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OUTBREAK OF HEMORRHAGIC FEVER WITH RENAL SYNDROME AMONG U.S. MARINES IN KOREA

EUGENE PON, KELLY T. McKEE, JR., BENEDICT M. DINIEGA, BRUCE MERRELL, ANDREW CORWIN, AND THOMAS G. KSIAZEK

U.S. Navy Environmental Preventive Medicine Unit 6, Pearl Harbor, Hawaii; Walter Reed Army Institute of Research, Washington, DC; Consolidated Preventive Medicine Service, U.S. Naval Hospital, Okinawa, Japan; U.S. Army Medical Research Institute of Infectious Diseases, Fort Detrick, Frederick, Maryland

Abstract. Fourteen of 3,754 U.S. Marines who participated in a joint United States-Republic of Korea training exercise during the autumn of 1986 developed hemorrhagic fever with renal syndrome (HFRS). Clinical and laboratory findings among cases included fever, headache, fatigue, gastrointestinal dysfunction, thrombocytopenia, and proteinuria. Ten individuals were hospitalized; 2 died. No subclinical infections were identified through a post-deployment screen of sera obtained from 2,053 exercise participants. Analysis of questionnaires identified no environmental, occupational, or temporal factors as risks for developing disease. However, 13 of the 14 cases occurred among individuals housed at 1 of the 2 base camps used during the exercise. This outbreak represents the largest cluster of HFRS cases among U.S. personnel in the Republic of Korea since the Korean conflict.

Hemorrhagic fever with renal syndrome (HFRS) is a rodent-borne zoonosis endemic across much of Europe and Asia that is responsible for considerable human morbidity and mortality.[1,2] A spectrum of clinical severity is recognized with HFRS, ranging from asymptomatic or mild infection to fulminant hemorrhagic fever and death. The etiologic agents are a group of at least 5 antigenically distinguishable viruses comprising the *Hantavirus* genus of the large virus family Bunyaviridae.[3] These viruses establish chronic infections in certain species of rodents and are transmitted to man primarily via aerosols or fomites from contaminated excreta.[4] Geographic (and, to a large degree, clinical) variation is determined by the distribution of the rodent species associated with each distinct virus.[1,5]

HFRS was initially recognized in the Republic of Korea (ROK) during the Korean conflict, when >3,000 cases occurred in United Nations forces.[6] In recent years, 500–800 cases have been serologically confirmed annually among civilian and military populations of the ROK.[7] Relatively few cases have been seen among U.S. military forces in the ROK each year, despite personnel being stationed or training in rural high-risk areas of the country.[7]

From October to December 1986, 14 cases of HFRS were identified among a 3,754-person contingent of U.S. Marines who participated in an annual training exercise in the ROK. This outbreak is the largest clustering of HFRS cases reported among U.S. personnel since the Korean conflict. We report an epidemiological investigation.

MATERIALS AND METHODS

Background

Joint ROK-U.S. military training exercises have been conducted annually during the fall in a region of the ROK immediately South of the demilitarized zone (DMZ) (Fig. 1). Although troops from a variety of locations in the Far East participate in these maneuvers, the principal U.S. military component comes from Navy Marine Corps units stationed in Okinawa, Japan. In 1986, exercises were conducted from 7 September through 15 November.

Training areas were widely scattered during the 1986 exercises, but ground operations from early October onward were concentrated in areas to the North and East of Seoul, near the rural village of Uncheon (Fig. 1). Base camps for 3,074 of the 3,754 Navy/Marine Corps personnel participating in the maneuvers were established in the Uncheon area. Most of the force (1,969 of the 3,074) were quartered at Base Camp 1, a campsite located within the perimeter of a permanent ROK Army post and used each year for this exercise. A similar camp, Base Camp 2, ~2 km to the Northwest, housed 1,105 individuals.

FIGURE 1. Endemic zone for hemorrhagic fever with renal syndrome (shaded area), Republic of Korea. Disease is recognized throughout mainland Korea, but most cases are reported from the shaded area.

The remaining 680 troops encamped at various locations distant from the Uncheon area.

The site for Base Camp 1 was a relatively cleared field containing low grasses, shrubs, and a few trees bordering a small stream. A wire fence surrounded the area, and agricultural fields (rice and peanuts) with homes were located nearby. Base Camp 2 was located in an area of similar topography, but had been used in previous years as a pistol range rather than a housing area. The perimeters of both campsites were overgrown with high grasses, weeds, and shrubs.

Housing facilities were similar in both base camps. Most personnel lived in groups of ≥6 in large, multi-purpose tents. During most of the exercise period, tents were floored with plywood sheets raised 3–6 in. above ground. Reports of rodent noises (and sightings) were frequent, despite ongoing control measures such as poisoning and trapping.

HFRS had not been recognized in association with this exercise previously. Training activities during the 1986 exercises were similar to those in previous years, although operations began about 1 month earlier than usual. The autumn of 1986 was relatively mild in the ROK; overall climatic conditions were dry and dusty until early November, when it began to rain and turn cold. There was no other unusual disease activity noted during the exercise.

Serological and epidemiological screening

An IgM capture enzyme immunoassay (EIA) system specific for hantaviruses was used. The assay is a modification of published methods, in which an anti-Hantaan virus rabbit serum followed by an anti-rabbit conjugate is used in place of a directly conjugated antiviral antibody (T. Ksiazek and others, personal communication).[20] For screening in the field, EIA titers >1:3,000 were considered positive. All sera were subsequently re-analyzed by EIA at USAMRIID under controlled conditions and confirmed by plaque-reduction neutralization (PRN) testing.[1] "Cases" were defined as individuals with IgM EIA antibody >1:3,000 and PRN antibody >1:20.

A 2 page epidemiological questionnaire was administered by study investigators or designees concurrent with blood collection. In addition to demographic and unit-identifier information, data about occupational duties, activities during and after work hours, duration of housing and work during the exercise period, possible environmental exposures, and clinical symptoms were sought. At the conclusion of the investigation, questionnaires were returned to a central location and the responses coded for subsequent data analysis.

During the early days of the investigation, units were chosen for screening based upon the presence of a suspected or confirmed HFRS case. However, as the investigation progressed and additional cases were identified, a decision was made to attempt as comprehensive a screening effort as possible. Consequently, all units participating in the exercise were contacted, and arrangements were made for interviews and bleeding.

Statistical analysis

Data were analyzed using procedures available on Statistical Analysis System (SAS Institute, Cary, NC) software. Discrete variables were compared either by χ^2 test with Yate's correction or by Fisher's exact test (2-tailed).

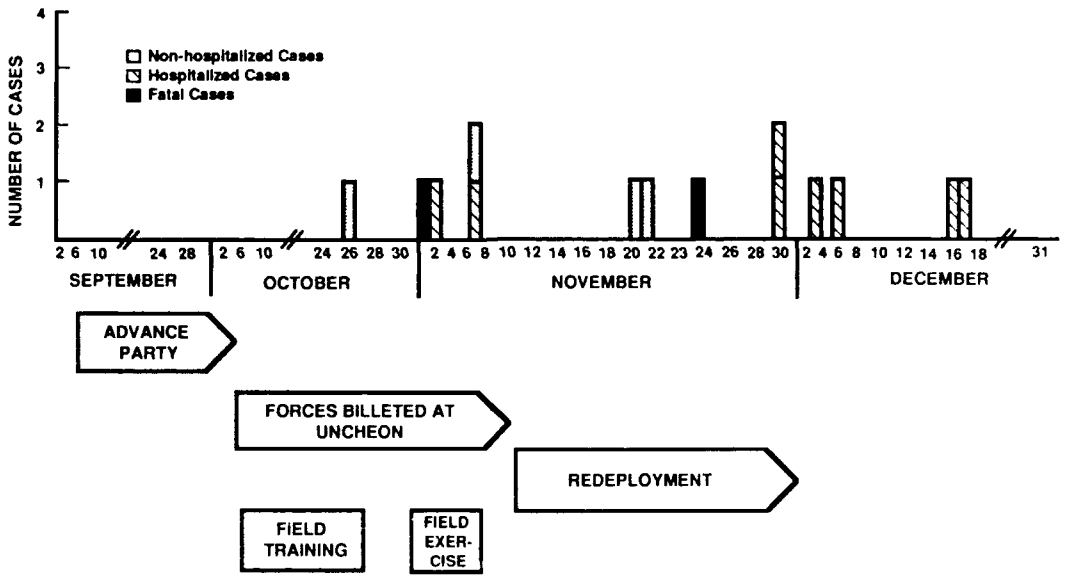

FIGURE 2. Cases of hemorrhagic fever with renal syndrome among U.S. Marines by date of symptom onset and exercise schedule.

RESULTS

The outbreak

On 1 November, a 19-year-old Marine developed a febrile illness which progressed over the ensuing 5 days to include cutaneous hemorrhage, renal failure, and hypovolemic shock. He was hospitalized in Seoul where a diagnosis of HFRS was made. He died within 24 hr. A second Marine involved in the exercise who became ill about the same time was evacuated to Hawaii, where the diagnosis of HFRS was confirmed. Over the next 1½ months, another 8 Marines became ill and were hospitalized with the disease (Fig. 2). One developed symptoms en route to Okinawa at the conclusion of the maneuvers, while the remainder became ill on Okinawa following the deployment; one of these individuals died. Four additional cases were identified retrospectively as a result of serological screening conducted on Okinawa (Fig. 2). All cases occurred in individuals who had been quartered in the Uncheon area.

Clinical investigation

We were able to identify 14 cases of HFRS associated with the exercise. All were symptomatic. Two individuals died. All hospitalized patients had fever, fatigue, and nausea vomiting; 9 had headache and conjunctival injection while 8 had myalgia and diarrhea (Table 1). Thrombocytopenia, proteinuria, and hematuria were present in all patients examined (Table 2). In the 2 patients that died, hypovolemic shock, hemorrhage, renal failure, and pulmonary edema with respiratory failure occurred.

Among non-hospitalized cases, fever, fatigue, headache, and gastrointestinal dysfunction were universal (Table 1). No clinical laboratory studies were performed on non-hospitalized cases.

Epidemiological investigation

On 8 December 1986, a post-exercise epidemiological investigation and serum screen of exercise participants was initiated. All of the soldiers tested for antibodies to hantaviruses completed the questionnaire within 2 months of their return from the ROK. We were able to study 2,053 of the 3,754 (54.6%) participants in the exercise. Among the 3,074 encamped in the Uncheon area, 1,985 (64.6%) were screened. Thirteen units were distributed between the 2 Uncheon area camps; screening coverage ranged from 33% to 100% by unit (data not shown).

Most of the exercise participants were ≤ 25 years of age (74.7%), white (70.7%), and junior enlisted personnel (78.2% at a grade of corporal

TABLE 1
Clinical findings among 14 U.S. Marines with HFRS

Patient	Age (years)	Race	Fever	Fatigue	Myalgias	Headache	Conjunctival injection	Nausea vomiting	Diarrhea	Petechiae
Hospitalized cases										
1*	19	Hispanic	+	+	+	+		+	+	
2	25	Black	+	+		+	+	+	+	
3	20	Black	+	+		+	+	+	+	
4*	35	White	+	+	+	+	+	+	+	+
5	19	White	+	+	+	+	+	+	+	+
6	22	White	+	+	+	+	+	+		+
7	31	White	+	+	+		+	+	+	+
8	20	White	+	+	+	+	+	+	+	+
9	24	White	+	+	+	+	+	+		
10	44	White	+	+	+	+	+	+	+	
Non-hospitalized cases										
A	20	White	+	+		+		+	+	
B	19	White	+	+	+	+			+	
C	19	White	+	+	+	+		+	+	
D	21	White	+	+	+	+		+		

* Expired.

or below). Comparison of cases and controls revealed no significant differences by χ^2 test for these parameters (data not shown). All cases occurred in males. Although an accurate sex distribution of exercise participants was not obtained via the questionnaires, there were very few females involved in the exercise. Distribution of personnel by job description was not determined.

The overall attack rate for HFRS was 4.6/1,000 among all soldiers deployed in the Uncheon area (14/3,074) and 7/1,000 among those screened (14/1,985) (Table 3). Cases derived from several different units, but 13 of the 14 were among the 1,969 individuals housed at Base Camp 1. One case occurred among the 1,105 persons quartered at Base Camp 2 (rate ratio = 7.3; 95% confidence interval = 0.96–55.7). Six of the 14 cases, including the 2 who died, occurred in Marines from a single engineering unit of 118 men and women (Unit A, Table 3). The attack rate for this unit was 50.8/1,000. All of the affected individuals in this unit were assigned to 2 of the 3 company platoons (attack rates = 54/1,000 and 94/1,000). Five different occupational specialties were represented among the 6 individuals affected, and there was no temporal clustering of cases from this unit. Heavy construction and demolition responsibilities, activities which might be considered higher risk for exposure to rodent-borne diseases, were determined to be more frequent in the unaffected platoon than in the 2 in which cases occurred. However, the entire company had been involved in campsite preparation activities such as grading, earth moving, and water purification.

Several types of environmental exposure were examined to ascertain whether acquisition of disease correlated with any particular activity. Questions concerning rodents, insects, water, dust, and participation in field portions of the exercise targeted likely possibilities for at-risk behaviors. As can be seen in Table 4, no environmental exposure correlated formally with disease acquisition. However, at least 10 of the cases lived in areas adjacent to scrub brush or relatively uncleared zones, such as were seen around the edges of the base camps. Unfortunately, no denominator data exist for analysis of this potential risk factor.

DISCUSSION

During the Korean conflict of 1950–1953, the disease known as epidemic or Korean hemorrhagic fever made its appearance among United Nations forces when the previously fluid hostilities bogged down during the spring of 1951 in areas surrounding the 38th parallel.[19] This region has since been the source of hundreds of HFRS cases among ROK soldiers and civilians each year. For reasons which are not understood, U.S. military personnel, present in substantial numbers in many of these same locations, tradition-

TABLE 2

Laboratory findings among 10 hospitalized U.S. Marines with HFRS

Patient	Initial WBC*	Maximum WBC*	Initial platelets*	Low platelets*	Initial creatinine†	Maximum creatinine†	Maximum BUN‡	Initial urinary protein	Initial urinary hemoglobin
1§	59 (4)¶	59 (4)	20 (4)	20 (4)	353 (4)	353 (4)	Not available	Not available	Not available
2	20 (4)	20.4 (4)	51 (4)	51 (4)	344 (4)	927 (7)	20 (9)	4+ (4)	3+ (4)
3	6.2 (10)	24.3 (13)	53 (10)	27 (14)	150 (10)	583 (16)	17 (17)	4+ (10)	4+ (10)
4§	15.1 (4)	45.1 (6)	68 (4)	29 (5)	106 (4)	565 (10)	10 (10)	4+ (4)	4+ (5)
5	4.9 (3)	5.8 (3)	138 (3)	28 (unknown)	124 (3)	124 (3)	2.7 (3)	4+ (3)	4+ (3)
6	4.6 (4)	8.1 (6)	150 (4)	66 (6)	62 (5)	106 (6)	2.5 (5)	4+ (5)	TR (5)
7	6.1 (1)	13.6 (2)	82 (1)	47 (2)	124 (1)	327 (9)	10 (9)	2+ (1)	4+ (2)
8	14.3 (6)	17.8 (6)	69 (6)	69 (6)	336 (6)	336 (6)	11 (6)	3+ (6)	4+ (6)
9	6.7 (2)	7.4 (3)	103 (2)	94 (3)	106 (3)	106 (3)	2 (3)	4+ (3)	Not available
10	10.4 (1)	17.9 (2)	68 (1)	20 (unknown)	132 (1)	309 (unknown)	6.7 (unknown)	4+ (1)	Not available

* Cells × 10^3/l.
† Micromole/l.
‡ Millimole/l.
§ Expired.
¶ Numbers in parentheses denote day after illness onset value was obtained.

TABLE 3

Attack rates (cases/1,000) for HFRS outbreak among U.S. Marines in the ROK

	Cases	Number deployed	Attack rate*
Overall	14	3,074†	4.6
By location of quarters			
Base camp 1	13	1,969	6.6‡
Base camp 2	1	1,105	0.9
By unit			
A	6	118	50.8
B	3	655	4.6
C	2	517	3.9
D	1	79	12.6
E	1	314	3.2
F	1	163	6.1

* Attack rate/1,000.
† Total quartered in Uncheon area.
‡ RR = 7.30 vs. Camp 2 (95% CI = 0.96–55.7).

ally have experienced few (generally <10) documented HFRS infections annually. Those cases reported usually are widely distributed geographically and temporally. The current HFRS outbreak thus afforded an opportunity to examine environmental and epidemiological features of this affliction among a number of American cases occurring over a short interval.

We identified 14 HFRS cases associated with this military exercise, 10 of whom were hospitalized. Although 4 cases were recognized retrospectively, all had been ill; no asymptomatic infections were found among 2,039 persons screened serologically. Mild illness is reported to occur in Far Eastern HFRS.[7] However, the present survey suggests that truly asymptomatic infection may be an infrequent event, at least in the context of exposure occurring in the field.

Clinical findings in the 14 cases of HFRS were similar to those previously described.[11] Although the 2 patients who died sustained severe renal failure and shock, the remaining individuals developed relatively mild illness requiring close monitoring but not intensive supportive care. Consistent with previous observations, these individuals failed to exhibit the 5 phases of disease progression (febrile, hypotensive, oliguric, diuretic, and convalescent) characteristic of severely ill individuals.[7,11–14]

We were able to evaluate potential risk factors for acquisition of HFRS in >50% of the participants in the military exercise. There were no apparent demographic factors predisposing to infection, and common environmentally-interac-

TABLE 4
Environmental exposures

		Cases	Controls	Total	χ^2 *P* value*
Rodents	Rodents seen				
	A lot	0	47	47	
	Some	4	885	889	$\chi^2 = 0.779$
	None	7	1,121	1,128	$P = 0.677$
	Rodents touched/handled				
	Yes	0	66	66	$\chi^2 = 0.727$
	No	11	1,958	1,969	$P = 0.394$
Insects	Insects seen				
	A lot	3	150	153	
	Some	4	895	899	$\chi^2 = 4.024$
	None	4	1,011	1,015	$P = 0.134$
	Insect tick bites				
	A lot	0	7	7	
	Some	1	414	415	$\chi^2 = 1.106$
	None	10	1,619	1,629	$P = 0.575$
Water	Swimming bathing wading				
	Yes	2	371	373	
	No	9	1,685	1,694	$P = 1$†
Dust	A lot	7	801	808	
	Medium	3	663	666	$\chi^2 = 3.992$‡
	Little	1	484	485	$P = 0.27$
	None	0	106	106	
Field	Participation in field portions of the exercise				
	Yes	4	1,265	1,269	
	Field—no. Garrison—yes	6	741	747	$\chi^2 = 2.307$ $P = 0.316$
	Other combination	0	14	14	

* Expected counts < 5 in < 25% of cells in χ^2 tables, likelihood ratio χ^2 test used.
† Fisher's exact test (2-tailed).
‡ χ^2 for trend (Mantel-Haenzel) = 3.225, $P = 0.073$.

tive activities or exposures were not identified. Despite a clustering of 6/14 cases in a single company of combat engineers, neither job-related nor recreational activities were shared by cases. Numerous rodent sightings were reported during the exercise, although it is unclear whether these observations represented increases over previous years. However, the occurrence of the exercises earlier in the year than usual, together with the relatively mild weather present during its early weeks, may well have affected rodent populations during this period. Most HFRS patients lived in tents located along topographical boundaries while in the base camps, areas where field-dwelling rodents would be expected to thrive.

Onset of illness in HFRS ranged over a 50-day interval. This fact, together with the highly variable incubation period for HFRS (reported range, 4–42 days) and the amount and variety of activity in which soldiers were engaged both inside and outside the base camp areas makes pinpointing exposures in time or place during this outbreak difficult.[7] However, the occurrence of 13/14 cases among Marines housed at 1 of the 2 base camps suggests strongly that this area was in some way involved in disease acquisition.

Infection of humans with *Hantaviruses* occurs generally as a consequence of intrusion into ecosystems occupied by reservoir rodents. Correlations between HFRS case numbers and small rodent populations have been confirmed repeatedly across Eurasia.[1,5,13,15] It is probable, however, that *Hantavirus* infections are not distributed evenly among rodent populations, even in hyperendemic areas, a concept expressed as "focal nidality of disease" by Soviet scientists.[16] A practical expression of this phenomenon may well rest in the numerous observations of small foci

of HFRS occurring in the midst of otherwise unaffected larger groups.[13,17] Sporadic outbreaks bearing a striking resemblance to the current case cluster were well documented during the Korean conflict.[18]

Two clinically similar but virologically and epidemiologically distinct forms of human HFRS currently are recognized in the Far East. In general, disease acquired in rural areas is highly seasonal, with most cases occurring in autumn and early winter. This type of HFRS has been linked virologically to Hantaan virus, and occurs as a consequence of exposure to its predominant rodent host, *Apodemus agrarius*.[1,2] A more urban or peridomestic form of HFRS occurs in the ROK as well; it is less seasonal in occurrence and may cause a somewhat milder clinical syndrome. This latter illness, caused by Seoul virus, is acquired following exposure to its rodent host, *Rattus rattus* or *R. norvegicus*.[1,5] Clinical, environmental, and epidemiological features of the current outbreak share elements with both virus/disease types. Additional virological and ecological investigations are ongoing in an attempt to further delineate the precise etiology.

Diagnosis of HFRS depends upon demonstration of specific anti-hantaviral antibodies in serum of infected individuals. The most widely used technique for detecting these antibodies is the indirect immunofluorescence assay (IFA), which yields positive results within a week following disease onset in most persons.[1] In the present study, we utilized an IgM-capture EIA for screening (and, coincidentally, for diagnosis) of HFRS. This assay has been evaluated under controlled conditions in Chinese HFRS patients (Meegan J, LeDuc J, Zheng ZM, Xiao S, Lee HW, Huggins J. Rapid diagnosis of HFRS using enzyme-linked immunosorbent assays. International Symposium on HFRS, 30 October–2 November 1988, Wuhan, People's Republic of China), while similar tests have demonstrated their utility for diagnosing disease in the USSR and Scandinavia.[19,20]

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Authors' addresses: Eugene Pon and Bruce Merrell, U.S. Navy Environmental Preventive Medicine Unit 6, Pearl Harbor, HI. Kelly T. McKee, Jr. and Thomas G. Ksiazek, U.S. Army Medical Research Institute of Infectious Diseases, Fort Detrick, Frederick, MD. Benedict M. Diniega, Walter Reed Army Institute of Research, Washington, DC. Andrew Corwin, Consolidated Preventive Medicine Service, U.S. Naval Hospital, Okinawa, Japan.

Reprint requests: Kelly T. McKee, Jr., Medical Division, USAMRIID, Fort Detrick, Frederick, MD 21701.

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