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Epidemiologic Characteristics and Military Implications of Hemorrhagic Fever with Renal Syndrome in Croatia

Rosanda Mulić, Darko Ropac

Institute of Naval Medicine, Croatian Navy, Split, Croatia

Aim. To analyze epidemiologic characteristics of hemorrhagic fever with renal syndrome in Croatia, including military implications of the disease and measures for its prevention.

Method. We analyzed data from obligatory infectious disease reports and notification of deaths due to infectious diseases, data on the hemorrhagic fever with renal syndrome epidemics in Croatia, and data collected by survey of the population, serological findings, and studies of wild rodents serving as reservoirs of the infection.

Results. During the 1987-2001 period, 235 cases of hemorrhagic fever with renal syndrome were recorded in Croatia, with 147 (62.6%) of them among Croatian Army soldiers. Mortality rate was up to 15.4% (mean 2.2%) (5/235). The highest number of cases was recorded in months of June and July, ie, during the warm season characterized by increased activity of both the animals acting as infection reservoirs and humans as hosts. The known natural foci of hemorrhagic fever with renal syndrome have been Plitvice and Slunj areas, Velika and Mala Kapela mountains, Zagreb area (Velika Gorica and Jastrebarsko), west Slavonia, Novska area, and Dinara Mountain. The disease has not been recorded in the littoral area and Adriatic islands. The identified causative agents include Dobrava and Puumala viruses of the genus *Hantavirus*, whereas rodents *Clethrionomys glareolus, Apodemus flavicollis, Apodemus agrarius,* and *Apodemus sylvaticus* serve as the main reservoirs of the infection. Typical biotopes of the infection in Croatia are deciduous woods. The measures of prevention in Croatia include pest control, disinfection, hygienic waste disposal, preventing rodent access to food and water, proper choice of camping sites, and health education.

Conclusion. Hemorrhagic fever with renal syndrome occurs predominantly in soldiers, in a sporadic or epidemic form. Because of the course of disease and potentially lethal outcome, the disease has a considerable impact on the field task performance and combat readiness of military units, and is of great importance for a military community. Accommodation in permanent buildings with appropriate common and personal hygiene standards is recommended.

Key words: *disease reservoirs; hantavirus; hantavirus infections; hemorrhagic fever with renal syndrome; military personnel; rodentia*

Hemorrhagic fever with renal syndrome is a zoonosis caused by viruses of the genus *Hantavirus,* family *Bunyaviridae*. Its natural foci are spread worldwide. Man is mostly infected by inhaling aerosol from excreta of infected mouse-like rodents in their natural biotope. However, other epidemiologic routes may also be involved. Hantaviruses cause two clinical syndromes: hemorrhagic fever with renal syndrome and hantavirus pulmonary syndrome (1). Hantavirus pulmonary syndrome is a relatively "novel" clinical entity caused by the Sin Nombre and Black Creek Canal viruses (1,2). Hemorrhagic fever with renal syndrome has been known for a long time, and it attracted increased interest during the Korean War (1951-1954), when it occurred in the form of large epidemics, with more than 3,000 affected soldiers. Subsequently, the causative virus was discovered and named after the river running along the 38th parallel dividing North and South Korea (3). The disease usually occurs sporadically; its epidemics frequently accompany armed conflicts and soldiers are the group at the highest risk in both war and peacetime conditions. Therefore, hemorrhagic fever with renal syndrome is an important disease from the viewpoint of military epidemiology (4-7).

In Croatia, hemorrhagic fever with renal syndrome was first described in 1954, thereafter occurring mostly sporadically or in the form of minor outbreaks until 1995, when the largest epidemic to date was recorded (8-12). Hemorrhagic fever with renal syndrome generally occurs in an endemic form. The infection is disseminated from several sources (reservoirs), which is characteristic of infections in natural foci (13).

Hemorrhagic fever with renal syndrome is of no major relevance for the general population of Croatia and public health service, but is important for armed forces because the entire inland area of Croatia is considered endemic for hemorrhagic fever with renal

syndrome (4). This means that, apart from the known natural foci, there must be others, as yet unidentified foci, implying real risk for the units in the field (4,13, 14).

Therefore, the aim of the study was to describe epidemiologic characteristics of hemorrhagic fever with renal syndrome in Croatia, and to discuss the military implications of the disease. Except for the Croatian Army, the disease may also be of relevance to other armed forces that may stay in Croatia within the frame of the Partnership for Peace or possibly as part of NATO forces (5-7).

Method

Data from the National Institute of Public Health on infectious disease reports (9), reports on hemorrhagic fever with renal syndrome epidemics in Croatia, especially in army units (4,12, 13), and data from the studies of hemorrhagic fever with renal syndrome natural foci were analyzed. Analysis of the military implications of the disease was based on our own data and long-term experience in the prevention and control of hemorrhagic fever with renal syndrome, including hemorrhagic fever with renal syndrome epidemic on the Dinara mountain in 1995 (15).

Results

Morbidity

During the last 15 years, out of a total of 235 patients with hemorrhagic fever with renal syndrome, 147 (62.6%) were Croatian Army soldiers (9-14). Until 1995, the disease used to occur sporadically or in minor outbreaks. The first epidemic of hemorrhagic fever with renal syndrome was recorded in 1967, when 14 forestry workers were infected at the Plitvice Lakes. The first hemorrhagic fever with renal syndrome outbreak in a military unit was recorded in October 1989, when 14 soldiers camping near Velika Gorica were affected (10). In 1992, 13 soldiers from Novska and Gorski Kotar were infected with hemorrhagic fever with renal syndrome. All these represented temporal clustering of sporadic cases and were not considered an epidemic (9). Among civilians, farmers working in the field, forestry workers, and tourists visiting natural foci were affected most often (11-14). The highest number of hemorrhagic fever with renal syndrome cases was recorded during 1995, when 129 patients were reported (Table 1). Since 1995, 10 cases per year have been recorded on average. During the spring and summer of 2002, hemorrhagic fever with renal syndrome infection was recorded in Croatian Army soldiers staying at the artillery range in Slunj, a known natural focus (9).

The 1995 Epidemic

Out of 129 patients with hemorrhagic fever with renal syndrome recorded in 1995, 120 were Croatian Army soldiers infected during their stay at Dinara (n = 69), Mala Kapela (n = 44), and in the Lipik-Okučani-Novska area in west Slavonia (n = 7). The patients were from different parts of Croatia, ie, from the Split-Dalmatia, Zagreb, Lika-Senj, Primorje-Gorski Kotar, and Varaždin counties. The remaining 9 patients were not Croatian Army members; 5 of them contracted infection in the Zagreb surroundings, whereas no data are available for the other 4 patients.

Table 1. Incidence of hemorrhagic fever with renal syndrome in Croatia during the 1987–2001 period

Year	No. of patients	No. of deaths (%)
1987	6	–
1988	–	–
1989	16	–
1990	2	–
1991	–	–
1992	13	2 (15.5)
1993	1	–
1994	7	–
1995[a]	129	3 (2.3)
1996	6	–
1997	8	–
1998	16	–
1999	15	–
2000	5	–
2001	11	–
Total	235	5 (2.2)

[a]"High rodent" year.

During the 1995 epidemic, the highest number of cases was recorded in April, which was directly related to the combat activities of the Croatian Army during the 1991-1995 war in Croatia (Fig. 1).

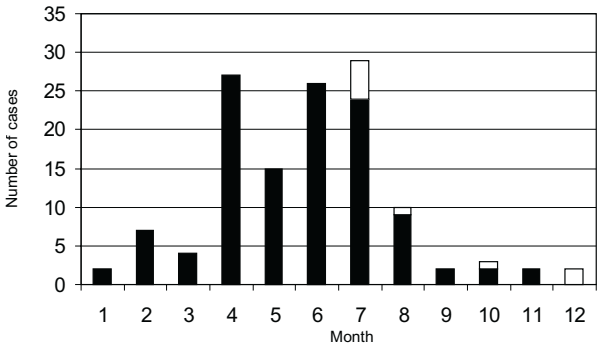

Figure 1. Hemorrhagic fever with renal syndrome epidemic in Croatia in 1995 (a "high rodent" year). Closed bars – soldiers, open bars – other cases.

Two of 120 soldiers (1.7%) affected with hemorrhagic fever with renal syndrome died. One of the two deceased soldiers contracted the infection in the natural focus of Mala Kapela (the virus type was not identified), and the other at the Dinara mountain (Dobrava virus).

Epidemiologic survey yielded the mean incubation time of 33 days, range 21-43 days. All infected Croatian Army soldiers with hemorrhagic fever with renal syndrome were men aged 20-40, with the mean age of 27 years. They were accommodated in wooden huts located in a typical biotope in beech forest abundant in mouse-like rodents. The aerogenic route of transmission was involved.

Since May 1995, no additional cases of hemorrhagic fever with renal syndrome infection have been recorded at these locations, which could be attributed to the transfer of military units to other locations. Based on the data available, along with clinical, laboratory, and epidemiologic verification of the hemorrhagic fever with renal syndrome diagnosis, the Dinara mountain was identified and mapped as a "novel"

natural focus of hemorrhagic fever with renal syndrome in Croatia (15).

The existence of natural hemorrhagic fever with renal syndrome foci on the Dinara mountain had not been recognized by that time. The respective locations on the Dinara mountain are known as Velika and Mala Poljanica and Crni Bunari (15,18).

Epidemiologic Characteristics

Seasonal occurrence is a significant epidemiologic characteristic of hemorrhagic fever with renal syndrome (1,2,10,13,14). The lowest number of cases is usually recorded in winter, whereas the seasonal peak of the disease prevalence occurs in summer months. This is so because the number and activity of mouse-like mammals serving as infection reservoirs are highest during warm season. In this period of the year, the exposure of susceptible hosts – humans – is also highest, as they frequently enter natural foci for various reasons. In case of army units, a variety of reasons may be involved: in wartime, some military action, and in peacetime, field training or public works. During the 1987-2001 period, the highest mean number of affected individuals was recorded in June and July (Fig. 2).

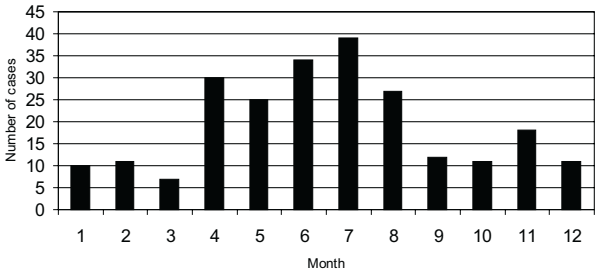

Figure 2. Distribution of patients with hemorrhagic fever with renal syndrome in Croatia according to months, 1987-2001.

Ecologic Characteristics of Natural Foci and Infection Reservoirs

The distribution of the natural foci of hemorrhagic fever with renal syndrome is shown in Fig. 3. The reservoirs of hemorrhagic fever with renal syndrome agents are small, wild, semisinanthropic and sinanthropic mouse-like rodents. Their excreta are the source of infection (1,2,14,16,17). In their population, the virus is maintained in the form of "silent" enzootic. The infection usually proceeds asymptomatically or with a mild clinical picture. The carrier state mostly persists for life. The virus is disseminated in the secreta and excreta of infected rodents (1,13, 16,17).

The data collected to date indicate that small rodents, such as bank vole (*Clethrionomys glareolus*) and yellow-necked field mouse (*Apodemus flavicollis*), are the main reservoirs of the infective agent in the endemoepidemic process in Croatia, especially at altitudes of 500 m above sea level. In lower areas, besides the above species, striped field mouse (*Apodemus agrarius*) and long-tailed field mouse (*Apodemus sylvaticus*) are the main reservoirs of the infective agent (4,10,12-14,16,17).

Figure 3. A map of Croatia with the foci of hemorrhagic fever with renal syndrome. Hatched area – clinically and epidemiologically determined foci. Cross hatched area – virologically verified foci.

The investigation conducted on Dinara in 1996 revealed the prevalence of carrier state in mouse-like rodents to be 12% (15). The results would have probably been different had the mouse-like rodent catch been organized during the "high rodent" year of 1995. The surge in the population of small rodents is followed by a fast decline due to infections, lack of food, and cold.

The natural focus of hemorrhagic fever with renal syndrome on Dinara is characterized by coexisting oak and hornbeam (*Querceto-Carpinetum*) and beech forests, with pastures at higher altitudes. The area is populated with yellow-necked mouse (*Apodemus flavicollis*), long-tailed field mouse (*Apodemus sylvaticus*), and bank vole (*Clethrionomys glareolus*) (18). The natural focus of hemorrhagic fever with renal syndrome at Plitvice is in beech forests and bush. The small rodent species living in the area include bank vole and yellow-necked mouse. The area of Velika Gorica is predominated by long-tailed field mouse, and to a lesser extent striped field mouse and bank vole. Studies in the Novska surroundings have shown striped field mouse to prevail in the area (11,13,14).

Prevention of Hemorrhagic Fever with Renal Syndrome Infection

Prevention of hemorrhagic fever with renal syndrome infection included housing and environmental pest control, housing disinfection, hygienic waste disposal, intensive health surveillance, and health education. As no vaccine was available, measures aimed at infection risk reduction, ie, housing and closest environment pest control with combined rodenticide baits, housing disinfection, prevention of rodent ac-

cess to food, hygienic waste disposal, and health education were used. The control of the epidemic was hampered by continuous turnover of soldiers in the field. Thus the military community suffered immunologic instability due to constant inflow of susceptible individuals.

Discussion

According to the recommendation of the World Health Organization from 1982, several similar clinical entities known by then under different names in particular regions of the world have since been termed hemorrhagic fever with renal syndrome (19). The mortality rate varies according to causative agent from 0.1% to 15% (1,2). In Croatia, the mean lethality from hemorrhagic fever with renal syndrome during the 1987-2001 period was 2.2%.

According to the latest phylogenetic classification, nine types of *Hantaviruses* (HTV) have been identified: Hantaan (HTN), Puumala (PUU), Seoul (SEO), Prospect Hill (PH), Dobrava (DOB), Thailand (THAI), Thottapalayam (TPM), Sin Nombre (SN), and Black Creek Canal (BCC) (1,2,4). Sin Nombre virus causes hantavirus pulmonary syndrome (1,2). However, pulmonary manifestations are also common in hemorrhagic fever with renal syndrome, and are usually detected by X-ray as interstitial infiltration and pleural effusion. Pathologic findings of the lungs were recorded in 35.1% of patients with hemorrhagic fever with renal syndrome treated during 1995 at the University Hospital of Infectious Diseases in Zagreb (12).

The agents causing hemorrhagic fever with renal syndrome present in the Balkan Peninsula include the Hantaan, Puumala, Seoul, and Dobrava viruses (4,5, 7). In Croatia, the disease has been serologically demonstrated to be caused mostly by the viruses Dobrava and Puumala (4). Serologic analysis revealed the infection with Dobrava virus to yield cross-reaction with Hantaan virus (4,20), which may compromise the interpretation of results. There is positive correlation between the severity of clinical picture of hemorrhagic fever with renal syndrome and viral serogroup (4,20). Dobrava virus was demonstrated in the severe forms of the disease during the 1995 hemorrhagic fever with renal syndrome epidemic in Croatia (4,12).

Infections with Dobrava virus were demonstrated in Slovenia, Greece, Albania, Bosnia and Herzegovina, Estonia, and Russia, characterized by severe clinical picture and associated with renal insufficiency, hemorrhages, and 10-15% mortality. Infections with Puumala virus show milder clinical manifestations and lower mortality rate (1,2,4,20-28). Studies carried out by Croatian researchers have indicated that there is no distinct margin in the geographical distribution of these two viruses, as both were detected in patients who had stayed in the same natural foci at the same time (4,12-14). Still, a higher rate of Dobrava virus and Puumala virus infection could be expected in the Dinara and Velika/Mala Kapela areas, respectively (4).

The reservoirs of hantavirus are mouse-like rodents. The natural, spontaneous infection of small mammals with hemorrhagic fever with renal syndrome agent shows a chronic and asymptomatic course, thus the focus is only identified when humans are involved. The intensity of enzootic process in a focus of hemorrhagic fever with renal syndrome is influenced by the number of mouse-like rodents, prevalence of carrier state, and virus concentration in their organs, the first two being of utmost importance for evaluation of the epidemiologic risk of a particular focus. Some authors believe that the possibility of hantavirus infection is low if the rate of rodent infection is below 28%, when only sporadic cases of the disease in humans should be expected (17,21). The rate of rodent viral infection is also highly relevant for the maintenance of epidemic potential in a natural focus. During the epidemics in the Balkan area, the rate of rodent infection ranged from 25% to 33% (17). In Europe, the main reservoirs of hemorrhagic fever with renal syndrome viral infection are mouse-like rodents of the species *Clethrionomys* and *Apodemus* (13,16). In Croatia, bank vole, yellow-necked mouse, field mouse, and long-tailed field mouse serve as main reservoirs.

Genetic similarities and serologic cross-reactions among hantaviruses are in correlation with the phylogenetic relationships among their reservoirs. In the natural foci in Croatia, bank vole is mostly a reservoir of Puumala virus, whereas yellow-necked mouse and striped field mouse are reservoirs of Dobrava and Hantaan virus, respectively (1,2,4,14,15).

Since Croatia borders with Bosnia and Herzegovina, Slovenia, Serbia, and Montenegro, the exchange of hantaviruses and their reservoirs among these countries appears to be quite possible (4). In the neighboring Slovenia, mild cases of hemorrhagic fever with renal syndrome caused by the strain Puumala and severe cases caused by the strain Dobrava have been described (23,24). The strains Puumala, Seoul, and Dobrava as well as some other genetically close to the strains Hantaan and Puumala (Vranica, Fojnica, and Plitvice) have been demonstrated to circulate in Bosnia and Herzegovina (25-27). Yellow-necked mouse is the main reservoir of the disease in Bosnia and Herzegovina. The mouse-like rodent density is lowest in spring, because the litter is dropped in warm season and rarified in winter. The population declines rapidly due to the lack of food and unfavorable living conditions. The population reaches its peak every three to four years, popularly known as "high rodent" years, characterized by obvious increase in the rodent population (14,16,28). Another characteristic feature of mouse-like rodents are frequent migrations that may entail changes in the natural focus margins, which can be: (a) vertical in mountainous areas in spring and fall; (b) diurnal, dictated by the search for food; (c) occasional, related to the lack of food or to extensive forest fire or flood; and (d) anthropocentric, when rodents approach humans and their environment due to the human penetration to their biotope or ecologic niche.

There are three epidemiologic types of acquiring hemorrhagic fever with renal syndrome infection according to the site and reservoir of infection: rural, urban, and laboratory type. In rural type, the reservoirs

of infection are mostly rodents of the species *Apodemus* and *Clethrionomys*, and the infection occurs in natural foci. The species *Rattus* (*Rattus rattus* and *Rattus norvegicus*) serve as the reservoir of infection in the urban type, and the infection occurs in urban settings. The laboratory acquisition of the infection can occur while working with naturally or experimentally infected rodents (16,28). According to our present data, the majority of the known cases of hemorrhagic fever with renal syndrome recorded in Croatia were of the rural type.

In Croatia, hemorrhagic fever with renal syndrome is recorded all over the year, with the greatest number of cases occurring from April until August, which corresponds to the seasonal occurrence of the disease also in Slovenia, Bosnia and Herzegovina, Serbia and Montenegro, Hungary, Bulgaria, and Greece (4,13,17,21-27). In Scandinavian countries, the highest number of hemorrhagic fever with renal syndrome cases are recorded in winter, when rodents approach houses and house lots in search for food, resulting in close contact between rodents and humans (29,30).

In three recorded hemorrhagic fever epidemics and in 1992 when patient clustering was observed, all patients with hemorrhagic fever with renal syndrome were men. Although some authors speculate about immunologic variation leading to the higher rate of hemorrhagic fever with renal syndrome in men (31), we believe that the greater proportion of men affected with hemorrhagic fever with renal syndrome was simply consequential to their higher, mostly occupational, exposure.

Besides Croatia, epidemic outbreaks of hemorrhagic fever with renal syndrome during the war were also recorded in the neighboring Bosnia and Herzegovina, in autochthonous population as well as in their army units. During the 1991-1995 war, a case of Seoul virus infection acquired from rat in an urban setting in Sarajevo was described (27). Bosnia and Herzegovina had been known for long as an endemoepidemic area of hemorrhagic fever with renal syndrome (32,33).

Two of the three hemorrhagic fever with renal syndrome epidemics recorded in Croatia involved military units, one of them occurring in peacetime (Pleso near Zagreb), and the other during the 1991-1995 war (Dinara, ref. 15), confirming that soldiers are a group at the highest risk in both peace and war. During the 1987-2001 period, 235 cases of hemorrhagic fever with renal syndrome were recorded, 147 (62.6%) of them among Croatian Army soldiers. The occupational risk in soldiers is related to the increased exposure to the infection in natural foci. In peacetime, soldiers occasionally stay outdoors for training and other occupational tasks, and in wartime for military actions. These are the reasons for the occurrence of epidemics as well as of sporadic cases of hemorrhagic fever with renal syndrome among soldiers. The occurrence of the disease in military units can considerably compromise combat readiness and field action performance. Therefore, recognition of the natural foci of hemorrhagic fever with renal syndrome is of utmost importance for armed forces to prevent the possibility of infection.

The occurrence of hemorrhagic fever with renal syndrome at a number of locations during the war in Croatia, some of which had been unknown before, then continuous occurrence of sporadic cases of the disease, and its occurrence in Croatian Army members staying outdoors for field training in spring and summer 2002, pointed to the high military implications of hemorrhagic fever with renal syndrome. The occurrence of the disease among soldiers and subsequent seroepidemiologic studies in the field led to the identification of the two new natural foci of hemorrhagic fever with renal syndrome in the Dinara mountain (15) and Novska area in west Slavonia (4,14). Recent studies in the natural focus of hemorrhagic fever with renal syndrome on Dinara have shown it to be restricted to the following quadrant: N43°57′45′′ to N44°04′50′′ geographic latitude, and E16°31′28′′ to E16°35′27′′ geographic longitude, at the altitude between 1,260 and 1,807 m above sea level.

No epidemics or sporadic cases of hemorrhagic fever with renal syndrome were acquired on Adriatic islands or in the littoral area. To our knowledge, no serologic studies in the islanders or littoral inhabitants, or of mouse-like rodents of the area have been conducted to date.

As there is no efficacious and reliable hemorrhagic fever with renal syndrome vaccine available, nonspecific measures are used in its prevention (28). Korean and Chinese researchers reported on the efficacy of their vaccines, describing only mild side effects. However, field studies throw serious doubt on the efficacy of the Korean vaccine *Hantavax* (34).

Because of the lack of efficacious vaccine, other measures are recommended for the prevention of hemorrhagic fever with renal syndrome, such as monitoring and assessment of the mouse-like rodent population, avoidance of field exercises in the known natural foci, hygienic waste disposal and pest control, strict health surveillance on camping of soldiers and other groups at occupational risk, and health education. Proper choice of location for accommodation is also an important preventive measure. The bushes and grass should be removed from the site. The food and water must be efficiently protected from contact with rodents. Although the efficiency of pest control in the wilderness is questionable, it should be performed by placing rodenticides into active rodent holes.

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Correspondence to:
Darko Ropac
Croatian Navy Institute of Naval Medicine
Šoltanska 1
21000 Split, Croatia
darko.ropac@morh.hr