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# Q Fever in Croatia: War-Induced Changes in Epidemiological Characteristics

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**A B S T R A C T**

*The article describes the epidemiological characteristics of Q fever in Croatia, during the period before and after the Homeland War. In the ten years prior to the Homeland War (1983–1992) 1053 cases of Q fever were recorded, 16.2% (171) of which on islands and in coastal areas. In the period after the Homeland War (1995–2008), a total of 654 cases was recorded, 59.9% (392) of which on islands and in coastal areas. In addition to reduced incidence, geographic distribution of the disease also changed. Before the war, the highest morbidity rate was recorded in the Sisak-Moslavina County. After the war, the Split-Dalmatia County recorded the highest morbidity rate because in the post-war period sheep from Bosnia and Herzegovina went to this county for winter grazing. The disease might be relevant to the Croatian Army and other armed forces that stay in Croatia as part of NATO forces.*

***Key words:*** *Q fever, epidemiology, Croatia*

## Introduction

Q fever is zoonosis, an acute or rarely chronic disease caused by the gram-negative bacterium *Coxiella burnetii (C. burnetii)*[1–3]. The most common reservoirs in the world and in Croatia are domesticated ruminants, primarily sheep, cattle, and goats[4–7]. *C. burnetii* is highly infective in aerosols[7]. In humans, infection usually occurs by inhaling contaminated particles from amniotic fluid or placenta, by contact with contaminated wool or materials contaminated with animal excreta, by ingestion of unpasteurized milk or milk products[4,5,7,8], and, very rarely, through blood transfusion[4,5], the transplacental route[9], or by sexual transmission[10]. About 60% of infections caused by *C. burnetii* are asymptomatic. Acute infection usually presents as a febrile state, pneumonia, or hepatitis, while other organs are less commonly affected. *C. burnetii* pneumonia is rarely fatal, and in such instances there is usually a coexisting condition that contributes to mortality[1–3,6]. Chronic Q fever occurs in less than 1% of infected patients, months or years after initial infection. In its chronic form, Q fever mostly presents as endocarditis, inflammation of intravascular implants, osteoarthritis, and chronic hepatitis[1,4–7]. It is likely that the age at which infection occurs and the dose of the agent determine whether or not Q fever is a mild self-limited febrile illness[3,11]. There are also suggestions that some infections may be totally asymptomatic[1,2,12,13].

Low infectious doses, very high resistance to environmental circumstances and aerogenic transmission make *C. burnetii* a potential agent of Q fever in epidemic proportions. It has military relevance not only in its potential use as a bioterrorism agent, but also because of the risk for natural infection in deployed military personnel.

Q fever epidemics in armies occur occasionally, with a small number of people suffering, but with high morbidity especially in the exposed group. Epidemics do not occur in the barracks, but outside their camps, the training fields, on exercises, etc., usually in the spring-summer months. Epidemics occur only in (sheep) stockbreeding regions and are spread by infective aerosol.

The aim of this study was to describe the changes in epidemiological characteristics of Q fever in Croatia caused by the Homeland War, and to discuss the military implications of the disease.

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## Materials and Methods

Data here analyzed were obtained from the National Institute of Public Health mandatory infectious disease reports that had been published in the Croatian Health Service Yearbook and Epidemiological news[14–16].

Level indicators (rates) and structure indicators (%) were used for data analysis, while dynamics was observed through time series analysis. Statistical analysis was done using GraphPad InStat. Correlation between two variables was calculated using Pearson test, the limit for significance was set to $p<0.05$.

Military implications of the disease were analysed based on our own data and long-term experience in the prevention and control of infectious diseases during the Homeland War (1991–1996) in Croatia.

The epidemiological characteristics Q fever in Croatia were observed in the period before (1983–1992) and after the Homeland War (1995–2008), with special focus on Split-Dalmatia and Sisak-Moslavina counties.

The Split-Dalmatia County is situated in the south of Croatia, on the Adriatic Coast (latitude 43°56´N, longitude 16°04´E to 17°18´E). It is the second largest county in Croatia, with total land (mainland and islands) area of 4,572 km$^2$. The islands and coastal belt, situated beneath the steep slopes of the Dinaric Alps, are characterized by a Mediterranean climate with mild and rainy winters, dry summers and a mean annual air temperature of 16.3°C. The northern, mountainous part is situated in the hinterland, at 380–1000 m above sea level, and has a sub-Mediterranean climate (mean annual air temperature 12.6°C). According to the 2001 census, the county had a population of 463,676 with 1:1.03 male to female ratio[14,16]. The second area observed, the Sisak-Moslavina County, is situated in central Croatia, between mountains Papuk and Gvozd (latitude 45°26´N, longitude 16°16´E). It is the third largest county in Croatia, with total land area of 4,448 km$^2$. This county shares its entire southern border with Bosnia and Herzegovina (B&H). The area is characterized by continental climate with sharp and snowy winters, dry summers and mean annual air temperature of 12.4°C. The northern, mountainous part is situated in the hinterland, at 100 m above sea level, and has a continental climate (mean annual air temperature 8.3°C). According to the 2001 census, the county had a population of 185,387 with 1:1.02 male to female ratio[14,16].

For the purpose of this study, we analyzed and compared the distribution of Q-fever in these two counties, and compared the incidence rates on islands and in coastal areas with the situation in continental areas.

The coastal and islands area includes all islands (1184 islands and reefs) and a narrow coastal belt stretching from Umag in the north (border with the Republic of Slovenia) to Dubrovnik area in the south (bordering Montenegro and Bosnia and Herzegovina). In this study, the rest of Croatia was considered inland area.

## Results

### *Morbidity*

In the ten years prior to the Homeland War (1983–1992) there were 1052 cases of Q fever, 171 (16.2%) of which were recorded on islands and in coastal areas and the rest (881; 83.8%) in continental areas. During that period, average annual incidence in Croatia was 2.2 *per* 100,000 inhabitants. The highest incidence was recorded in 1984 (Mb 4.18 *per* 100,000 inhabitants)[14–16]. Eight epidemics were registered during this period[15].

In the 1991–2008 period there were no epidemics among Croatian soldiers, only sporadic cases[14,15].

The largest outbreak of Q fever in Croatia with more than 300 cases was described in 1984. The outbreak spread over the northern part of Croatia, and the majority of cases were reported between March and May. There was a high degree of space and time coincidence between this outbreak and the presence of nomadic herds and Bosnian sheep and the time of their lambing, which points, with a high degree of probability, to the sheep as the source of infection. Supporting this assumption is the fact that more than 80% of the diseased had some kind of contact with these animals[17].

In the second observed period of 14 years following the Homeland War (1995–2008) a total of 654 cases were recorded, of which 59.9% (392) on islands and coastal area.

**TABLE 1**
DISTRIBUTION OF PATIENTS WITH Q FEVER ACCORDING TO SEX, PERIOD 1983–1992 AND PERIOD 1995–2008

| Area | Number. (%) of cases | | | |
|---|---|---|---|---|
| | Before Homeland War | | After Homeland War | |
| | Male | Female | Male | Female |
| Sisak-Moslavina County | 132 (63.8) | 75 (36.2) | 19 (76.0) | 6 (34.0) |
| Split-Dalmatia County | 18 (90.0) | 2 (10.0) | 172 (85.6) | 29 (14.4) |
| Republic of Croatia | 611 (58.1) | 441 (41.9) | 431 (65.9) | 223 (34.1) |
| p* | 0.006 | | <0.001 | |

* $\chi^2$-test

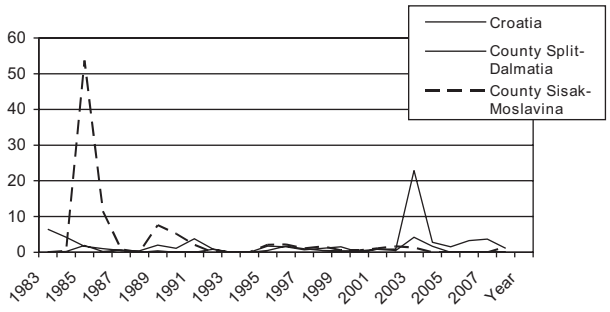


*Fig. 1. Incidence (Mb %ooo) of Q fever in Croatia during the period before (1983–1992) and after (1995–2008) the homeland War.*

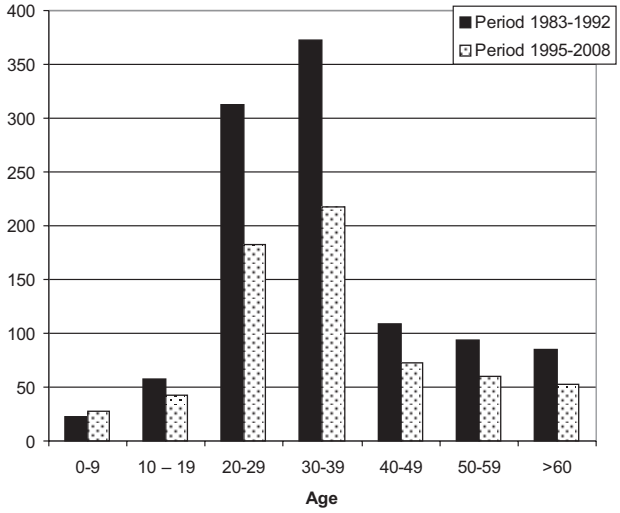


*Fig. 2. Distribution of Q fever in Croatia by age, period 1983–1992, and period 1995–2008*

The total number of cases in that period decreased and the mean annual incidence was 1.05 *per* 100,000 inhabitants. Seven epidemics were registered in that period of time.

In the Sisak-Moslavina County the highest morbidity was recorded in 1985, when it was 53.7 *per* 100,000 inhabitants; in the Split-Dalmatia County the highest morbidity was recorded 2003, when it was 22.9 *per* 100,000 inhabitants (Figure 1). The high morbidity rates were caused by Q fever epidemics, which first occurred in these two regions in the above years.

### *Distribution by age and sex*

The distribution of Q fever by age in Croatia shows no significant differences in either of the two observed periods. All age groups are affected. In both periods, the highest morbidity was recorded in the 20–39 age group i.e. working age people, which is connected to higher exposure (Figure 2).

Gender distribution in both observed periods indicated a male predominance, which is related to higher exposure. In the total number of cases in both periods (1706), there were 1042 males (61.1%). In both periods

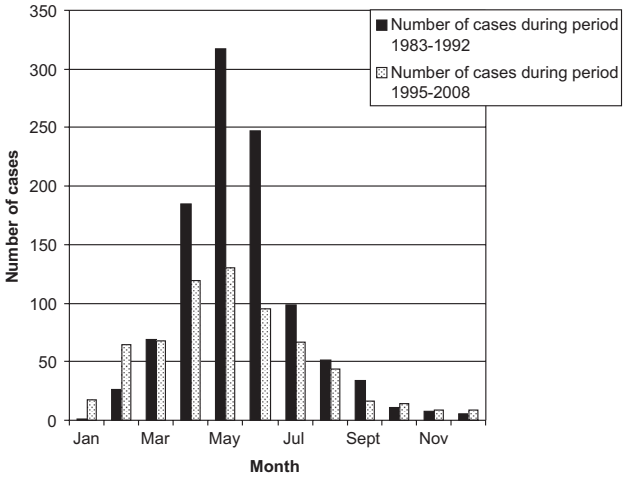


*Fig. 3. Distribution of Q fever in Croatia according to months, period 1983–1992, and period 1995–2008.*

the number of affected males was statistically much higher than the number of affected females (Table 1).

### *Seasonal occurrence*

Seasonal occurrence is a significant epidemiological characteristic of Q-fever. The lowest number of cases is usually recorded in winter, whereas the seasonal peak of the disease occurs in spring months. This is due to the fact that in humans the infection usually occurs by inhaling contaminated particles from amniotic fluid or placenta, and due to the fact that the lambing period is in spring. During the 1983–1992 and 1995–2008 periods, the highest mean numbers of affected individuals were recorded in April, May and June (Figure 3).

### *Geographic distribution*

*C. burnetii* is widely distributed in Croatia, and human cases of Q fever have been reported from almost every county. The mean pre-war incidence in Croatia was 2.2 *per* 100,000 inhabitants. In the period before the war, the highest number of cases was recorded in the Sisak-Moslavina County, with 20 cases more at annual level.

In the post-war period the mean incidence was half that of the previous period (1.1 *per* 100,000 inhabitants) and the highest number of cases was recorded in the Split-Dalmatia County (Figure 4).

## Discussion and Conclusion

Since the first description of Q fever in 1937, the disease has been reported in most countries of the world. In Croatia, Q fever was first described in 1948. Reporting on Q fever has in Croatia been mandatory since 1954[17]. Every year a higher or smaller number of cases is recorded, and 1984 and 2003 were epidemic years[14,15]. Q fever is endemic in the whole rural territory of Croatia, including the coastal area and islands[17–22]. The main reser-

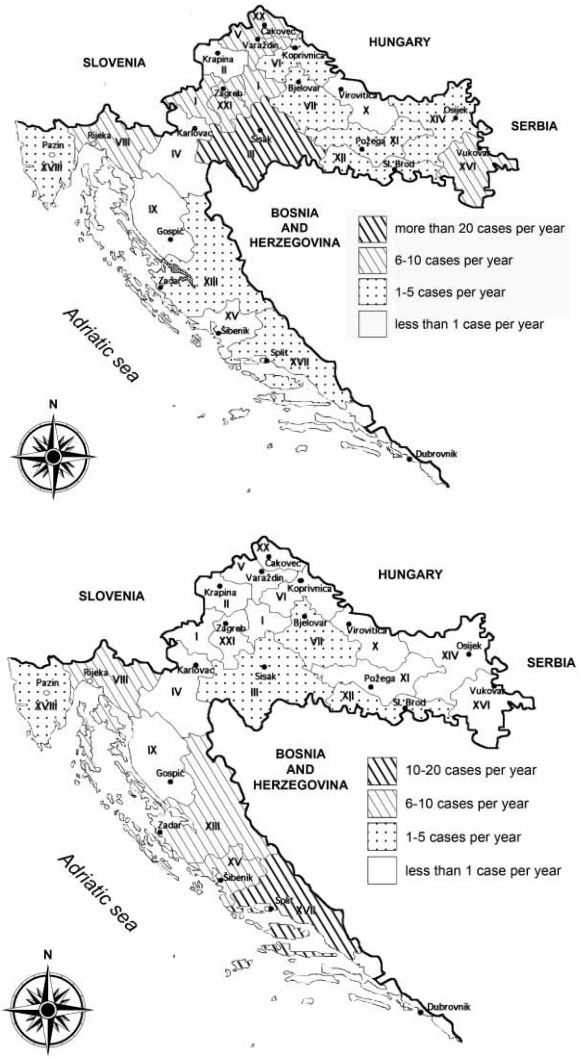


*Fig. 4. Average incidence and distribution of Q fever in Croatia during period 1983–1992 and average incidence and distribution of Q fever in Croatia during period 1995–2008.*

voirs in Croatia are sheep[17,22]. Persons at risk of Q-fever include soldiers, abattoir workers, dairy farmers, workers involved in meat dairy processing and veterinarians. Since the Homeland War Q fever in Croatia usually occurs sporadically[14,15,18].

Before the war in former Yugoslavia, in November and December the sheep went to Croatia for winter grazing, despite the legal regulations prohibiting such practice[17]. In search of winter pastures, tens of thousands of sheep would graze Croatian pastures in the entire continental part of Croatia including Gorski Kotar, which is a predominantly mountainous area. During lambing (from January to March), sheep with latent *C. burnetii* infection secrete huge amounts of the organism into the environment, on pastures and fields, especially from amniotic bands and placent. *C. burnetii* can survive for months as spores, thus presenting a source of infection even for those who are not in direct contact with sheep[17,18,20].

The war for Croatia's independence lasted from 1991 until 1996. Between 1992 and 1995 one third of Croatian territory was occupied; this period was therefore not taken into consideration due to lack of information and insight into disease distribution.

After the war, due to changes in geopolitical relations and the establishment of a »proper« border to Bosnia and Herzegovina, sheep grazing disappeared in that part of Croatia that borders with B&H in the Sisak-Moslavina County. Judging from the incidence of Q fever and the fact that most cases nowadays occur in the Split-Dalmatia County, the sheep cross the border from the south-west, from that part of the border that in Bosnia and Herzegovina is mostly populated with Croatian people. Cross-border winter grazing in Croatia is still illegal because the regulations prohibit such practices, which is why there are no official data on this in expert literature[14,15,17].

Other epidemiological characteristics of Q fever in Croatia, except for geographic distribution, present no changes: seasonal, age and sex distribution of cases remain the same. The highest number of human infections is reported during the spring months, which is to be expected due to higher amounts of infective material.

There are no differences between the age and sex structure of the diseased and the findings described in literature[17–22]. In the population of Croatia, Q fever is present in all age groups. Males predominate, but the highest number of cases is registered in the 20–39 age group because these are persons of working age and the most exposed to infection. Few humans get infected from contact with sheep; most of them probably acquire the infection by simply taking the same roads as the sheep. A description of an epidemic that occurred in Croatia exists, where the infected employees worked in a factory situated in the direction of the northern wind that blew from pastures where sheep had stayed. The clinical picture predominantly showed fever higher than 38°C, headache, arthralgias, myalgias, fatigue, coughing, and crepitation and rhonchi on the lungs[20]. A similar epidemic has been described in a small town in southern France – wind blew through a steppe where sheep gathered after lambing, and persons whose homes were exposed to the wind were more often infected with Q fever than their neighbors[23].

Most patients (50–60%) who are infected with Q fever are asymptomatic[1]. Due to asymptomatic or mild clinical pictures, the disease is often not reported. This results in discrepancies between the real and reported number of cases. The classic presentation is a flulike illness manifested by fevers, sweats, cough (productive at times), myalgias, and arthralgias. The dominant clinical presentation of Q fever is pneumonia. Chest radiograph confirmed the diagnosis of interstitial pneumonia in all hospitalized patients[20]. In Croatia there are descriptions of cases with chronic fatigue syndrome after Q fever[24].

In Croatia, like elsewhere in the world, the clinical picture of acute Q fever predominates and can go unnoticed unless it is followed by pneumonia because of its

similarity to influenza (flu-like syndrome or »febrile condition«)[2,20,24]. About 60% of infections caused by *Coxiella burnetti* are asymptomatic[1,6]. Rare cases of chronic Q fever and Chronic Fatigue Syndrome (CFS) after Q fever have been described in Croatia[18,24]. The diagnostic criteria for CFS include fatigue for six months or more together with at least four of the following symptoms: lack of concentration or/and memory that interferes with normal activities, sore throat, tender cervical or axillary lymph nodes, joint pain without swelling, muscle pain, headache, no refreshing sleep, and malaise lasting longer than 24 hours after exertion[12].

Mortality associated with acute infection is generally low (>1%) but may be as high as 2.4%[1,3–7]. In the observed period when 1706 persons were infected with Q fever in Croatia, no deaths occurred[14,15].

Outbreaks of Q fever commonly occur after lambing because *C. burnetii* is reactivated in ewes during pregnancy. Because of multiplication of *C. burnetii* in the placental villi, high numbers of coxiellae (i.e., as many as one billion organisms *per* gram of placenta) may be present in placenta, amniotic fluid, and fetal membranes[22,25].

Infected birth products can contaminate the ground and dry periods may enhance the formation and propagation of infectious dusts and aerosols. The epidemic that broke out in Croatia in 1983 was investigated and described in detail and was related to the lambing of nomadic sheep from Bosnian areas[17].

### *Prevention of Q fever*

Various preventive measures such as health control, vaccination of animals, adequate disinfection and disposal of animal products containing *C. burnetii* have been implemented to prevent the occurrence and spread of the disease.

The control of Q fever in humans should aim at sources of infection in animals, using either sanitary management or vaccination. Sanitary management applied to populations with low level infection uses »test and slaughter« based on serologic identification of infected animals. Vaccination immunizes young breeding stock before natural exposure, thereby preventing the transmission cycle in the herd. Vaccination of humans at risk of infection (e.g., abattoir workers, veterinarians) should be carried out as soon as a safe vaccine is available[26,27]. An investigational inactivated vaccine, made from infected egg yolk sacs, has been used to protect laboratory workers handling live *C. burnetii*. Human Q fever vaccine is commercially available in Australia and Eastern Europe, but not in Croatia.

Because of the lack of person-to-person spread, there is no need to isolate patients hospitalized with Q fever[1,6,27]. Simple measures, such as the consumption of only pasteurized milk, serve to eliminate cases of Q fever that are transmitted in this manner. In Cyprus, the incidence of *C. burnetii* infection among the sheep and goats was reduced by a program in which aborted material was destroyed, affected dams isolated, and the premises disinfected. Control of ectoparasites on cattle, sheep, and goats is also important in the control of Q fever[28].

In conclusion, Q fever is of reasonable relevance for the general population of Croatia and public health service. It is of more relevance for the armed forces because the whole territory of Croatia is endemic for Q fever. That means real risk for the units in the field, especially during spring-summer period.

Due to the Homeland War, the region with the highest number of Q fever cases »shifted«. Before the war it was in the Sisak-Moslavina County whereas today it is the Split-Dalmatia County.

Due to epidemiological characteristics of *Coxiella burnetii* (highly resistant, the most infectious of all bacteria) regardless of health and veterinary preventive, it is not realistic to expect the eradication of this disease in the near future.

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## Q GROZNICA U HRVATSKOJ: RATOM IZAZVANE PROMJENE EPIDEMIOLOŠKIH KARAKTERISTIKA

### S A Ž E T A K

U radu su opisane epidemiološke osobitosti Q groznice u Hrvatskoj u razdoblju prije i poslije Domovinskog rata. Tijekom deset godina prije Domovinskog rata (1983–1992) u Hrvatskoj je zabilježeno ukupno 1053 oboljela od Q groznice od čega je 171 (16,2%) oboljelih bilo na otocima i priobalju. U razdoblju nakon Domovinskog rata (1995–2008) oboljelo je ukupno 654 osoba od čega 59,9% (392) na otocima i priobalju. Osim pada incidencije, došlo je do promjene zemljopisne distribucije bolesti: prije rata područje s najvišim morbiditetom bila je Sisačko moslavačka županija jer su, za vrijeme bivše zajedničke države, ovce iz Bosne među kojima je bilo dosta njih inficirano Q groznicom, nesmetano prelazile granicu radi ispaše na granici te županije s Bosnom i Hercegovinom. Poslije rata situacija se promijenila. Županija s najvišim brojem oboljelih je Splitsko-dalmatinska, jer se u poslijeratnom razdoblju zimska ilegalna ispaša ovaca iz BiH odvija na području ove županije.