korean War, an HFRS outbreak occurred, culminating in 1,000 US military soldiers developing fever and bleeding tendency in 1951. Numerous foreign countries have reported the characteristics of this disease; the major symptoms include fever, headache, and chills, generally accompanied by loss of appetite, vomiting, bleeding tendency and renal failure. The patients' oral temperature ranged from 38.8°C to 40°C and persisted for 4 – 5 days. The latent period was believed to be about 2 – 3 weeks. At the time, it was difficult to diagnose HFRS because the causative pathogen was not identified and no screening method was available. HFRS was suspected if the patient had been exposed to an epidemic region; developed symptoms such as fever, chills, malaise, headache, and low back pain; experienced hot flushes; had mucosal or conjunctival congestion. A typical patient showed albuminuria on day 4 of onset, with albuminuria being considered definitive evidence for HFRS.

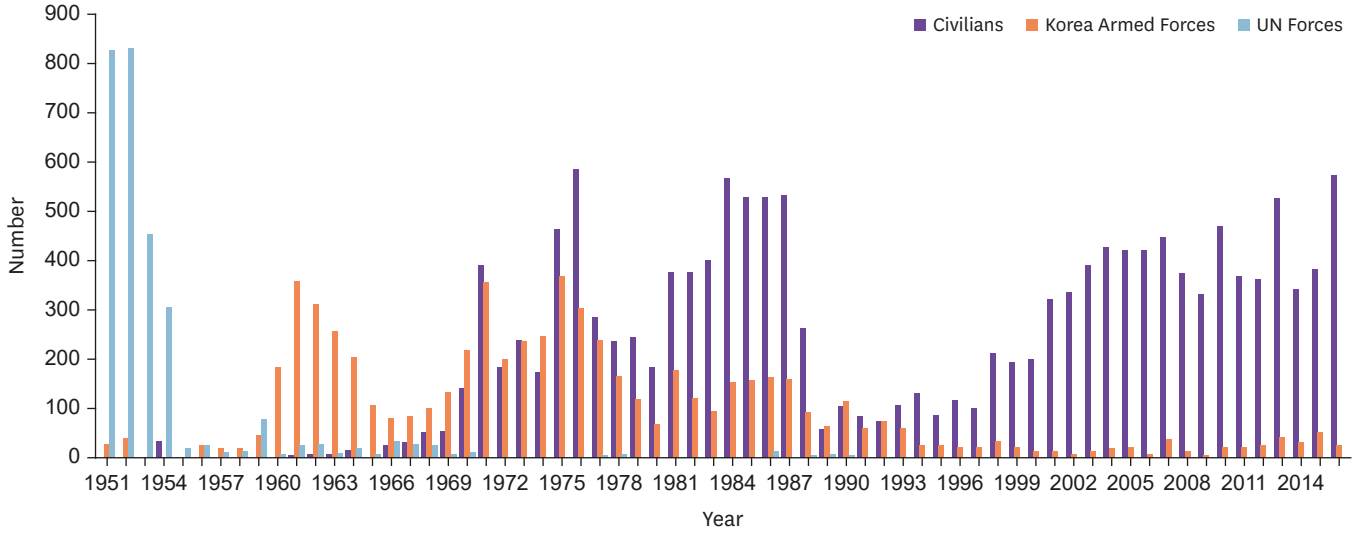

Figure 3. Incidence of hemorrhagic fever with renal syndrome in Korea since 1951.

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B. Clinical course

The typical clinical course of HFRS is classified into five phases: febrile, hypotensive, oliguric, diuretic, and convalescent [8]. The febrile phase persists for about 4 – 6 days and petechial bleeding usually occurs in the palate, axilla and chest on the third day of fever onset. The hypotensive phase persists from a few hours to 3 days and may be absent in patients with mild HFRS. Patients with severe HFRS may experience shock. The oliguric phase persists for 3 – 6 days. This phase is characterized by relief of symptoms that had developed in the febrile phase and elevation or restoration of normal blood pressure, but symptoms of renal failure may begin to manifest. The diuretic phase is marked by an increase in urine output for several days to several weeks, then most patients begin to show improvements and return of appetite (convalescence).

A recent report suggests that in 74% of patients definitively diagnosed with HFRS, the disease was not suspected as the cause of acute renal failure until a few days after admission, because the patient did not exhibit the typical five-phase course as documented in the past. Whereas most HFRS patients experience the febrile and diuretic phases, the incidence of hypotensive and oliguric phases was relatively low. Approximately 48 – 86% of patients with HFRS had abdominal pain, and gastrointestinal symptoms such as nausea, vomiting, and diarrhea were common. As a result, fever, renal failure, and gastrointestinal symptoms were proposed as the clinical characteristics of HFRS [9].

HFRS can be classified into four clinical types according to its clinical course: 1) oliguric type, marked by a typical clinical course and is the most severe form; 2) non-oliguric type, which lacks the oliguric phase and has better prognosis; 3) non-typical type, which lacks the hypotensive and oliguric phases and is characterized by the presence of proteinuria during the initial febrile phase and its resolution after the febrile phase; and 4) asymptomatic type.

The fatality rate differs according to the patient and period. Smadel reported a fatality rate of <5% in about 500 UN soldiers who were treated at the US 8,228th Mobile Army Surgical Hospital, and most deaths occurred at the end of the first week or early second week after onset [1]. In a previous study that analyzed admissions to the Hemorrhagic Fever Hospital from April to December 1952, 46 out of 828 patients died, with a fatality rate of 5.6%; most died from shock, while only a few died following hemorrhagic complications [10]. Among 9,409 patients with HFRS in Korea from 1951 to 1978, the mortality rate was 6.5% [11]. The fatality rate of HFRS in Korean civilians was high, exceeding 25% in the 1960s, after which it began to decline by 1985; it had substantially decreased to 1% [12].

Hypoalbuminemia in the acute phase has been associated with the severity of HFRS. A study on military patients with HFRS from 2000 to 2004 reported that leukocytosis, an elevation of aspartate aminotransferase, and microscopic hematuria in early days of onset are associated with renal failure with oliguria [13]. Compared with patients with HFRS caused by the Hantaan virus, patients with urban HFRS caused by the Seoul virus showed less bleeding and renal damage but more severe hepatic dysfunction [14].

C. Pathological findings

In a pathology report on a case of death by HFRS in late 1951, bleeding in the renal medulla, right atrium, and submucosa of gastrointestinal tract; necrosis in the renal medulla, anterior pituitary lobe, and adrenal gland; and monocyte infiltration in the myocardium, pancreas, spleen, and liver were reported as characteristic findings [15]. There were prominent vascular

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changes, such as capillary congestion, diapedesis of red blood cells, bleeding, and increased capillary permeability; interstitial edema and retroperitoneal edema were believed to occur as a result of increased capillary permeability [16]. Particularly, retroperitoneal edema was observed in 75% of patients who died in the hypotensive phase but was rarely observed in patients who died in the oliguric or diuretic phase.

5. PREVENTIVE MEASURES AND MANAGEMENT

A. Prior to the discovery of the Hantaan virus

Epidemic hemorrhagic fever in Korea was first officially reported in the medical community in 1951. However, there have been opinions that it existed as an endemic before 1951 based on verbal statements that there had been Korean people with similar symptoms in the past and on various epidemiological observations. The reason for the low awareness in the medical community despite being an endemic was speculated to be due to the lack of knowledge, disinterest in the disease, and the absence of a large epidemic [17]. However, there are several opinions regarding the origin of the disease. Lee et al. suggested the possibility of an accidental introduction of HFRS through the Chinese army during the Korean War, following an outbreak in the Amur valley and Vladivostok in the early 20th century and its introduction in Manchuria during the Manchurian incident [12].

Until it was confirmed as a separate disease called epidemic hemorrhagic fever by the US military in 1953, HFRS was commonly mistaken as leptospirosis and no preventive measures had been established. As a result of continuous HFRS epidemics and increases in the mortality rate, diverse academic studies were collated and findings were shared. In 1944, Smorodinsef of the Soviet Union speculated that the pathogen for HFRS is a virus, and Kitano et al. in Japan argued that *A. agrarius* is the major reservoir. The US military founded a hemorrhagic fever center in Seoul in 1952 for research but failed to isolate the pathogen.

In the Korea Armed Forces, a hemorrhagic fever research unit was launched in 1960 and operated until the 1970s, but the unit also failed to identify the pathogen. However, given that HFRS is a viral disease and that infection is mediated by *A. agrarius* became well known, preventive measures such as alerting the farming population and soldiers to avoid contact with rats and exterminating rats, were actively enforced. Furthermore, to treat acute renal failure caused by HFRS, hemodialysis, a very advanced treatment at the time, was introduced in Korea by the US military in 1952, and a hemodialysis unit was first launched in 1965 in the Capital Armed Forces General Hospital.

B. After the development of a vaccine for the Hantaan virus

A vaccine for the Hantaan virus (Hantavax™, Green Cross Corporation, Yongin, Korea) was developed in 1988 and marketed in 1990. It is prepared by inoculating the Hantaan virus isolated from patient's blood to Vero E6 cells, culturing it in the brain of a mouse and inactivating it with formalin. Hantavax™ vaccination was administered through local health centers and the Korea Armed Forces from 1992. Currently, it is generally administered to residents in high-risk regions and military personnel. Vaccination was performed widely between 2005 and 2010, with about 100,000 military personnel vaccinated each year (**Fig. 4**). As of 2017, however, the Korea Armed Forces performs vaccination under limited conditions. In the last 3 years, the vaccine has only been administered to units with a confirmed case of HFRS.

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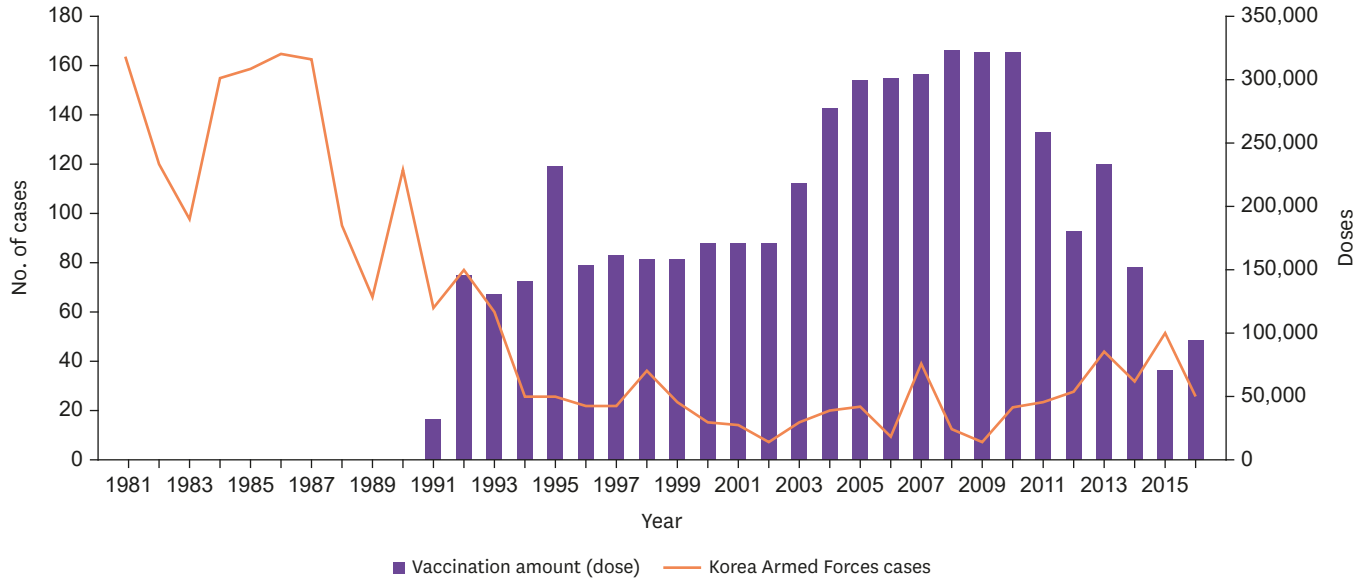

Figure 4. Distribution of Hantavax™ and changes in the incidence of HFRS in the Korea Armed Forces.

C. Preventive measures for and management of HFRS since the 2000s

(1) Promotion of effective vaccination and development of a new vaccine

Because HFRS outbreaks mostly occur in regions near the truce line in Korea, vaccination is virtually the only protection against the virus among military personnel working in such regions and local residents-particularly farmers. Therefore, proving the effects of the HFRS vaccine and devising efficient vaccination plans have been considered a major task for Korea's health authorities and Ministry of Defense.

In a 2016 study that aimed to prove the long-term immunogenicity of the vaccine, the neutralizing antibody conversion rate was founds to be 1.4% one year after the first and second doses of vaccination and 40.6% one year after the third dose. This finding suggests that the existing three-dose vaccination schedule should be modified to increase the number of doses or adjust the interval between doses [18]. Furthermore, the conversion rate of the vaccine in a recent study conducted by the Ministry of Defense was 58.9%. These findings suggest that the HFRS vaccine does have effects but they are small. Therefore, a novel vaccine must be developed or the vaccination schedule for the existing vaccine must be modified to effectively manage patients with HFRS.

(2) Surveillance of HFRS vectors

Since the discovery the Hantaan virus in *A. agrarius* in the 1970s, Korean researchers, including the team at Korea University, have continuously been capturing rodents that may mediate hantaviruses, including the Hantaan virus and Seoul virus. This effort persisted for a prolonged period and the resulting data have become an asset for acquiring information about viral vectors in a number of epidemic regions. Since the 2000s, the vector surveillance regions have been expanded from civilian regions to military stations with the support of the Korea Armed Forces and US Armed Forces. From 2000 to 2017, Korea University has collected and is storing a total of 13,919 rodent specimens, and these samples are used for molecular genetics research.

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Figure 5. Korea military training ground with restricted entry.

(3) Diagnosis and surveillance of HFRS

Korea designated HFRS as group 3 communicable disease and is monitoring its incidence in line with the Infectious Disease Control and Prevention Act. Furthermore, since the 2000s, the government has developed and distributed a quick diagnostic kit for HFRS. Currently, a quick diagnostic kit that can concurrently test for three Korean-type febrile diseases in the fall, namely, scrub typhus, leptospirosis, and HFRS, is widely used. For patients definitively diagnosed with HFRS, local health centers collect their data in an epidemiology report.

(4) HFRS research using molecular genetic technology and utilization of research findings

Since 2015, Korea University and the Agency for Defense Development have been conducting joint research on Hantaviruses with the US Department of Defense using a novel molecular genetics technology. Genetic information for hantaviruses is acquired from the HFRS vectors that have been accumulated over the past 40 years and are stored in a geographic information system. These data are compared with the genetic information for hantaviruses extracted from patients with HFRS to approximate the location of infection. This has been used to perform an in-depth molecular epidemiological investigation of HFRS since 2016. The process involves the acquisition of genetic information about the hantavirus from the HFRS patient's blood sample and its comparison with genetic information extracted from a vector captured from the suspected location of infection. Based on this investigation, the approximate region of infection is obtained, which the Korea Armed Forces uses to identify hazardous regions, provide vaccinations to military personnel training and working in those regions, and restrict access to those regions (**Fig. 5**).

REFERENCES

1. Smadel JE. Epidemic hemorrhagic fever. Am J Public Health Nations Health 1953;43:1327-30.
PUBMED | CROSSREF
2. Brown WL. Trench nephritis. Lancet 1916;187:391-5.
CROSSREF
3. Casals J, Henderson BE, Hoogstraal H, Johnson KM, Shelokov A. A review of Soviet viral hemorrhagic fevers, 1969. J Infect Dis 1970;122:437-53.
PUBMED | CROSSREF

https://doi.org/10.3947/ic.2019.51.4.405

4. Lee HW. The miracle of the Hantaan River. 1st edition. Seoul: Sigongsa. 1999;25-32, 246-54.
5. French GR, Foulke RS, Brand OA, Eddy GA, Lee HW, Lee PW. Korean hemorrhagic fever: propagation of the etiologic agent in a cell line of human origin. Science 1981;211:1046-8.
PUBMED | CROSSREF
6. Karabatsos N. International catalogue of arboviruses, including certain other viruses of vertebrates. Texas: American Society of Tropical Medicine and Hygiene; 1985;445-6.
7. Kim WK, Kim JA, Song DH, Lee D, Kim YC, Lee SY, Lee SH, No JS, Kim JH, Kho JH, Gu SH, Jeong ST, Wiley M, Kim HC, Klein TA, Palacios G, Song JW. Phylogeographic analysis of hemorrhagic fever with renal syndrome patients using multiplex PCR-based next generation sequencing. Sci Rep 2016;6:26017.
PUBMED | CROSSREF
8. Lee MH. Korean Hemorrhagic Fever. 2nd ed. Seoul: Seoul National University Publishing; 1986.
9. Shin DH, Han SK, Choi PC, Lee YH, Shin DH. Acute abdominal pain in patients with hemorrhagic fever with renal syndrome in the emergency department. J Korean Soc Emerg Med 2010;21:191-8.
10. Giles RB, Sheedy JA, Ekman CN, Froeb HF, Conley CC, Stockard JL, Cugell DW, Vester JW, Kiyasu RK, Entwisle G, Yoe RH. The sequelae of epidemic hemorrhagic fever; with a note on causes of death. Am J Med 1954;16:629-38.
PUBMED | CROSSREF
11. Lee MC, Cho KS, Yang KH, Park SD. Korean hemorrhagic fever. J Korean Soc Virol 1979;9:7-12.
12. Lee JK, Hwang SI. Hemorrhagic fever with renal syndrome: historical aspects. Korean J Med Hist 2004;13:37-61.
PUBMED
13. Kim YO, Yoon SA, Ku YM, Yang CW, Kim YS, Kim SY, Choi EJ, Chang YS, Bang BK. Serum albumin level correlates with disease severity in patients with Hemorrhagic Fever with Renal Syndrome. J Korean Med Sci 2003;18:696-700.
PUBMED | CROSSREF
14. Kim YS, Ahn C, Han JS, Kim S, Lee JS, Lee PW. Hemorrhagic fever with renal syndrome caused by the Seoul virus. Nephron 1995;71:419-27.
PUBMED | CROSSREF
15. Steer A. Pathology of hemorrhagic fever: a comparison of the findings; 1951 and 1952. Am J Pathol 1955;31:201-21.
PUBMED
16. Lukes RJ. The pathology of thirty-nine fatal cases of epidemic hemorrhagic fever. Am J Med 1954;16:639-50.
PUBMED | CROSSREF
17. Dodge HJ, Griffin HE, Gauld RL, Kim YS. Epidemic hemorrhagic fever in a Korean farm population; epidemic observation during 1954. Am J Hyg 1956;63:38-51.
PUBMED
18. Song JY, Woo HJ, Cheong HJ, Noh JY, Baek LJ, Kim WJ. Long-term immunogenicity and safety of inactivated Hantaan virus vaccine (Hantavax™) in healthy adults. Vaccine 2016;34:1289-95.
PUBMED | CROSSREF