CHAPTER 7

# EPIDEMIOLOGY OF CRIMEAN-CONGO HEMORRHAGIC FEVER IN THE BALKANS

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## 7.1. INTRODUCTION

Crimean-Congo hemorrhagic fever (CCHF) is viral hemorrhagic fever with high significance in the Balkan Peninsula (Fig. 7-1), with a case fatality rate (CFR) of up to 40% and a high propensity for nosocomial spread. Epidemic outbreaks as well as sporadic cases have continuously been recorded in this area since 1952. There is strong evidence that *Hyalomma marginatum marginatum* ticks are implicated in the ecology of CCHF and serve as a principal vector of the virus in this region. Although the majority of documented cases have a history of tick bite, farmers having contact with the livestock have been found as a risk population for contracting the disease. Person-to-person transmissions, resulting in family outbreaks, as well as nosocomial transmissions in hospital settings, were frequently reported in the Balkans. Hospitalized patients, usually presented with a severe clinical course, were treated with supportive and replacement therapy. With regard to the availability of drugs and the country, antiviral drug ribavirin was effectively administered. Depending on the country, various preventive measures against the infection and spread of the disease are used. In general, after every outbreak or epidemic of CCHF, a better knowledge and awareness of the disease were obtained in general population, in high-risk groups and particularly among health-care workers.

## 7.2. KOSOVO

The first description of CCHF from Kosovo was a report of eight fatal cases in the village of Nishor of Suharekë [16]. However, the first recognized CCHF outbreak in former Yugoslavia was reported in 1970 among shepherds in the village of Čiflik on the border of Macedonia and Kosovo (Fig. 7-1). Based on



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*Fig. 7-1.* Map of the Balkan Peninsula.

epidemiological data, eight family members contracted the disease from the index case that was infected by tick bite. By retrospective analysis, using a complement fixation test and differential gel precipitation, a diagnosis of CCHF was confirmed in 10 out of 13 patients, two of whom died [31]. The results of serological examination of 97 sera from healthy residents of the village Čiflik revealed three positive individuals [23]. An outbreak of viral hemorrhagic fever was also noted in Kosovo during the period 1991–1992. Ninety-two sera from 76 hospitalized subjects suspected of CCHF were available for retrospective laboratory testing. Using enzyme immunoassays, we confirmed five CCHF cases by the detection of both IgM- and IgG-specific antibodies and further five cases (family members) by detection of specific IgG antibodies only. Ten years later, reverse transcription polymerase chain reaction (RT-PCR) was applied retrospectively to 19 stored serum samples from serologically confirmed CCHF cases. Viral RNA could be detected in all IgM-positive samples up to day 12 of illness. The sequence analysis of the partial S segment of the polymerase chain reaction (PCR) products revealed that the CCHF virus (CCHFV) responsible for the 1991–1992 outbreak in Kosovo is closely related to a CCHFV strain Drosdov [4].

The next CCHF outbreak in Kosovo occurred between June and November 1995. Based on the records of the Institute of Public Health in Pristine, Kosovo, the total number of CCHF patients in the 1995 epidemic was 65 with seven deaths. From 1996 to 2000, there were 33 sporadic cases with seven fatalities in Kosovo (Table 7-1) [8, 19].

*Table 7-1.* Confirmed cases of CCHF and HFRS in Kosovo from 1995 to 2005

| Year | CCHF cases | CCHF fatal | Mortality rate (%) | HFRS cases |
|---|---|---|---|---|
| 1995 | 65 | 7 | 10.8 | 24 |
| 1996 | 23 | 5 | 21.8 | 4 |
| 1997 | 0 | 0 | 0 | 0 |
| 1998 | 1 | 0 | 0 | 0 |
| 1999 | 7 | 2 | 28.6 | 1 |
| 2000 | 2 | 0 | 0 | 0 |
| 2001 | 30 | 7 | 23.3 | 2 |
| 2002 | 14 | 3 | 21.4 | 4 |
| 2003 | 8 | 0 | 0 | 3 |
| 2004 | 12 | 2 | 16.7 | 2 |
| 2005 | 5 | 1 | 20 | 2 |

During the spring and summer of 2001, the largest epidemic thus far occurred in this region. From 155 suspected CCHF cases, the diagnosis was confirmed in 30 patients. Among them, 28 patients were confirmed as acute CCHF by the presence of specific anti-CCHF IgM antibodies and/or positive PCR. Two additional cases were confirmed on clinical and epidemiological records – one was a contact with the index case and the second died in the emergency room with typical clinical signs of the disease. The CFR during the 2001 epidemic was 23.3% (Table 7-1). The mean age of the patients was 38 years (range from 8 to 76 years). Male patients were more often affected (70%). When 46 sera from healthy family members of the patients affected during the epidemic in 2001 were tested, seven were found IgG-positive and one IgM- and IgG-positive. Since the last epidemic on average ten sporadic cases are registered every year in the known endemic regions of CCHF in Kosovo (Table 7-1). CCHF cases in Kosovo were distributed among 18 municipalities with a high incidence in Klinë, Rahovec, Skënderaj, Malishevo, and Suharekë (Fig. 7-2) [19]. It is worth mentioning, that beside CCHF, sporadic cases of hemorrhagic fever with renal syndrome (HFRS) are diagnosed every year in Kosovo (Table 7-1.) [5]. But endemic regions of HFRS are different from those of CCHF [8].

### 7.2.1. Mode of transmission

Although, the main source of infection during the 2001 CCHF epidemic was tick bite (58%), there were five secondary cases reported [19]. From the second registered CCHF case during this epidemic, three hospital-acquired infections were confirmed and, in addition, two intrafamiliar cases occurred. One case in each group was fatal. No tertiary cases were detected. The viral RNA sequences obtained from the acute sera samples from these nosocomial cases were analyzed. Phylogenetic relationship determined that the causative agent was a CCHFV, which is closely related to the Drosdov strain [5]. Similar observation was reported by Papa and coworkers in a case from Kosovska Mitrovica in


*Fig. 7-2.* Map of Kosovo. Highlighted municipalities have the highest incidence of CCHF.

Kosovo which occurred during the same epidemic in 2001. The physician who had treated the index patient on admission to the hospital was infected [26]. In the CCHF outbreaks and epidemics described above, a large proportion of cases were found among health-care workers and relatives of patients. Therefore, prompt confirmation of the diagnosis in the first suspected case(s) is important for the treatment of patients, protection of medical staff, and prevention of larger outbreaks [6, 29]. Additionally, since the early clinical manifestations of CCHF and HFRS are virtually identical, rapid microbiological diagnosis of suspected cases is mandatory for distinguishing these two hemorrhagic fevers, mainly in the areas such as Kosovo, where both diseases

coexist. In our experience, the combined use of real-time PCR for the detection of viral RNA and a serological assay for the detection of specific IgM antibodies are the approaches of choice for a rapid and specific diagnosis of acute CCHF [10]. A similar experience was reported by Drosten and coworkers who described a case from 2000 in Kosovo, with complete clinical, laboratory, and virological results. The viral RNA sequence obtained from the patient's serum sample drawn on day 3 of illness revealed the presence of a distinct strain of CCHFV circulating in the Kosovo Black Sea region [9].

### 7.2.2. Reservoirs and vectors

Three years after the 1970 outbreak, 269 ticks were collected from the cattle in the region where the disease had appeared and three strains of CCHFV were recovered. Two strains, designated "Čiflik 1" and "Čiflik 6", were isolated from the tick pools of *H. marginatum marginatum* and one strain "Čiflik 11" from the pool of *Ixodes ricinus* ticks [13]. During the 5-year period of 1973–1978, 691 sera were collected from the livestock in four different localities in Kosovo and Macedonia. The presence of CCHF antibodies was found on average in 14% of animals in a range from 2.3% to 32.6% in 1977 [14]. The highest prevalence of specific antibodies (32.6%) was found in sheep. While the prevalence in older cattle was 15.4%, calves were found positive in only 4.3% [24]. These data suggest that domestic animals, especially sheep and cattle, should be considered the principle host of adult ticks – the vectors of the virus. The ticks were collected from the domestic animals that were investigated for the presence of CCHF antibodies. Of 1,816 ticks examined, *H. marginatum marginatum* was found to be the most frequent in the region surveyed (58%), followed by the *Rhipicephalus bursa* (27.7%), *Boophilus calcaratus* (9.1%), *I. ricinus* (4.8%), and *Haemophysalis punctata* (0.4%) [24]. At the time of the 2001 epidemic the ticks were collected from pasturing cows owned by some patients. From the tick specimens collected, 267 were *H. marginatum marginatum*, four *Rhipicephalus sanguineus*, and one *Boophilus* sp. Among 272 ticks collected from 28 cows, 43 (15.8%) ticks of *H. marginatum marginatum* were determined to be infected with CCHFV. Amplicons obtained by using conventional RT-nested PCR were sequenced and the sequences from ticks were compared with the sequences from CCHF patients from different regions in Kosovo. The sequences from the ticks were identical, and the observed similarity between the sequences from ticks and patients was 98.6–100% [10]. These data again confirm that *H. marginatum marginatum* ticks are implicated in the ecology of CCHF and serve as a principal vector of the virus in this region. All investigated endemic regions of CCHF in Kosovo belong to the type of the Pond Caspian steppe, with dry, hot summers and cold winters, and abundant rainfall. This represents an excellent ecological niche for the ticks of the genus *Hyalomma*, whose seasonal dynamic coincides with the seasonal dynamic of CCHF in Kosovo [17, 19].

### 7.2.3. Treatment of patients

The signs and symptoms of CCHF in Kosovo resemble those described for the disease in other countries. However, there are some minor differences that were observed by the local physicians. For example, the incubation period after a tick bite is usually 7–10 days; whereas, the time to the onset of the disease in nosocomial cases is only 2–5 days. These data are just the opposite to what has been seen in the patients in South Africa [32]. Although inapparent infections and moderate forms are registered in each epidemic or yearly sporadic cases, a severe course of the disease is prevalent. During the 2001 epidemic, on average more than 50% of the patients showed hemorrhagic signs including hematomas (83.3%), petechiae (76.7%), epistaxis (70%), gingival hemorrhage (63.3%), conjunctival injection (63.3%), melena (43.3%), metrorrhagia (13.3%), and hematuria (3.3%). Other prominent clinical signs that were present in more than 80% of the same group of patients include fever, anorexia, vertigo, headache, hepatomegaly, elevated liver transaminases, and hypotension [19]. Similar clinical and/or laboratory observations were described for the sporadic cases from Kosovo [9, 26]. As mentioned above, Kosovo is an area where two viral hemorrhagic fevers coexist, CCHF and HFRS. Their seasonal occurrence is similar and the early clinical manifestations are virtually indistinguishable [1]. Hence, prompt and accurate diagnosis in suspected case(s) is needed, not only to prevent nosocomial spread of CCHF, but also to apply the adequate supportive and replacement therapies that are different for each of the disease. One of the most important reasons for a prompt and accurate diagnosis of CCHF is the specific treatment of patients. It has been shown that a broad-spectrum antiviral drug ribavirin was effective for treating the CCHFV infections [12, 18, 22, 37]. A drawback of ribavirin therapy is the need to administer the drug early in the course of disease, namely within 4 days after the onset of symptoms [22]. Given that specific IgM antibodies against the CCHFV are first detectable about 7 days after the onset of illness, a rapid and accurate diagnosis of CCHF can be made only by an adequate molecular method [10, 30]. Intravenous ribavirin (donation of ICN Pharmaceuticals) was used only in the last six severe CCHF patients at the time of the 2001 epidemic in Kosovo. Ribavirin was not applied during the epidemic peak due to the delayed approval by the Department of Health and Social Welfare. In all six patients, recovery was observed a short time after the initiation of treatment, without any side effects of the drug [1, 8]. Additionally, in a report of nosocomial transmission of CCHFV in a hospital in Belgrade in 2001, oral ribavirin was effective in treating the secondary case [26].

### 7.2.4. Preventive measures

The most often affected populations in CCHF endemic areas in Kosovo are the farmers who work outdoors and own cattle. After the 2001 epidemic, public health measures in the country included continuous information and education about the potential risks of the population who live in endemic areas by using

widespread distribution of printed materials. This included personal protective measures such as regular examination of clothing and skin for ticks, their proper and safe removal, and the use of repellents. Furthermore, people were asked to take every precaution to avoid exposure to virus-contaminated animal blood or tissues. In addition, tick control was started in Kosovo by using acaricide treatment of livestock. But farmers are not consistent in using it adequately. During the 2001 epidemic in Kosovo, three health-care workers were affected as a result of a nosocomial transmission. Among them, two physicians in residence at ENT and a cleaning lady who died 10 days after the onset of the disease. None of them wore gloves. WHO Global Alert and Response Team who assisted in the response of the 2001 epidemic focused on the measures to improve infection control practice and to provide protective equipment and clothing with requisitions for appropriate barrier nursing at the Infectious Disease Clinic of the Pristine University Hospital. Since the 2001 epidemic, a total of 39 CCHF cases have been reported, with no nosocomial transmission.

### 7.3. BULGARIA

CCHF was first recognized in the country in early 1950 and became a notifiable disease in 1953. By retrospective analysis, at least 10 CCHF cases from three localities were hospitalized in the Burgass district from 1946 to 1952. In the period from 1953 to 1974, 1,105 sporadic cases were recorded with morbidity rate of 0.71% and mortality rate of 17.2% [17]. An immunization program was introduced in 1974 to protect health-care workers and military personnel in known endemic areas. Hence, from 1975 to 1996, the number of reported cases was reduced to 279, with a CFR of 11.4% [27]. Since 1997, a total of 170 sporadic cases have been reported to the Bulgarian Ministry of Health (MOH), 37 of them were fatal (Table 7-2) [7]. After the isolation of CCHFV from the blood of two patients in 1968, broad investigations of CCHF began in Bulgaria. The results from serologic survey showed the presence of asymptomatic infection in humans [34]. The degree of seropositive persons varied in different localities, but it was approximately 18% in humans tending cattle. In a 5-year study on CCHF

*Table 7-2.* Confirmed cases of CCHF in Bulgaria from 1997 to 2005

| Year | No. of cases | No. of fatal cases | Mortality rate (%) |
|---|---|---|---|
| 1997 | 20 | 4 | 20 |
| 1998 | 15 | 3 | 20 |
| 1999 | 5 | 2 | 40 |
| 2000 | 10 | 1 | 10 |
| 2001 | 18 | 5 | 27.8 |
| 2002 | 56 | 12 | 21.4 |
| 2003 | 14 | 2 | 14.3 |
| 2004 | 18 | 6 | 33.3 |
| 2005 | 14 | 2 | 14.3 |

in endemic regions, antibodies were detected in 9.1% of 580 people bitten by ticks, in 7.5% of 5,398 persons involved in raising cattle, and in 0.5% of other labor groups residing in these foci [17]. Most cases were reported from Plovdiv (central Bulgaria), Haskovo and Kardgali (southeastern Bulgaria), Shumen (northeastern Bulgaria), and Burgass (eastern Bulgaria) (Fig. 7-3) [34].

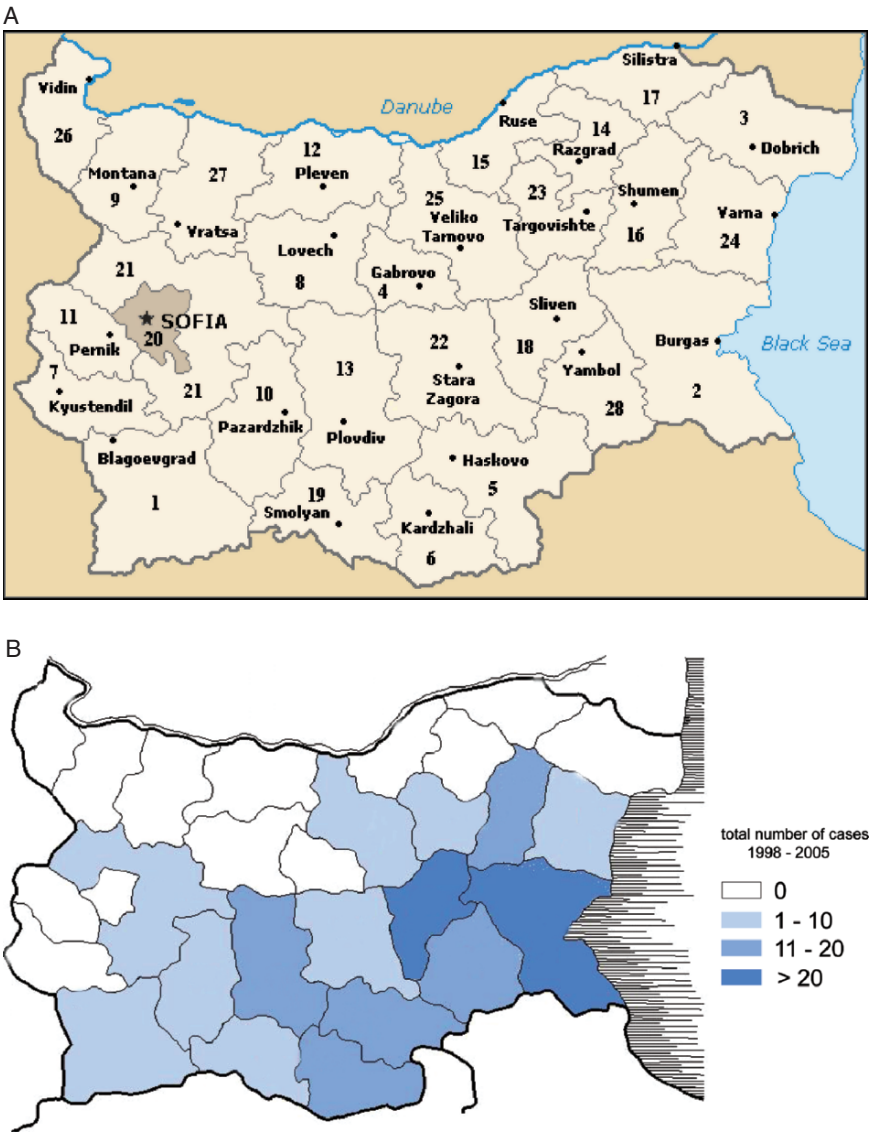


*Fig. 7-3.* (A) Map of Bulgaria showing the 28 provinces. (From www./Wikipedia.org.) (B) Geographical distribution of CCHF cases in a period from 1998 to 2005. (Courtesy of Dr. W. Monev, NCIPD, Sofia, Bulgaria.)

### 7.3.1. Mode of transmission

Most patients have been bitten by a tick; therefore, ticks are considered as the main source of infection. However, infections through a direct contact with CCHF patients also occurred. In the period from 1953 to 1965, 42 CCHF cases with 17 fatalities were caused by nosocomial infection in hospital [17]. There is no evidence of exposures of patients to the blood of infected animals or to the infection by the slaughter of livestock. Based on the available literature, there is no data of possible infection occurring in laboratory personnel.

### 7.3.2. Reservoir and vectors

Most of Bulgaria is an ecologically favorable environment for CCHFV circulation. Increased chances for human–tick contact and other ecological and climatic factors, during the 1950–1960 period of agricultural collectivization, provided the opportunity for a serious CCHF epidemic to develop. The seasonal dynamic of CCHF, appearing in April, reaching its peak in June, and disappearing in October is followed by a month of the seasonal dynamic of adult *H. marginatum marginatum* ticks [17]. Between 1968 and 1972, the CCHFV was isolated from human patients and from *H. marginatum marginatum*, *R. sanguineus*, and *Boophilus annulatus* ticks. In an early study in Bulgaria, it was shown that cattle were the chief host of adult *H. marginatum marginatum*. This tick species represented 90% of the 4,856 ticks taken from cattle, of the 1,278 ticks from horses, and of the 431 ticks from sheep. The results from this early investigation in Bulgaria showed that the prevalence of antibody to CCHFV in the sera of sheep is 28%, in cattle 47%, and in horses 82% [17]. When Levi performed entomological study in an endemic CCHF region in central Bulgaria (Pazardzhik), European hare, little owl, and blackbirds were found as the main hosts of the immature stages of the *H. marginatum marginatum* ticks. He further described that earlier detaching nymphs molt into adults in the hot Bulgarian fall and over winter before feeding; later detaching nymphs remain over winter in the fed state and molt the following spring [21]. Some other tick species, such as *Dermacentor marginatus*, *H. punctata*, and *I. ricinus*, were shown to maintain enzootic circulation of CCHFV in some areas. The virus has not been isolated from the common field mouse or other rodents and insectivores which are numerous in Bulgarian CCHF areas and are also known as tick hosts [17].

### 7.3.3. Treatment of patients

During the period from 1975 to 1996 mean age of patients registered was 52 years (range 11–79 years). Most patients were men (74%) because they were more frequently exposed to tick bites during the outdoor activities. The disease occurs in general from March to July which is in accordance with the ticks' activity. The main clinical symptoms include: fever, malaise, nausea, epistaxis, petechiae, and

bleeding, mainly from gastrointestinal tract [27]. Pronounced laboratory findings were leukopenia, thrombocytopenia, and elevated liver enzymes. The Institute of Infectious and Parasitic Diseases in Sofia, Bulgaria, prepared a human immunoglobulin against CCHFV. The preparation was made of the plasma of donors boosted with one dose of vaccine against CCHFV. Forty units were defined as the potency of 1 mL of specific immunoglobulin preparation, with an immunodiffusion titer of 1:4. It was suggested to use a dose of 1,500 units for a passive immunization against CCHF and an administration of a single dose of 3,000 units for the therapy of CCHF [36]. There is very little, and often vague, information available on the efficacy of this immunoglobulin preparation. Namely, the authors claimed that the intravenous immunoglobulin preparation, designated as "CCHF-Venin", was successfully used in seven CCHF patients in the summer of 1989. The patients recovered quickly after the administration and their bleeding tendency ceased. No side effects were observed. However, the described study lacks a control group of patients [35]. There is no information available on the temporary use of the "CCHF-Venin" for the treatment of patients in Bulgaria.

### 7.3.4. Preventive measures

Various preventive measures are used in Bulgaria to protect against CCHF. The treatment of livestock with acaricide is a widespread practice in the country, although it may be impractical due to extensive farming conditions which prevail in the areas where *Hyalomma* ticks are the most prevalent. It seems that public health measures including information and education of the residents in high endemic areas about the potential risks of infection are effective [7]. Based on the registry of the MOH, it is obvious that the incidence of CCHF in Bulgaria decreased significantly after the introduction of immunization program for medical workers and military personnel in 1974 using the inactivated vaccine made by Vassilenko in 1970. The vaccine was subsequently given to 583 volunteers in 1970 and 1971; it was concluded that the vaccine was highly efficient [17]. This vaccine consists of mouse brain preparation inactivated by chloroform, heated at 58°C, and adsorbed on $Al(OH)_3$. The first two doses are given on days 0 and 30, the third dose is given 1 year later, and another, a booster dose, 5 years later [33]. As a result of specific immunization, the morbidity rate due to the CCHFV has visibly dropped. No infections have been reported from vaccinated military personnel since the immunization program began [20].

## 7.4. ALBANIA

In Albania, a country which is situated in the southwestern part of the Balkan Peninsula (Fig. 7-4), the first CCHF case was recognized in 1986. Since then, a number of cases have been reported each year. The majority of cases have

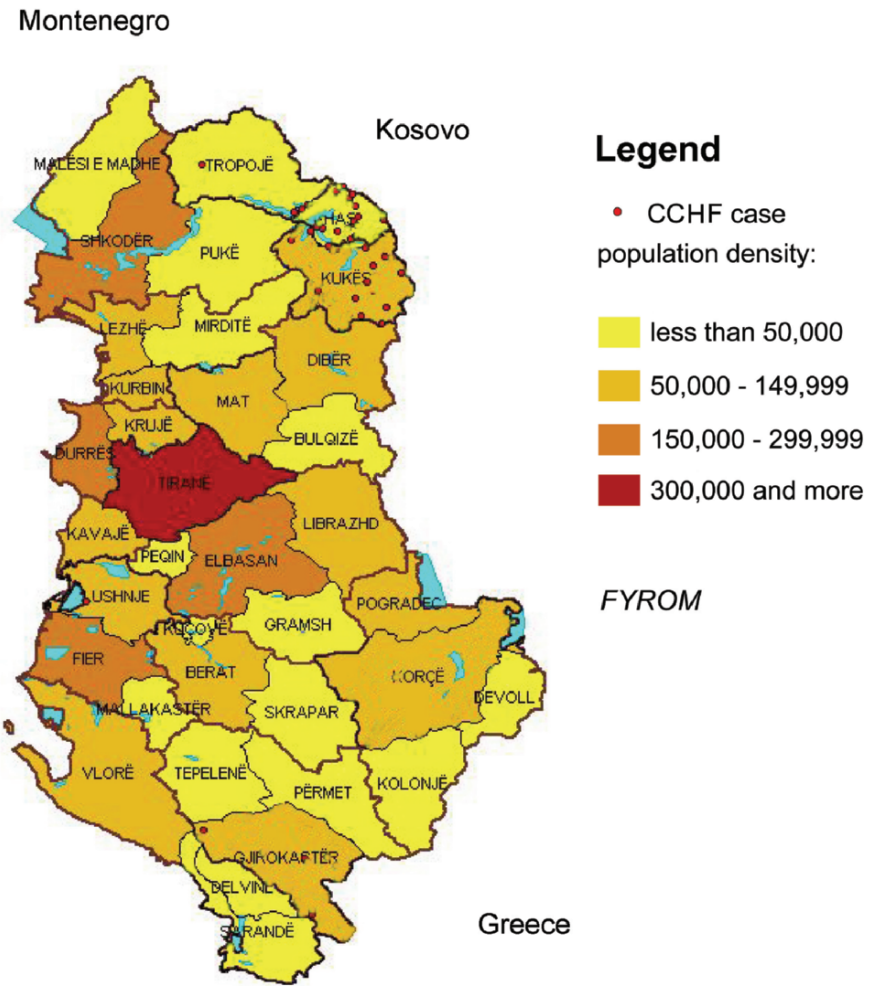


*Fig. 7-4.* Map of Albania showing the geographical distribution of CCHF cases in 2003 and 2004. (Courtesy of Dr. S. Bino, PHI, Tirana, Albania.)

been observed in Kukes area, in the northwestern part of the country. But sporadic CCHF cases have been reported throughout the country, including Tirana, Mirdita, Lezha, Gjirokastra, and Skapar [11]. From the end of May to September 2001, eight cases of CCHF were identified in Albania. Most of the cases (7 of 8) were recorded in the Kukes area, as was also the case in previous years. None of the patients died during this outbreak [25], although the mortality rate of the disease in the years 1985–1987 was as high as 16.6% [11].

### 7.4.1. Mode of transmission

For the 2001 outbreak, it is obvious that the main source of infection was tick bite or a lifestyle that included tending livestock. In the same outbreak, a cluster of three cases within a family was also reported [25]. However, person-to-person infections had been documented earlier in Albania. Furthermore, Eltari showed that, out of 233 sera from healthy population, 1.3% had antibodies to CCHFV [11]. During the 2001 community outbreak, one nosocomial infection was observed. The patient was a male nurse who was infected while performing an electrocardiogram on a patient, hospitalized with a diagnosis of acute hemorrhagic syndrome (that was later confirmed to be CCHF). The nurse's skin apparently intact was exposed to the patient's vomit (hematemesis) [15].

### 7.4.2. Reservoirs and vectors

Although there is no data available on the reservoirs or the vectors of CCHFV in Albania, we can presume that the ticks of the genus *Hyalomma* serve as the main vector. Similarly as elsewhere in southern Balkan Peninsula, owing livestock and performing outdoor pasture is a common lifestyle. During the outbreak of 2001, the tick population was extremely high. This was due to an optimal climatic condition, such as mild winter which allowed ticks to survive. In addition, the early arrival of spring accelerates tick activity. The same phenomenon was observed in 2001 in a neighboring country Kosovo [8].

### 7.4.3. Treatment of patients

The clinical presentation of the disease in Albania is in accordance with the one seen in the rest of the Balkan countries. In the above-mentioned outbreak, five out of eight patients had petechiae and severe hemorrhagic manifestations. Most of the cases displayed marked thrombocytopenia. The median age of the patients was 28 years (range 8–66 years). The disease lasted approximately 2 weeks [25]. When necessary, the patients received symptomatic treatment, consisting of replacement of blood components and use of corticosteroids [15]. Ribavirin was not used as postexposure prophylaxis or as a drug for treatment. No fatal case was reported in the 2001 outbreak.

## 7.5. GREECE

So far, CCHF has not been diagnosed in humans in Greece, although the virus was isolated from *R. bursa* ticks, collected in May 1975 from goats of a flock in Vergina village, 80 km west of Thessaloniki. During the 5-year period from 1971 to 1976, 118 tick pools were collected from goat, sheep, and cattle. The most abundant tick species was *R. bursa* (31 tick pools), followed by *R. sanguineus* (23 tick pools), *Ixodes gibosus* (16 tick pools), and *Hyalomma anatolicum* (15 tick

pools), respectively. Using the agar gel precipitation assay and the above-mentioned CCHFV strain, designated as AP92, antibodies were detected in 139 of 422 (32.9%) goat sera and in 34 of 294 (11.6%) sheep sera collected in numerous locations in northern Greece [28]. Sixty-five sera from lifelong residents of the county, where the virus was recovered, were tested for the presence of antibodies against CCHF in 1980–1981. Four residents (6.1%) were found positive. The mean age of seropositive persons was 56 years (range 35–72 years) [3]. The results from a broad serosurvey study, which included 3,040 serum samples from apparently healthy residents from 26 of 54 counties in Greece, revealed an overall prevalence of 1.1% with a range from 0% to 6.3%. With an attempt to confirm the existence of the disease in Greece, 409 serum samples were taken from patients with clinical picture resembling CCHF. None of the patients were found positive [2]. The presence of CCHFV in ticks and seropositive individuals in Greece without any recognized disease is unique in the Balkan Peninsula.

## REFERENCES

1. Ahmeti S (1991) Virusne hemoragijske groznice na Kosovu 1986–1989 – nova tumacenja patogeneze i klinickih manifestacija bolesti (Thesis in Croatian). In: Medical Faculty. University of Zagreb, Zagreb, p 130
2. Antoniadis A, Alexiou-Daniel S, LeDuc JW, Peters CJ (1988) Crimean-Congo Hemorrhagic Fever in Greece. In: 1st International Symposium on Hantaviruses and Crimean-Congo Hemorrhagic Fever Virus, Halkidiki, Greece, p 48
3. Antoniadis A, Casals J (1982) Serological evidence of human infection with Congo-Crimean hemorrhagic fever virus in Greece. Am J Trop Med Hyg 31:1066–1067
4. Avsic-Zupanc T, Ahmeti S, Petrovec M, Rossi CA (1999) Retrospective analysis of an outbreak of Crimean-Congo hemorrhagic fever in the Kosovo during 1991–1992. Am J Trop Med Hyg 61:318–319
5. Avsic-Zupanc T, Petrovec M, Duh D, Dedushaj I, Ahmeti S (2002) Description of nosocomial and intrafamiliar spread of CCHF in Kosovo during the 2001 epidemic. In: The World of Microbes. EDK, Paris, France, Paris, 27th July to 1st August 2002, Le Palais des Congres de Paris, p 87
6. Burt FJ, Leman PA, Smith JF, Swanepoel R (1998) The use of a reverse transcription-polymerase chain reaction for the detection of viral nucleic acid in the diagnosis of Crimean-Congo haemorrhagic fever. J Virol Methods 70:129–137
7. Christova I (2006) Epidemiology of CCHF in Bulgaria (personal communication)
8. Dedushaj I (2001) Epidemics of CCHF in Kosovo (personal communication)
9. Drosten C, Minnak D, Emmerich P, Schmitz H, Reinicke T (2002) Crimean-Congo hemorrhagic fever in Kosovo. J Clin Microbiol 40:1122–1123
10. Duh D, Saksida A, Petrovec M, Dedushaj I, Avsic-Zupanc T (2006) Novel one-step real-time RT-PCR assay for rapid and specific diagnosis of Crimean-Congo hemorrhagic fever encountered in the Balkans. J Virol Methods 133(2):175–179
11. Eltari E, Cani M, Cani K, Gina A (1988) Crimean-Congo hemorrhagic fever in Albania. In: 1st International Symposium on Hantaviruses and Crimean-Congo Hemorrhagic Fever Virus, Halkidiki, Greece, p 34
12. Fisher-Hoch SP, Khan JA, Rehman S, Mirza S, Khurshid M, McCormick JB (1995) Crimean Congo-haemorrhagic fever treated with oral ribavirin. Lancet 346:472–475
13. Gligic A, Stamatovic L, Stojanovic R, Obradovic M, Boskovic R (1977) The first isolation of the Crimean hemorrhagic fever virus in Yugoslavia. Vojnosanit Pregl 34:318–321

14. Gligic A, Stojanovic R, Obradovic M, Boskovic R (1980) Serological examination of Crimean-Congo hemorrhagic fever infections of domestic animals in natural foci. Zbl Bakt Suppl 9:263–266
15. Harxhi A, Pilaca A, Delia Z, Pano K, Rezza G (2005) Crimean-Congo hemorrhagic fever: a case of nosocomial transmission. Infection 33:295–296
16. Heneberg D et al. (1968) Crimean hemorrhagic fever in Yugoslavia. Vojnosanit Pregl 25:181–184
17. Hoogstraal H (1979) The epidemiology of tick-borne Crimean-Congo hemorrhagic fever in Asia, Europe, and Africa. J Med Entomol 15:307–417
18. Huggins JW (1989) Prospects for treatment of viral hemorrhagic fevers with ribavirin, a broad-spectrum antiviral drug. Rev Infect Dis 11 (Suppl 4):S750–S761
19. Humolli I (2003) Epidemiological and serological characteristics of CCHF epidemics in Kosova (Thesis in Albanian). In: Medical Faculty. University of Pristina, Pristina, p 110
20. Kovacheva T, Velcheva D, Katzarov G (1997) Studies on the morbidity of Congo-Crimean hemorrhagic fever before and after specific immunoprophylaxis (article in Bulgarian). Infectology 34:34–35
21. Levi V (1972) Seasonal activity of the ticks of the family Ixodidae in focus of Crimean hemorrhagic fever in Paradzjik region. Suvrem Med 23:44–50
22. Mardani M, Jahromi MK, Naieni KH, Zeinali M (2003) The efficacy of oral ribavirin in the treatment of Crimean-Congo hemorrhagic fever in Iran. Clin Infect Dis 36:1613–1618
23. Obradovic M, Gligic A (1981) Crimean-Congo hemorrhagic fever virus antibodies in people living in natural reservoirs. Vojnosanit Pregl 38:342–346
24. Obradovic M, Gligic A, Stojanovic R, Stamatovic L, Boskovic R (1978) Serological and arachno-entomological investigation of natural foci of Crimean hemorrhagic fever in various regions of Yugoslavia. Vojnosanit Pregl 35:253–256
25. Papa A et al. (2002) Crimean-Congo hemorrhagic fever in Albania, 2001. Eur J Clin Microbiol Infect Dis 21:603–606
26. Papa A, Bozovi B, Pavlidou V, Papadimitriou E, Pelemis M, Antoniadis A (2002) Genetic detection and isolation of crimean-congo hemorrhagic fever virus, Kosovo, Yugoslavia. Emerg Infect Dis 8:852–854
27. Papa A, Christova I, Papadimitriou E, Antoniadis A (2004) Crimean-Congo hemorrhagic fever in Bulgaria. Emerg Infect Dis 10:1465–1467
28. Papadopoulos O, Koptopoulo G (1980) Crimean-Congo hemorrhagic fever (CCHF) in Greece: isolation of the virus from *Rhipicephalus bursa* ticks and a preliminary serological survey. In: Vesenjak-Hirjan Jea (ed.) Arboviruses in the Mediterranean Countries. Gustav Fisher Verlag, Stuttgart, Yugoslavia, pp 117–121
29. Rodriguez LL et al. (1997) Molecular investigation of a multisource outbreak of Crimean-Congo hemorrhagic fever in the United Arab Emirates. Am J Trop Med Hyg 57:512–518
30. Shepherd AJ, Swanepoel R, Leman PA (1989) Antibody response in Crimean-Congo hemorrhagic fever. Rev Infect Dis 11 (Suppl 4):S801–S806
31. Stamatovic L, Panev D, Gerovski V, Miladi-Novic T, Grdanoski S, Radovic S (1971) Epidemija krimske hemoragične groznice. Vojnosanit Pregl 28:237–241
32. Swanepoel R et al. (1987) Epidemiologic and clinical features of Crimean-Congo hemorrhagic fever in southern Africa. Am J Trop Med Hyg 36:120–132
33. Todorov S, Kovacheva T, Velcheva D, Katzarov G (2001) Congo-Crimean hemorrhagic fever-prophylaxis and treatment (article in Bulgarian). Contemp Med 42:54–60
34. Vasilenko S et al. (1971) Investigations on Crimean-Congo hemorrhagic fever in Bulgaria II. Serological examinations of people and animals in endemic and nonendemic areas for CCHF (article in Bulgarian). Epidemiol Microbiol Infect Dis 8:150–156
35. Vassilenko SM, Vassilev TL, Bozadjiev LG, Bineva IL, Kazarov GZ (1990) Specific intravenous immunoglobulin for Crimean-Congo haemorrhagic fever. Lancet 335:791–792
36. Vassilev T, Valchev V, Kazarov G, Razsukanova L, Vitanov T (1991) A reference preparation for human immunoglobulin against Crimean/Congo hemorrhagic fever. Biologicals 19:57
37. Whitehouse CA (2004) Crimean-Congo hemorrhagic fever. Antiviral Res 64:145–160