ORIGINAL ARTICLE

UDC: 616-036.22:616.92/.93-022.3
https://doi.org/10.2298/VSP161217034R

Factors associated with maintenance of human Q fever in Vojvodina, Serbia

Faktori koji doprinose održavanju humane Q groznice u Vojvodini, Srbija

Mioljub Ristić*†, Mirjana Štrbac*, Sara Savić‡, Gorana Dragovac*†, Svetlana Ilić*, Snežana Medić*, Branka Vidić‡, Vladimir Petrović*†

***Institute of Public Health of Vojvodina, Novi Sad, Serbia; University of Novi Sad, †Faculty of Medicine, Novi Sad, Serbia; ‡Scientific Veterinary Institute, Novi Sad, Serbia**

Abstract

Background/Aim. Q fever occurs worldwide and can be found in humans as well as in domestic mammals. The aim of this study was to describe the epidemiological characteristics of Q fever and evaluate correlation between the Q fever occurrence and weather conditions. **Methods.** We conducted a descriptive epidemiological study using data of the Institute of Public Health of Vojvodina, Scientific Veterinary Institute, Novi Sad, and the Republic Hydrometeorological Service of Serbia, from 2006 to 2015. **Results.** Out of 272 human Q fever cases, 114 (41.9%) patients were aged between 20 and 39 years. Between January and May, a total of 193 (71.0%) cases of disease were registered. In the Central Banat and South Banat, a strong positive correlation between an increase in Q fever detection and an increase of average wind speed (ρ= 0.69719 and ρ=0.62303, respectively) was observed, while a strong negative correlation was determined between the average rainfall with the number of Q fever cases in the Central Banat, the South Banat and Srem district (ρ = -0.78033, ρ = -0.70675 and ρ = -0.70431, respectively). During a 10-year period, a strong positive correlation was found between the human Q fever cases compared to the number of cattle and sheep Q cases in the Srem district (r = 0.7989 and r = 0.7966, respectively). Direct contact with domestic animals was the most frequent route of Q fever transmission in Vojvodina. **Conclusion.** The timely sharing of information between the animal and human health sectors as well as between neighbouring countries is crucial for an appropriate and an early outbreak response, especially during windy and dry months of the year. Additionally, it is essential that people who are exposed to a risk of infection must be permanently educated about reducing the risk of transmission of infection.

Key words:
q fever; zoonoses; disease outbreaks; risk factors; serbia.

Apstrakt

Uvod/Cilj. Kju groznica je rasprostranjena širom sveta, a otkrivena je kako među ljudima, tako i među domaćim sisarima. Cilj ovog istraživanja je bio da se opišu epidemiološke karakteristike Kju groznice i da se proceni povezanost između pojave Kju groznice i klimatskih uslova. **Metode**. Sprovedena je deskriptivna epidemiološka studija upotrebom podataka Instituta za javno zdravlje Vojvodine, Veterinarskog instituta iz Novog Sada i Republičkog hidrometeorološkog zavoda Srbije, u periodu od 2006. do 2015. godine. **Rezultati**. Od ukupno 272 slučaja humane Kju groznice, 114 (41,9%) pacijenata su bili uzrasta od 20 do 39 godina. Od januara do maja registrovano je ukupno 193 (71,0%) slučaja oboljenja. U Srednjem i Južnom Banatu uočena je jaka korelacija pozitivnog smera između porasta broja obolelih od Kju goznice i porasta prosečne jačine vetra (ρ= 0,69719 i ρ=0,62303), dok je jaka korelacija negativnog smera, između prosečnih vrednosti padavina i broja registrovanih slučajeva Kju groznice, registrovana u Srednjem Banatu, Južnom Banatu i Sremu (ρ = -0,78033, ρ = -0,70675 i ρ = -0,70431). Tokom desetogodišnjeg perioda, utvrđena je i jaka korelacija pozitivnog smera između broja obolelih od Kju groznice i broja obolele stoke, odnosno obolelih ovaca u Sremskom okrugu (r = 0,7989 i r = 0,7966). Direktan kontakt sa domaćim životinjama bio je najčešći put prenosa Kju groznice u Vojvodini. **Zaključak**. Pravovremena razmena informacija između sektora za zdravstvenu zaštitu životinja i sektora za zaštitu zdravlja ljudi, kao i između susednih zemalja, od ključnog je značaja za odgovarajući i rani odgovor na epidemijsko javljanje oboljenja, posebno tokom vetrovitih i suvih meseci u godini. Osim toga, za osobe koje su izložene riziku od obolevanja, neophodno je sprovođenje stalne edukacije o smanjenju rizika od prenošenja infekcije.

Ključne reči:
kju groznica; zoonoze; epidemije; faktori rizika; srbija.

Correspondence to: Mioljub Ristić, Institute of Public Health of Vojvodina, Futoška 121, 21 000 Novi Sad, Serbia.
E-mail: mioljub.ristic@mf.uns.ac.rs

Introduction

Q fever is a zoonosis caused by the gram-negative bacterium *Coxiella burnetii* (*C. burnetii*). Domestic animals are the main source of the infection. Humans are infected mainly through inhalation of aerosolized particles contaminated with *C. burnetii* excreted by an infected animal [1]. The disease is considered as a re-emerging or endemic zoonosis in many countries [2–4], including the Autonomous Province of Vojvodina (Vojvodina), the northern region of Serbia [5].

The disease was registered in many animal species, including mammals, birds and arthropods. In animals, *C. burnetii* infections are generally asymptomatic. However, *C. burnetii* infections in mammals can cause pneumonia, abortions, stillbirths as well as delivery of weak lambs, calves or kids, which are the most frequent clinical signs of the disease [6]. Furthermore, in the majority of cases, abortion occurs at the end of gestation without specific clinical signs. Just before abortion, in the last weeks of pregnancy, massive *C. burnetii* multiplication was detected in placenta, which is the most common source of the infection [7]. Additionally, infected animals shed *C. burnetii* in their feces, urine, milk and birth products. Milk shedding is more frequent and lasts longer in cows and goats than in sheep [6], but sheep shed more and longer in vaginal discharges than goats and can shed bacteria at subsequent pregnancies [8].

The contaminated products form aerosols that can be spread several kilometers by the wind. In contrast with urban areas, where Q fever occurs mainly as sporadic cases, in rural areas diseases usually occur as outbreaks [9].

Q fever is essentially an airborne disease. The predominant mode of spreading the infection occurs after inhalation of aerosols generated from infected placentas, body fluids or contaminated dust resulting from contaminated manure and desiccation of infected placenta and body fluids [10]. Ingestion of raw dairy products is a minor route of transmission. Transmission by direct contact with the skin or mucosal contact with contaminated products and vertical transmission of Q fever are very rare [9, 11, 12]. In humans, about 60% of the Q fever infections are asymptomatic [12]. In accordance with this, and because of the common nonspecific or atypical course of the disease [9], many of human Q fever cases are unrecognized. In patients who develop acute clinical features, Q fever usually presents with fever, chills, and headache (similar to a flu-like disease), or as atypical pneumonia or hepatitis [9, 12]. In about 5% of the cases, disease may become chronic leading to an often fatal endocarditis, chronic fatigue syndrome and repeated abortions [12, 13].

Several studies suggest the role of wind and rainfall in the transmission of the *C. burnetii* between ruminants and from ruminants to humans [14–18].

The aim of this study was to improve our understanding about the epidemiological characteristics of human Q fever in Vojvodina and particularly to determine possible relationships with occurrence of disease and weather conditions as well as to examine the relation between the number of animal and human Q fever cases.

Methods

Study area and population

The Autonomous Province of Vojvodina, with a population of almost 2 million, is located in the northern part of the Republic of Serbia (situated at the crossroads between Central and Southeast Europe). Vojvodina is divided into seven districts and 44 municipalities, and it is bordered by Croatia to the west, the Romania to the east, the Hungary to the north and the Bosnia and Herzegovina to the southwest. It has a multi-ethnic and multi-cultural identity with some 26 ethnic groups and six official languages. Overall, the climate is a moderate continental with a mean maximum temperature in July (the average monthly temperature is 21.4°C) and mean minimum temperature during January (the average monthly temperature is -1.3°C). During the colder part of the year east and southeast wind, koshava, dominates [19].

Collection of data of human Q fever cases

A retrospective, observational study was conducted. Data for this study were obtained from the communicable disease registration of the Centre for Disease Control and Prevention of the Institute for Public Health of Vojvodina (IPH) in the 10-year period (from 2006 to 2015) [20].

Data on human cases were collected as part of the routine system of infectious disease surveillance in Vojvodina. The questionnaire consists of questions that are related to the basic information on socio-demographic characteristics of patients, the date of onset and questions about all clinical signs/symptoms of the disease, hospitalization, and included the data about the potential sources and modes of Q fever transmission. Questionnaires of all registered human Q fever cases were filled by district epidemiologists in six local departments of the Public Health of Vojvodina and by epidemiologists in the Centre for Disease Control and Prevention of IPH.

Laboratory confirmation of human Q fever

All sera samples from the patients with suspicion of Q fever diseases were analysed at the Serbian Reference Laboratory for Q fever, the Center for Microbiology of the Department of Public Health of Zrenjanin. Human Q fever cases were confirmed by enzyme-linked immunosorbent assay (ELISA). Serologic evidence of a positive IgM and/or IgG antibody result to phase II antigen *C. burnetii* was used. Among all of the patients, those results of the first serology tests were equivocal or negative; to obtain a definitive laboratory confirmation of Q fever, paired serum samples at least two weeks apart were performed.

Veterinary data

Veterinary data were obtained from the Scientific Veterinary Institute, Novi Sad. Samples from cattle and sheep were examined during the regular annual reports and monitoring of animal health protection, ordered by the program of measures for each year on the territory of the Republic of Serbia. We provided only veterinary data from the Srem district of Vojvodina.

Laboratory confirmation of animal Q fever

According to the recommendation proposed by the World Organisation for Animal Health (OIE) and Manual of Diagnostic Test and Vaccines for Terrestrial animals (mammals, birds and bees) [21], ELISA method was used for detection of antibodies against *C. burnetii* in blood samples of cattle and sheep.

In addition, for the following purposes such as: identification of populations free from infection, contribution to eradication policies, identification of the prevalence of infection, surveillance and determination of immune status in individual animals or populations post-vaccination, ELISA method was considered as the diagnostic method of choice.

All animal samples were tested in the Scientific Veterinary Institute, Novi Sad.

Meteorological Data

Data on wind speed and rainfall were obtained from the Republic Hydrometeorological Service of Serbia [19].

Monthly average of wind speed and rainfall for the Central Banat, the South Banat and the Srem district were provided. We considered only the strong breeze (≥ 6 Beaufort wind force scale) which is the most common and strongest wind and blows for several consecutive days in Vojvodina.

Data analysis

Through descriptive epidemiological study, data were analysed chronologically, demographically and topographically for the observed period (from 2006 to 2015).

We used the basic statistical indicators, general and specific incidence rates. Incidence rates were calculated using the annual number of registered human cases as a numerator and the number of inhabitants in Vojvodina according to the two Censuses for the Republic of Serbia (2002 and 2011 year) as a denominator and multiplied by 100,000 persons per year.

Spearman's and Pearson's correlation coefficient were used to compare frequencies of qualitative data and determining the direction of association between two continuous variables, respectively. Average values of wind were shown as a monthly value of wind speeds above 6 of Beaufort scale and measured in meters per second (m/s). Average monthly rainfall for the observed 10-year period was measured in millimeters (mm).

Comparisons of categorical data between groups were made by Fisher's exact test (two-tailed). Differences were considered statistically significant if they were $p < 0.05$. Data analysis was performed using the SPSS version 22 software.

Results

Figure 1 summarises the general trend of Q fever incidence in Vojvodina during 2006–2015. A total of 262 serologically confirmed and 10 clinically classified cases of Q fever were reported with the highest incidence rates in 2006 (2.3/100,000) and in 2012 (3.7/100,000).

Most patients in the territory of Vojvodina 258/272 (94.9%,) were registered in three districts of Vojvodina: the Central Banat, the South Banat and Srem. Observing these mentioned districts, with the exception of 2011 and 2012, when cases of Q fever were more frequently registered in the Srem district, the disease was mainly detected in the Central Banat or South Banat districts. Although the outbreak occurrence of human Q fever in three districts registered during four years (2006, 2010, 2012 and 2013), a total of 152/258 (58.9%) patients were classified as sporadic Q fever cases (Figure 2).

Figure 3 presents a number of the registered human Q fever cases in three districts of Vojvodina. Outbreak cases in four outbreaks were predominantly opposite to sporadic human Q fever cases.

Figure 4 shows the age and sex distribution of the patients in Vojvodina. Q fever cases were reported in patients of all age categories older than 10 years. The youngest patient was 13 years old while the oldest one was 89 years old.

During 2006–2015, a majority of confirmed cases were registered among patients in the age groups from 20 to 59 years old, 229/272 (84.2%). A total of 197/272 (72.4%) cases were males. Further, among patients in each of the age group (10–19, 20–29 and 30–39, years), participation of male patients amounted above 80% of all reported cases.

When observing each year individually, over four years (2006, 2011, 2013 and 2015), most cases were registered in April, and in 2007 and 2009, the highest percentage of cases were detected in May. During 2008, 2010, 2012 and 2014 the highest percentage of the reported cases was detected in March, November, January and February, respectively (Figure 5).

Average monthly wind speed and rainfall data over the 10-year period were compared to cumulative total monthly number of human Q fever cases in three districts of Vojvodina (Figure 6). In these three districts, as the average monthly wind speed increased and monthly rainfall declined from February to April, cases of acute Q fever appeared to increase, and then dropped during June to November, when wind speed declined and rainfall increased.

There was a strong positive correlation detected between the increase in Q fever cases and the increase in wind speed in the Central Banat and South Banat (Spearman's $\rho = 0.69719$, $p = 0.01173$ and $\rho = 0.62303$, $p = 0.03045$, respectively), while no significant correlation between the number of Q fever cases compared with the average of the wind speed in the Srem district ($\rho = 0.5498$, $p = 0.06404$) was detected. There a statistically significant negative correlation between the average rainfall and the number of Q fever cases in the Central Banat, the South Banat and Srem ($\rho = -0.78033$, $p = 0.00275$; $\rho = -0.70675$, $p = 0.01017$, and $\rho = -0.70431$, $p = 0.01056$, respectively) was detected.

When the number of sick cattle and sheep was increased after 2011, we noticed the epidemic of Q human fever in 2012 in the Srem district of Vojvodina. Comparison between human Q fever cases with the number of cattle and sheep Q fever cases confirmed cases showing a strong positive correlation (Pearson's $r = 0.7989$ and $r = 0.7966$, respectively) (Figure 7).

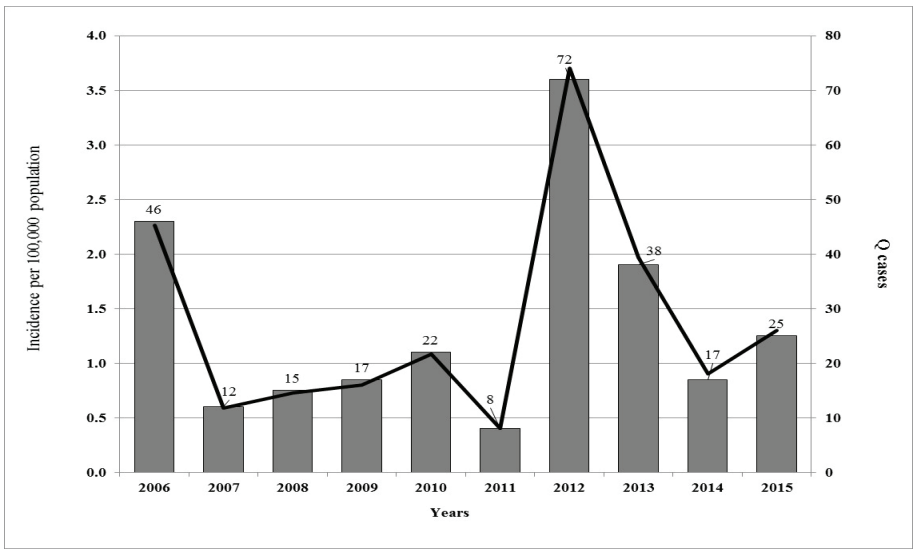

Fig. 1 – Human Q fever incidence in Vojvodina, Serbia, 2006–2015.

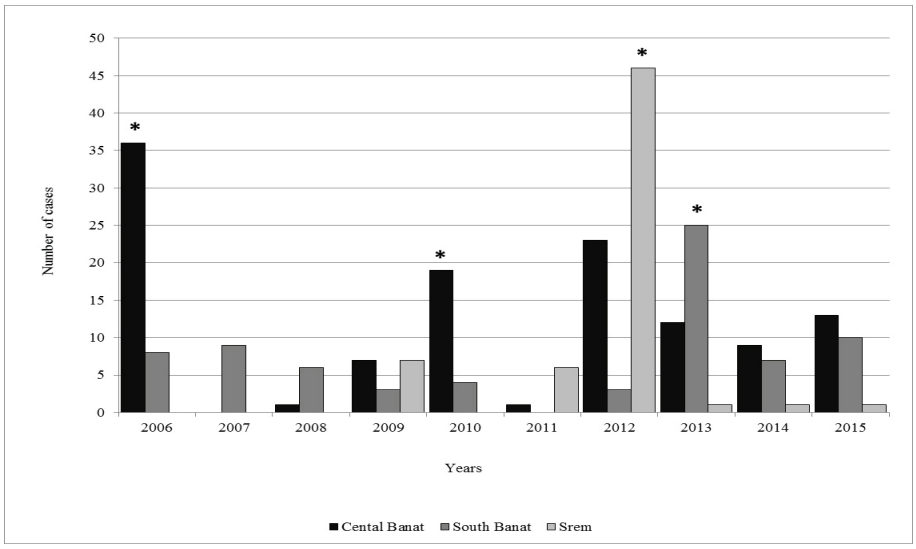

Fig. 2 – Reported human Q fever cases in three districts of Vojvodina, Serbia, 2006–2015. * – indicates the outbreak occurrence by districts and by years.

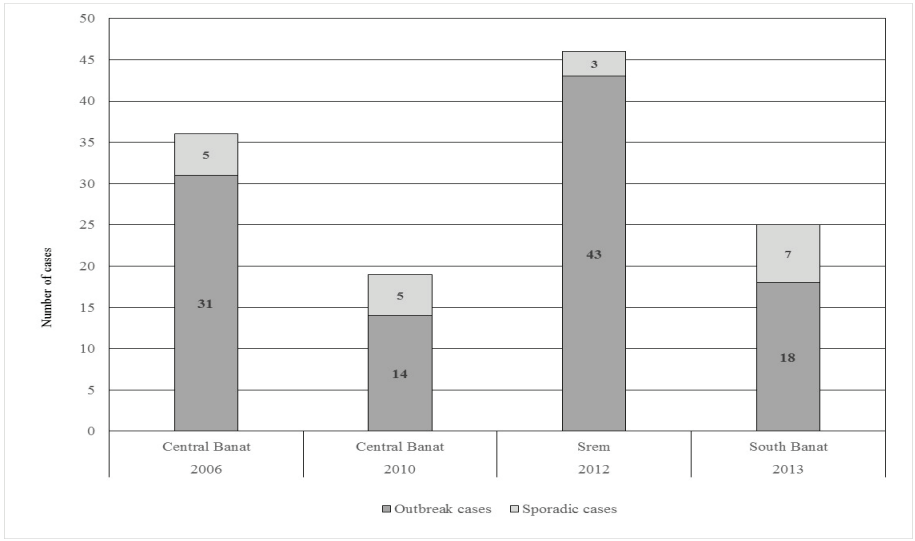

Fig. 3 – Reported human Q fever cases during four outbreak in three districts of Vojvodina, Serbia, 2006–2013.

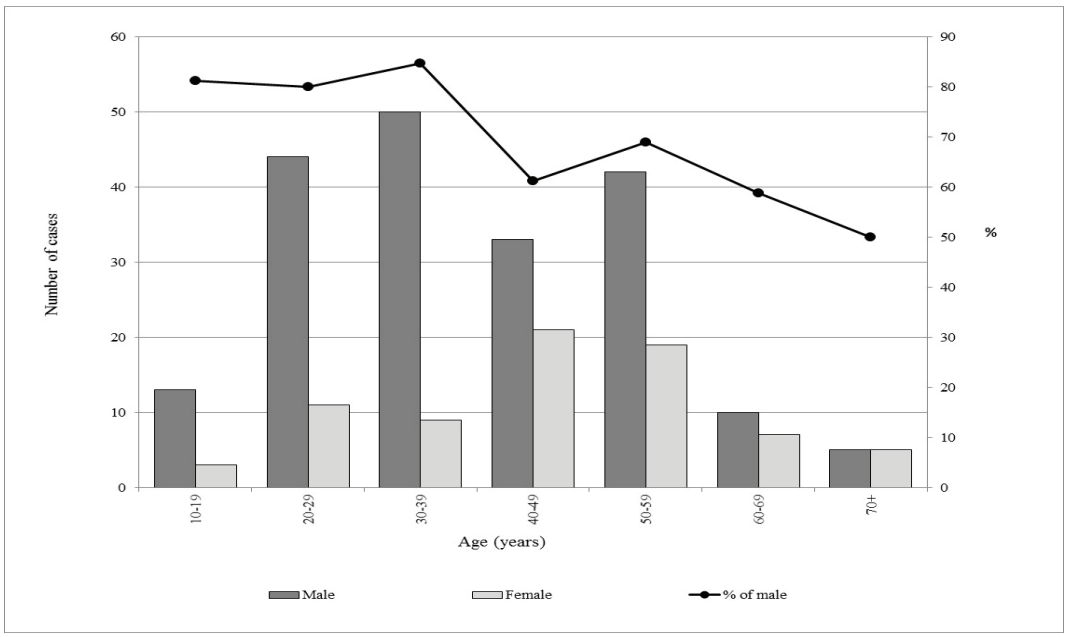

Fig. 4 – Age and sex distributions of Q fever cases in Vojvodina, Serbia, 2006–2015.

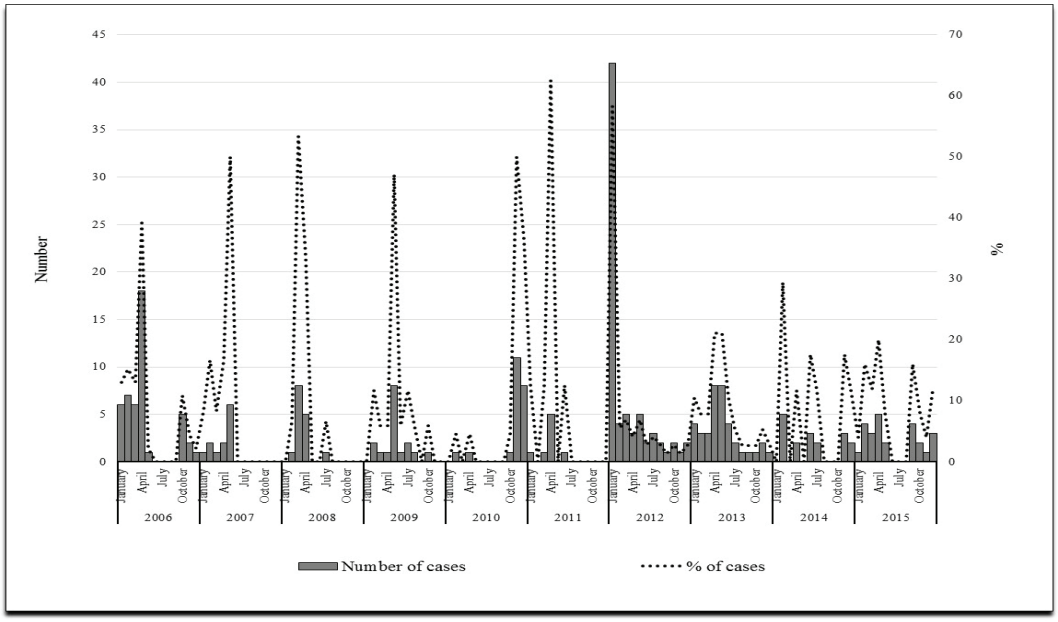

Fig. 5 – Seasonal distribution of human Q fever in Vojvodina, Serbia, 2006–2015.

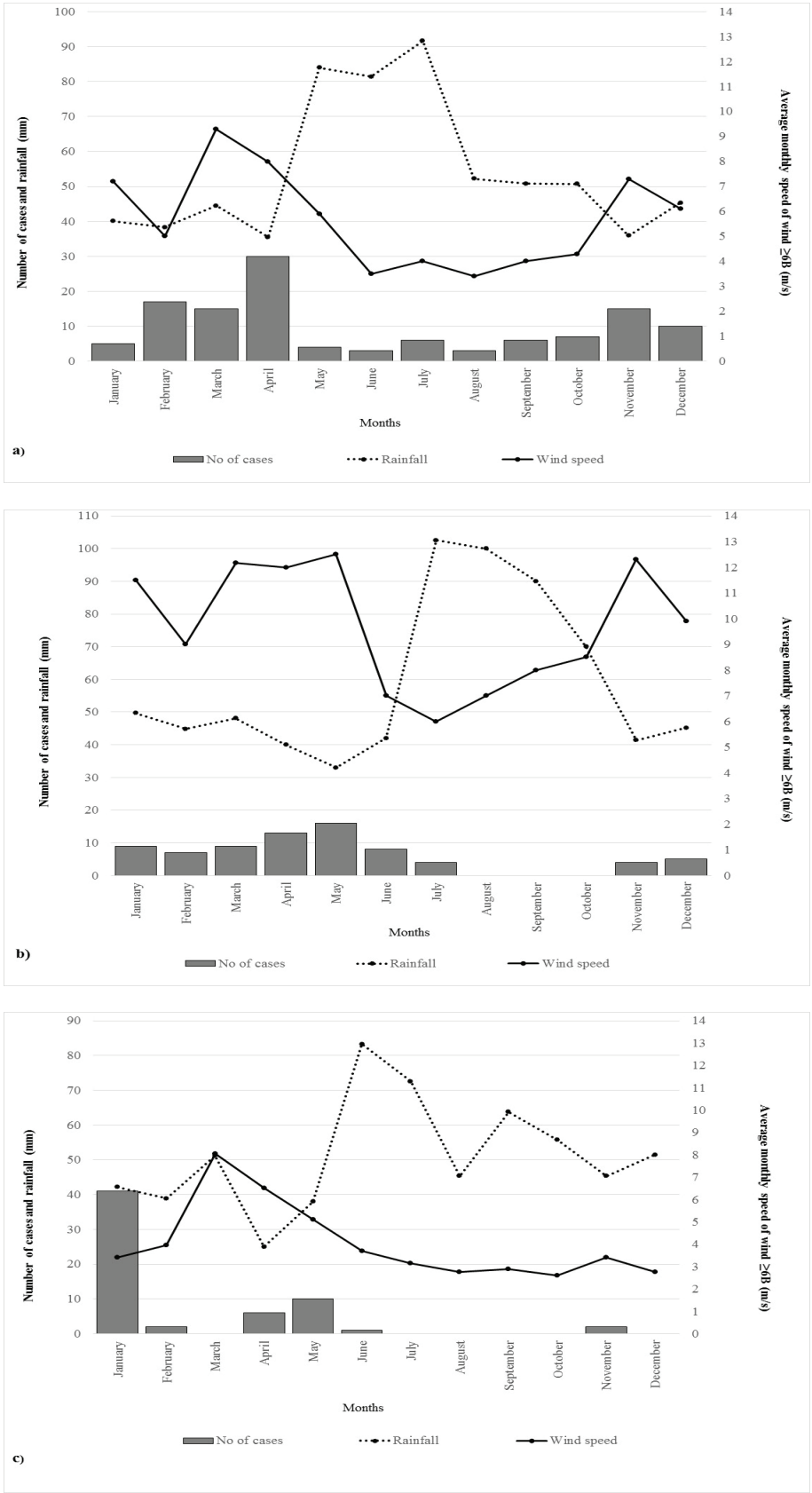

Fig. 6 – Correlation between average monthly wind speed (≥ 6 Beaufort wind force scale) and rainfall with human Q fever cases in three districts of Vojvodina, Serbia, 2006–2015: a) Central Banat, b) South Banat, c) Srem.

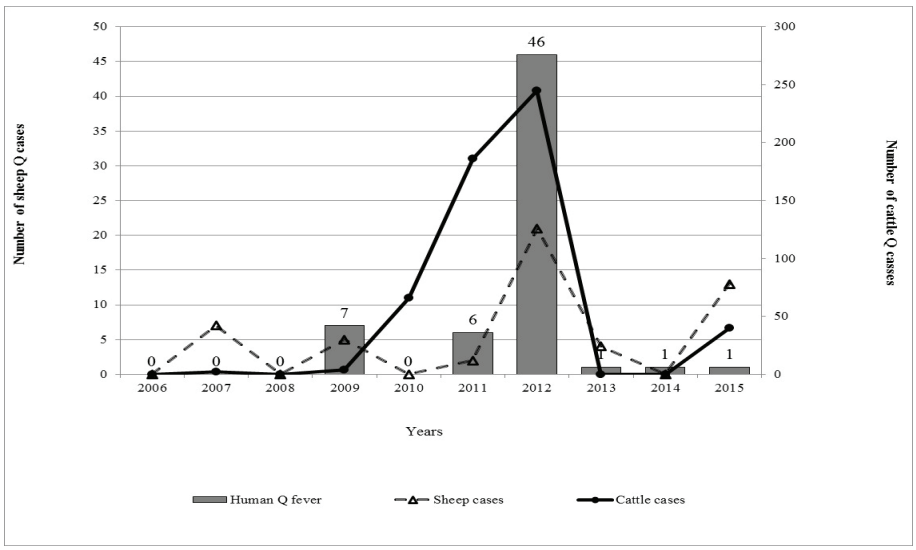

Fig. 7 – Reported human, cattle and sheep Q fever cases in the Srem district of Vojvodina, Serbia, 2006–2015.

Observed hospitalized and outpatients of Q fever cases, revealed no difference between sex and age groups. We found that hospitalized patients were more frequently registered in the South Banat and in urban areas of Vojvodina, while the patients who were more frequently registered at primary health care level (outpatients) were from the Srem district and from the rural areas of the Province. Hospitalized cases with Q fever were more likely to be registered during May-July and outpatients were more frequently detected during November-January (Table 1).

We analysed sources and modes of Q fever transmission from 2006 to 2015 among 236 patients in Vojvodina (Table 2). One half of the total number of cases (120) with available data had direct daily contact with their domestic animals during the maximum incubation period, which was the only possible way of spreading the infection, while every third patient had not been in any contact with animals. Out of the total number of patients, 14.8% cases had a contact with domestic animals in the neighbourhood, but only 2.6% of patients previously consumed cattle milk or sheep cheese. Further, we determined that contacts with domestic animals from the patients' neighbourhood were associated with hospitalization ($p < 0.0001$) (Table 2).

Table 1

Differences among hospitalized and outpatients with Q fever infection in Vojvodina, Serbia, 2006–2015

Characteristics	Total (n = 272)	Inpatients (n = 187)	Outpatients (n = 85)	*p* value*
	n (%)	n (%)	n (%)	
Gender				
male	197 (72.4)	137 (72.3)	60 (70.6)	0.6625
Age group (years)				
≤ 30	74 (27.2)	45 (24.1)	29 (34.1)	0.1056
30–59	173 (63.6)	121 (64.7)	52 (61.2)	0.5888
≥ 60	25 (9.2)	21 (11.2)	4 (4.7)	0.1123
Disctrict				
Srem	62 (22.8)	27 (14.4)	35 (41.2)	< 0.0001
Central Banat	121 (44.5)	79 (42.2)	42 (49.4)	0.2938
South Banat	75 (27.6)	73 (39.1)	2 (2.4)	< 0.0001
South Bačka	1 (0.4)	1 (0.5)	0 (-)	ND
West Bačka	5 (1.8)	5 (2.7)	0 (-)	ND
North Banat	5 (1.8)	2 (1.1)	3 (3.5)	0.1781
North Bačka	3 (1.1)	0 (-)	3 (3.5)	ND
Area				
urban area	98 (36.0)	83 (44.4)	15 (17.6)	< 0.0001
rural area	174 (64.0)	104 (55.6)	70 (82.4)	< 0.0001
Months				
November–January	91 (33.5)	51 (27.3)	40 (47.1)	0.0022
February–April	108 (39.7)	77 (41.2)	31 (36.5)	0.5052
May–July	52 (19.1)	44 (23.5)	8 (9.4)	0.0073
August–October	21 (7.7)	15 (8.0)	6 (7.0)	1.0000

***Fisher's exact test; ND: Not determined.**

Table 2

Sources and modes of Q fever transmission among inpatients and outpatients in Vojvodina, 2006–2015

Sources and modes of transmission	Total (n = 236)	Inpatients (n = 168)	Outpatients (n = 68)	*p* value*
	n (%)	n (%)	n (%)	
Contact with animals	120 (50.8)	71 (42.3)	49 (72.1)	< 0.0001
No contacts with animals	75 (31.8)	57 (33.9)	18 (26.4)	0.2842
Livestock in the neighbourhood	35 (14.8)	34 (20.2)	1 (1.5)	< 0.0001
Consuming cattle milk or sheep cheese produced from uncooked milk	6 (2.6)	6 (3.6)	0 (-)	ND

***Fisher's exact test; ND: Not determined**

Discussion

Epidemiological surveillance of human Q fever in Vojvodina was implemented from 1964. The highest incidence rate of Q fever in Vojvodina was registered in 1976, when 900 human Q fever cases were reported. This was the largest outbreak of Q fever in Europe. After this, Q fever has remained to have an endemo-epidemic character in Vojvodina and until 1990 it was presented as the leading zoonosis in Vojvodina [20]. The main reason for endemo-epidemic maintenance of Q fever was in the fact that the nomadic herds of sheep came from the western regions of former Yugoslavia to Vojvodina, particularly in winter months. This practice was present until 1990, before the Wars in Yugoslavia. Consequently, after the War (1991–1995), a serious decrease of livestock was detected, leading to the significant reduction of the number of human Q fever in Vojvodina (under 5 per 100,000 inhabitants) [22], but interestingly, it increased in the neighbouring countries (Croatia and the Bosnia and Herzegovina) [23, 24].

When observing the data from the European countries (28 Member States and four non-Member States), there was a decreasing trend of confirmed Q fever cases between 2009 and 2013. In 2013, a total of 648 confirmed cases of Q fever in humans were reported in the European countries with a notification rate of 0.17 per 100,000 population, and two deaths due to Q fever were reported by Germany and Latvia [25].

Our results showed that the incidence rate of human Q fever in Vojvodina during the last ten years ranged between 0.4 and 3.7 per 100,000 inhabitants with the evident cyclic incidence peaks which correspond to years in which outbreaks were recognized. Although there were four outbreaks registered, most of the patients in Vojvodina were classified as sporadic human Q fever cases.

Three districts of Vojvodina (the Central Banat, the South Banat and Srem) were identified as the most important endemic Q fever territories, and covered 95% of all registered cases in Vojvodina. Possible explanation for this may be the fact that all three districts bordered with certain neighbouring countries where the endemic Q fever zones were also registered [23, 24, 26]. Thus, the Srem district is bordered by Croatia and Bosnia and Herzegovina, while the Central Banat and the South Banat are bordered by Romania. Using the available data from the World Health Organization report, between 2006 and 2010, the incidence rate of Q fever in Croatia, Hungary and Romania during each year was under 1 per 100,000 inhabitants, while in Bosnia and Herzegovina, it varied from 0.5 to 1.9 per 100,000 population [26]. Further, the explanation for noticeable differences in the number of registered cases across certain districts of Vojvodina is probably because many physicians did not recognize the Q fever in a number of cases, and because of an exchange of livestock fund between these regions. Additional assumptions could be made regarding that the Serbian reference laboratory for confirmation of human Q fever disease is situated in the Central Banat (Department of Public Health of Zrenjanin, Vojvodina), where the largest number of Q fever cases in Vojvodina 121/272 (44%) was identified. Nonetheless, insufficient collaboration between different professions and disciplines, including epidemiologists, microbiologists and veterinarians, in different parts of Vojvodina, can be considered as the reason for the evidence variation of registered human Q fever cases.

It is common knowledge that Q fever among young population has been rarely reported due to the fact that it is manifested as a milder disease or as an asymptomatic infection [27]. In accordance with the above mentioned, we recognized the human Q fever cases only in the patients who were 10 years old and older and the largest number of cases was registered in the economically active citizens in Vojvodina.

Similar to the results of several published studies [1, 28, 29], we found that Q fever in Vojvodina occured more frequently among males than females. We have determined that nearly three quarters of our patients were males. Thus, our findings are in good agreement with the fact that males attributed to risk of occupational exposure, and that females may develop clinical illness less frequently than males because of the protective role of estradiol [30]. However, we did not find a significant difference in gender, between hospitalized and outpatients in Vojvodina.

Q fever infections in humans in Vojvodina were seasonal, with 193 (71%) reported cases in January through May, when lambing, sheep shearing and other activities in which humans are more frequently in contact with potentially infected animals, contributed to the transmission of infection. However, similarly to the findings of other authors [28], we also found that the human Q fever cases were notified throughout the year, suggesting that human Q fever infections may also have non-seasonal influences. Thus, cases in Australia did not show a distinct seasonal trend [31].

So far as it is known, the significance of each domestic animal in the epidemiology of Q fever is different in various regions and it depends on the number of animals, and the level of their infection [1, 10]. Because infection in animals is

usually asymptomatic or limited to abortion and production losses, identifying the source of human infection is sometimes difficult. If the infectious materials contaminate the environment, *C. burnetii* can survive for months, and is resistant to desiccation and temperature extremes [28].

In our territory, cattle and sheep were considered as the main animal reservoirs of *C. burnetii* [20]. Although we covered only the district of Srem in Vojvodina, we first precisely illustrated that the increase and decrease in the human Q fever cases were strongly correlated with a variation in the number of sick cattle or sheep. Similar results were reported by other authors [32, 33]. Besides, some authors suggested that the number of goats was in the positive correlation with the human Q fever cases [1].

As far as we know, this is the first study that demonstrated relationships between values of wind velocity and rainfall with the number of human Q fever cases in our country. Similar to the results of other several studies [15, 17, 18, 33]; our results showed that the spread of *C. burnetii*-infected aerosols was accelerated by low rainfall and high wind velocity. From the observed three districts of Vojvodina (the Central Banat, the South Banat and Srem), we found that the largest number of human Q fever cases were registered during the first four months of the year, when the highest values of wind speed were also registered. Also, during the 2010, when the outbreak of Q fever in the South Banat was registered [20], the largest number of cases was registered in November and December. Although it is known that the South Banat has the highest values of wind speeds in Vojvodina, the average wind velocity in December 2010 was higher than of all other wind speed values which were noticed in the same month through observed 10 years.

In addition, the smallest number of human Q fever cases was noticed between June and October, when the rainfall ranged 42 millimeters to 102 millimeters per month. This period is designated as the rainy part of the year in mentioned districts.

When observing the health care level where the patients were registered, we provided evidence that outpatients were more frequently registered in the Srem district than in the other districts of Vojvodina. We think that the reason for noticed differences could be due to enhanced awareness and better clinical recognition of the disease in the Srem district during outbreak of human Q fever in 2012. Furthermore, in accordance with the fact that the access to the secondary and tertiary health care settings is not equal for all citizens of Vojvodina, the patients in urban area were more likely to be hospitalized than outpatients, while the patients in rural areas were more frequently registered at the primary health care levels.

Although the reason for this is unclear, we have found that the inpatients were more frequently registered during May-July, while the outpatients were more frequently detected during November-January. We think that the reason for determining seasonal predictors for hospitalization perhaps is the fact that during spring and summer months, with the absence of many other acute respiratory infections, physicians become more aware of human Q fever. In accordance with this, they more often refer the patients to secondary or tertiary health care levels for definitive diagnostic confirmation.

The most common route of transmission from infected animals to humans is inhalation of aerosols or dust containing *C. burnetii*. However, we noticed that every third patient in Vojvodina had no contacts with animals and 36% of all human Q fever cases were in urban areas of Vojvodina. Our findings are in good agreement with the previously published evidence that the *C. burnetii* was highly infectious. *C. burnetii* can cause disease with a small inoculum (between one to five microorganisms) [3, 4], and may be transported by the wind far away from its original source [12]. The risk of *C. burnetii* infection in humans is highest within a 5 kilometers radius from the anticipated source [16].

Consumption of unpasteurized dairy products may also result in human infection [28]. In our study, only 2.6% patients previously consumed uncooked animal products.

Human Q fever infection in Vojvodina was previously described as the professional disease, affecting those in contact with livestock such as farmers and veterinarians [20]. However, due to the decline of economic activity, increasing trend of losing work among people who worked with animals, and consequently a reduction of professional exposure to animal potentially infected with Q fever [34], the human Q fever in the last ten years more frequently was registered among adult nonprofessional population in Vojvodina. Nevertheless, our results showed that a large number of human Q fever cases were registered among people in contact with domestic animals, and they presented one half of all other sources of human Q fever infection. Further, our data showed that patients in contact with animals were more frequently registered at the primary health care level (outpatients), while the patients who had contacts with domestic animals in their neighbourhood were associated with hospitalization. A possible explanation for this could be related to the fact that during outbreak years in Vojvodina, as a result of implementation of active surveillance of Q fever, mainly among people in the epidemic areas who had direct contact with domestic animals, a large number of outpatients were registered. Also, the largest number of patients in contact with domestic animals in their neighbourhood was registered during the interepidemic periods, and because they did not visit a physicians in time, they experienced complications as a consequence and they were more often hospitalized than others.

We recognize certain limitations that should be addressed in the future work. First, because most of Q fever infections remain asymptomatic or give nonspecific signs and symptoms, the true incidence rate of human Q fever in Vojvodina is probably higher. Although three districts of Vojvodina were recognized as endemic area in Vojvodina, we believe that many of cases across other four districts were underestimated. Second, despite the fact that we found a positive correlation between available data on the number of human and animal Q fever cases only in the Srem district of Vojvodina, more extensive studies in Vojvodina are required to elucidate this issue. Finally, in our questionnaire we did not predict taking data about the clinical presentation of the disease, and acute or chronic course of infection. Due to the mentioned limitations, we could not determine the final patient outcomes.

Conclusion

A better recognition of human Q fever cases, especially in rural area, can be improved through education of physicians on all health care levels. In addition, the timely sharing of information between the animal and human health sectors as well as among neighbouring countries is crucial for an appropriate and early outbreak response. People who are professionally exposed to a risk of infection must be educated about the disease.

To provide a more precise estimation of incidence rate among the population of Vojvodina, all patients with symptoms compatible with Q fever infection need to be tested or a seroepidemiological study would have to be done to include other asymptomatic cases.

A vaccination strategy for humans with a high risk occupation, and improving the vaccination coverage for animals, especially after the lambing season, can directly contribute to reduction of the number of Q fever cases, hospitalization, complications as well as to prevention of outbreaks in humans in Vojvodina.

Acknowledgments

The authors are grateful to all physicians and all epidemiologists in the local departments of Public Health of Vojvodina who participated in the human Q fever surveillance system in Vojvodina during the last ten years. Our special thanks to Žanka Subić (Department of Public Health of Zrenjanin, Vojvodina, Serbia) and Milica S. Hadnađev-Kostić (University of Novi Sad, Faculty of Technology, Novi Sad, Serbia) for their invaluable contributions to this study.

Conflict of interest

This investigation was carried out as part of routine activities without additional funding sources.

R E F E R E N C E S

1. *Lai CH, Chang LL, Lin JN, Liao MH, Liu SS, Lee HH*, at al. Association of Human Q Fever with Animal Husbandry, Taiwan, 2004-2012. Emerg Infect Dis 2015; 21(12): 2217–20.
2. *de Valk H*. Q fever: new insights, still many queries. Euro Surveill. 2012; 17(3): pii=20062.
3. *Maurin M, Raoult D*. Q fever. Clin Microbiol Rev 1999; 12(4): 518–53.
4. *Palmela C, Badura R, Valadas E*. Acute Q fever in Portugal. Epidemiological and clinical features of 32 hospitalized patients. Germs 2012; 2(2): 43–59.
5. *Medić S, Kaluski DN, Seguljev Z, Obrenović J, Rudan P, Lazarević M,* at al. Q fever outbreak in the village of Noćaj, Srem County, Vojvodina Province, Serbia, January to February 2012. Euro Surveill. 2012; 17(15): pii: 20143.
6. *Lang GH*. Coxiellosis (Q fever) in animals. In: *Marrie TJ*, editor. Q fever, the disease. Boca Raton: CRC press; 1990. p. 23–48.
7. *Sánchez J, Souriau A, Buendía AJ, Arricau-Bouvery N, Martínez CM, Salinas J*, at al. Experimental Coxiella burnetii infection in pregnant goats: a histopathological and immunohistochemical study. J Comp Pathol 2006; 135(2–3): 108–15.
8. *Berri M, Souriau A, Crosby M, Rodolakis A*. Shedding of Coxiella burnetii in ewes in two pregnancies following an episode of Coxiella abortion in a sheep flock. Vet Microbiol 2002; 85(1): 55–60.
9. *Espejo E, Gil-Díaz A, Oteo JA, Castillo-Rueda R, García-Alvarez L, Santana-Báez S,* at al. Clinical presentation of acute Q fever in Spain: seasonal and geographical differences. Int J Infect Dis 2014; 26: 162–4.
10. *Hellenbrand W, Breuer T, Petersen L*. Changing epidemiology of Q fever in Germany, 1947-1999. Emerg Infect Dis 2001; 7(5): 789–96.
11. *Parker NR, Barralet JH, Bell AM*. Q fever. Lancet. 2006; 367(9511): 679–88.
12. *Arricau-Bouvery N1, Rodolakis A*. Is Q fever an emerging or re-emerging zoonosis? Vet Res 2005; 36(3): 327–49.
13. *Hatchette TF, Marrie TJ*. Atypical manifestations of chronic Q fever. Clin Infect Dis 2001; 33(8): 1347–51.
14. *Tissot-Dupont H, Torres S, Nezri M, Raoult D*. Hyperendemic focus of Q fever related to sheep and wind. Am J Epidemiol 1999; 150(1): 67–74.
15. *Tissot-Dupont H, Amadei MA, Nezri M, Raoult D*. Wind in November, Q fever in December. Emerg Infect Dis 2004; 10(7): 1264–9.
16. *Schimmer B, Ter Schegget R, Wegdam M, Züchner L, de Bruin A, Schneeberger PM*, at al. The use of a geographic information system to identify a dairy goat farm as the most likely source of an urban Q-fever outbreak. BMC Infect Dis 2010; 10: 69.
17. *Nusinovici S, Frössling J, Widgren S, Beaudeau F, Lindberg A*. Q fever infection in dairy cattle herds: increased risk with high wind speed and low precipitation. Epidemiol Infect 2015; 143(15): 3316–26.
18. *Harris P, Eales KM, Squires R, Govan B, Norton R*. Acute Q fever in northern Queensland: variation in incidence related to rainfall and geographical location. Epidemiol Infect 2013; 141(5): 1034–8.
19. *Republic Hydrometeorological Service of Serbia (RHMS).* Available from: http://www.hidmet.gov.rs/eng/meteorologija/klimatologija.php [accessed 2016 June 20]
20. *Institute of Public Health of Vojvodina*. Communicable diseases in Vojvodina, 2006-2015. Annual report. Belgrade: Institute of Public Health of Vojvodina; 2016. (Serbian)
21. World Organisation for Animal Health (OIE) 1 & 2, electronic version 2016. chapter 2.1.16. Available at: http://www.oie.int/fileadmin/Home/eng/Health_standards/tahm/2.01.16_Q_FEVER.pdf.
22. *Ćosić G, Đekić J, Đurić P, Šeguljev Z, Petrović M, Rajčević S*. Epidemiological characteristics of Q fever in Vojvodina Province, Serbia, 1985-2009. Arch Biol Sci (Belgrade) 2012; 64(4): 1363-68.
23. *Luksić B, Punda-Polić V, Ivić I, Bradarić I, Bradarić N*. Clinical and epidemiological features of hospitalized acute Q fever cases from Split-Dalmatia County (Croatia), 1985-2002. Med Sci Monit 2006; 12(3): CR126–31.
24. *Punda-Polić V, Radulović S*. Sero-survey of Q fever in the northwestern part of Bosnia and Herzegovina. Croat Med J 1997; 38: 345–47.
25. EFSA and ECDC (European Food Safety Authority and European Centre for Disease Prevention and Control), 2015. The European Union summary report on trends and sources

of zoonoses, zoonotic agents and food-borne outbreaks in 2013. EFSA J 2015; 13(1): 3991.
26. WHO. Centralized information system for infectious diseases (CISID). Available from: http://www.data.euro.who.int/cisid/. 2016.
27. *Maltezou HC, Raoult D*. Q fever in children. Lancet Infect Dis 2002; 2(11): 686–91.
28. *McQuiston JH, Holman RC, McCall CL, Childs JE, Swerdlow DL, Thompson HA*. National surveillance and the epidemiology of human Q fever in the United States, 1978-2004. Am J Trop Med Hyg 2006; 75(1): 36–40.
29. *Monno R, Fumarola L, Trerotoli P, Cavone D, Giannelli G, Rizzo C*, at al. Seroprevalence of Q fever, brucellosis and leptospirosis in farmers and agricultural workers in Bari, Southern Italy. Ann Agric Environ Med 2009; 16(2): 205–9.
30. *Leone M, Honstettre A, Lepidi H, Capo C, Bayard F, Raoult D*. Effect of sex on Coxiella burnetii infection: protective role of 17beta-estradiol. J Infect Dis 2004; 189(2): 339–45.
31. *Garner MG, Longbottom HM, Cannon RM, Plant AJ*. A review of Q fever in Australia 1991-1994. Aust N Z J Public Health 1997; 21(7): 722–30.
32. *Reedijk M, van Leuken JP, van der Hoek W*. Particulate matter strongly associated with human Q fever in The Netherlands: an ecological study. Epidemiol Infect 2013; 141(12): 2623–33.
33. *de Rooij MM, Borlée F, Smit LA, de Bruin A, Janse I, Heederik DJ,* at al. Detection of Coxiella burnetii in Ambient Air after a Large Q Fever Outbreak. PLoS One 2016; 11(3): e0151281.
34. *Španović M*. Trends of the established occupational communicable diseases among workers in the territory of Vojvodina [dissertation]. Novi Sad: Faculty of Medicine, University of Novi Sad; 2016. (Serbian)

Received on December 17, 2016.
Revised on January 31, 2017.
Accepted on February 08, 2017.
Online First March, 2017.