THE FREQUENCY OF Q-FEVER IN FARM ANIMALS IN WESTERN MACEDONIA

Ismije SAITI[*], Kristaq BËRXHOLI[**]

[*] *Faculty of Natural Sciences and Maths, Study Program of Biology, State University of Tetova, Tetovo, Macedonia*
[**] *Department of Veterinary Public Health, Faculty of Veterinary Medicine Agricultural University of Tirana, Tirana, Albania*
Corresponding author: Ismije Saiti, Faculty of Natural Sciences and Maths, Study Program of Biology, State University of Tetova, Tetovo, Macedonia, Ilindenska Str. B.b., Tetovo, Macedonia, phone: +38978246835, e-mail: ismije.saiti@unite.edu.mk

Abstract. The Q fever is a zoonotic disease, caused from *Coxiella burnetii*, an obligate intracellular, pleomorphic coccobacillus possessing a prototypic gram-negative bacterial cell wall structure. The aim of study was to examine the frequency of Q fever in farm animals (sheep, goats and cows) and the frequency variation according to species in five regions in Western Macedonia (Tetovo, Gostivar, Kicevo, Debar and Struga). The data from this study indicate for the presence of Q fever in these areas. A total of 1,120 farm animals were examined, of which 178 serums resulted positive, with a scale of 15.89% positivity. The infection is quite widespread in all of the five regions and varies from 8.0% in Gostivar up to 27.71% in Kicevo. As regards the variation of frequencies based on species, the infection is widespread in all three species and in every region under surveillance; in sheep, it varies from 14.65% in Gostivar to 42.04% in Kicevo; in goats, from 2.89% in Gostivar to 14.28% in Debar; and in cows it varies from 4.42% in Gostivar to 12.96% in Kicevo. The serums were conserved in -30 °C and as a serological test ELISA from ID vet Monpelie France was used, which was carried out based on its relevant protocol using purified antigen of *C. burnetii*.

Keywords: Q-fever, Elisa test, *Coxiella burnetii*, relative frequency, farm animals.

INTRODUCTION

Q fever is a ubiquitous zoonotic disease caused by *C. burnetii*, with protean clinical manifestations that are not yet fully understood [47]. It was first described by Derrick [9] in 1935 in Queensland, Australia, during an outbreak of a febrile illness among abattoir workers. Subsequently, Burnet and Freeman [4] isolated a fastidious intracellular bacterium from guinea pigs that had been injected with blood or urine from Derrick's patients and named it *Rickettsia burnetii*. This bacterium was morphologically and biochemically similar to other gram-negative bacteria. On the basis of cultural and biochemical characteristics, Philip [41] classified *R. burnetii* in a new genus, *Coxiella*, named after Herald R. Cox, who first isolated this microorganism in the United States. This genus contained only one species, *C. burnetii*. Since then, it has been isolated from several mammals and from ticks, and it may persist in the environment *C. burnetii* has a worldwide distribution from its reservoirs (including mammals, birds, and ticks), and the development of Q fever is strongly related to exposure to farm animals (primarily cattle, sheep, and goats) and particularly parturient animals (including cats and rabbits) because the organism is reactivated in pregnant animals. In one reported case, an obstetrician developed symptoms of Q fever 1 week after delivering a child to a woman who had Q fever [45]. Q fever is primarily transmitted by: (1) aerosolization and contaminated hides [39]; (2) ingestion of raw milk and goat cheese; (3) transfusions of blood products; (4) mother to offspring (ie, vertical) transmission; and (5) tick bites. Even wind patterns may make a difference by spreading aerosolized organisms downwind [6]. Although the respiratory system is the main organ system affected, the gastrointestinal (GI) and cardiac systems can also be affected. *C. burnetii* lives inside acidic lysosomes, a point that has therapeutic implications [40] and it has 2 morphologic variants [33]: the small-cell variant (SCV) (0.2 x 0.7 microns), which survives well in the environment because of its resistance to heat and desiccation, pressure, and chemical agents [31] and the large-cell variant (LCV), which multiplies in the host monocyte and macrophage. These variants are antigenically different [50]. The large-cell variant exploits and persists within the acidified phagolysosome of the monocytes and macrophages, using it as a nursery [8]. Marrie and Raoult postulated that the morphologic variants create an impairment in the bacterial responses within the host, enabling the persistence of the illness in chronic cases [32]. Proliferation of organisms within the phagolysosome eventually ruptures the host cell. Like other gram-negative bacteria, *C. burnetii* possesses a lipopolysaccharide as a virulence factor that is also responsible for an antigenic phase variation, an important property that was first utilized for serologic diagnosis by Bengtson in 1941 [8, 15, 32, 50]. The infection has 2 phases, which are analogous to the lipopolysaccharide rough and smooth phase of Enterobacteriaceae organisms. The phase 1 form is responsible for acute Q fever infections. The phase 2 form has been identified during transmission of *C. burnetii* in immunoincompetent hosts, such as embryonated hen eggs or cell-culture systems [46]. In humans, infection results from inhalation of contaminated aerosols from amniotic fluid or placenta or contaminated wool. Therefore, Q fever is an occupational hazard. At greatest risk are persons in contact with farm animals, but also at risk are laboratory personnel who work with infected animals [19]. Mammals also shed *C. burnetii* in milk, and thus, consumption of raw milk could be a source of infection [12, 37 , 49]. Sexual transmission of Q fever has been demonstrated in the mouse [25] and has been suspected in humans [29]. Sporadic cases of human-to-human transmission following contact with an infected parturient woman have been reported and have been suspected to occur by direct aerosol transmission. It has also been proven to occur via transplacental transmission, resulting in congenital infections

[28, 45], via intradermal inoculation [3, 11], and via blood transfusion [5, 44]. Ticks transmit *C. burnetii* to domestic mammals but not to humans [22]. *C. burnetii* may persist asymptomatically in humans throughout life. However, pregnancy, a cardiac valvular abnormality, a vascular aneurysm or prosthesis, hemodialysis [26], and immunodeficiency, including AIDS [16, 20, 27, 42, 43], may promote reactivation of dormant *C. burnetii*. In Europe, acute Q fever cases are more frequently reported in spring and early summer. They may occur at all ages, but they are more frequent in men than in women. Q fever is usually benign, but mortality occurs in 1 to 11% of patients with chronic Q fever [43]. *C. burnetii* is endemic in every part of the world except New Zealand [17, 21]. In southern France, 5 to 8% of cases of endocarditis are due to *C. burnetii*, and the prevalence of acute Q fever is 50 cases per 100,000 inhabitants [49]. Seroepidemiological surveys have shown that 18.3% of blood donors in Morocco, 26% in Tunisia [38], 37% in Zimbabwe [23], 44% in Nigeria [2], 10 to 37% in northeast Africa, and 14.6 to 36.6% in different areas of Canada [30, 34] had anti-*C. burnetii* antibodies. Large outbreaks of Q fever have also been reported in the Basque country in Spain [1], in Switzerland [10], in Great Britain [14], in Berlin, Germany [48], and more recently, in southern France (unpublished data).In addition to its high infectivity, *C. burnetii* is an extremely virulent organism, as just a single bacterium can cause infection [40].

MATERIALS AND METHODS

The study in question includes data related to the frequency of the Q-Fever in farm animals (sheep, goats and cows) in five regions in Western Macedonia: Tetovo, Gostivar, Kicevo, Debar and Struga. A total of 1,120 serums were collected. They were taken randomly without any preference. The serums were extracted from blood through centrifugation and after the 2ml plastic ampoule was set, they were kept at -30°C until they were used. ELISA was the method that was applied in this case. The ELISA kit was imported from ID vet – Montpelier in France. The functioning principle of the kit is as follows: the serums (that are to be examined) will be diluted in micro titration plates at 1:10. They are then incubated for 45 minutes and after rinsing, the conjugate is added and then other ingredients to finish with the stoppage solution. The incubation times have been strictly abode by in conformity with the preset criteria in the respective kit. The measurement of OD was made using a 450nm ELISA reader. The calculation of results (for every examined serum) was done based on the following formula:

$$S / P = \frac{\text{ODsample - ODNC}}{\text{ODPC - ODNC}}$$

where upon: NC = Negative Control; PC = Positive Control; OPD sample = OD of the examined sample.
The assessment of the examined serums is based on the data taken from the above-cited formula having in consideration that:

S/P ≤ 40% = Negative; 40% - ≤ 50 % suspicious; ≥ 50 % positive

Results were processed by using statistical methods, such as the line equation of linear regression and the correlation coefficient. The study in question was carried out at the Virology Lab of the Faculty of Veterinary Medicine in Tirana, Albania.

RESULTS

Preliminary processing of the data obtained from the work sample consisted of 1120 farm animals (sheep, goats and cows) shows that the average Q fever in the farm animals sample of western Macedonia, which has been subject to serological testing, results near 15.89%. The serums were collected from animals without any visible specific clinical signs in terms of the presence of the Q-Fever. The serologic examination confirmed the presence of the infection in almost all zones, though with a different level in different areas and in different species. The affected animals are usually asymptomatic, which requires serologic examinations to be carried out in order to realize the real situation. In the region of Western Macedonia, there are a few or no data at all in terms of the dissemination of this infection in animals, let alone human beings. Apart from the epidemiological situation of the Q-Fever in animals, we have investigated it in the human population in the same regions where animals have been observed and for the first time in Macedonia, we have noticed the presence of the infection with about 21.9% positivity from a total of 520 examined human serums [18], yet, based on the findings of the foreign authors, we think that the infection of the people comes as a result of the presence of the infections in animals which plays an important role in spreading the cause in the environment, as well as through its airborne distribution. Hence, 1120 sera of farm animals were tested, of which 178 of them tested positive and are presented in the tables below by region and animals species.

The work sample of farm animals

The work sample data: Name of region – i; the total number of animals tested by regions – Ni; numerical frequency of animals positive with Q fever (EQ) – Yoi(num) and the relative frequency of animals positive with Q fever –Yoi(%) are shown in Table 1.

The flow of the observed relative frequency of farm animals with Q-Fever in the region has been given in the figure 1.

The variation of frequencies in farm animals with Q-Fever based on the species (sheep, goats, cows)

In Table 2 the data extracted from Table 1, for $\mathbf{y_{oi}}$ **(%)** referred to values $\mathbf{x_{mi}}$ (years), of the middle of intervals of the total number of examined farm animals in the five respective regions, as well as acquired results from their processing, in accordance with a linear function model.

Table 1. Data of the work sample divided in five regions with farm animals

I	Ni	Yoi (num)	Yoi (%)
Region	Total number of examined animals	Numeric frequency of animals with positive Q-Fever	Relative frequency of animals with positive Q-Fever
TETOVO	322	42	13.04%
GOSTIVAR	298	24	8.05%
DEBAR	151	40	26.49%
KICEVO	166	46	27.71%
STRUGA	183	26	14.20%
Total:	**1120**	**178**	**15.89%**

Table 2. Data from the work sample divided into five regions based on the species

Region	Species	Total number of examined farm animals	Numeric frequency of Q-Fever positive farm animals	Xmi (years) Middle of species interval	Yoi (%) Relative frequency of Q-Fever positive farm animals	Line equation of linear regression, correlation and their significance
Tetovo	Sheep	126	30	151.05	23.80%	**y=-0.001x + 0.3587 r=-0.84 0.025<p<0.050**
	Goats	72	4	236.05	5.55%	
	Cows	124	8	322.05	6.45%	
Total		**322**	**42**	-	**13.04%**	-
Gostivar	Sheep	116	17	151.05	14.65%	**y= - 0.0006x + 0.2143 r=-0.79 0.025<p<0.050**
	Goats	69	2	236.05	2.89%	
	Cows	113	5	322.05	4.42%	
Total		**298**	**24**	-	**8.05%**	-
Debar	Sheep	82	32	151.05	39.00%	**y= - 0.0017 x + 0.607 r=-0.92 0.025<p<0.050**
	Goats	21	3	236.05	14.28%	
	Cows	48	5	322.05	10.41%	
Total		**151**	**40**	-	**26.49%**	-
Kicevo	Sheep	88	37	151.05	42.04%	**y= - 0.0017 x + 0.6121 r=-0.79 0.025<p<0.050**
	Goats	24	2	236.05	8.33%	
	Cows	54	7	322.05	12.96%	
Total		**166**	**46**	-	**27.71%**	-
Struga	Sheep	96	18	151.05	18.75%	**y= - 0.0006 x + 0.2741 r=-0.97 0.025<p<0.050**
	Goats	26	3	236.05	11.53%	
	Cows	61	5	322.05	8.19%	
Total		**183**	**26**	-	**14.20%**	-
Total sum		**1120**	**178**	-	**15.89%**	

Using the method of least squares, the line equation of linear regression has also been determined for the interval of examined farm animals for all regions, which resulted as below:

$Y_{e(TETOVO)} = -0.001x + 0.3587$ (1)

$Y_{e(GOSTIVAR)} = - 0.0006x + 0.2143$ (2)

$Y_{e(DEBAR)} = - 0.0017 x + 0.607$ (3)

$Y_{e(KICEVO)} = - 0.0017 x + 0.6121$ (4)

$Y_{e(STRUGA)} = - 0.0006 x + 0.2741$ (5)

as well as the correlation coefficients between variables: $r_{(Tetovo)} = - 0.84$; $r_{(Gostivar)} = - 0.79$; $r_{(Debar)} = - 0.92$; $r_{(Kicevo)} = - 0.79$ dhe $r_{(Struga)} = - 0.97$. The significance level 0.05>p>0.025 has been determined by respective formulas and statistical charts of critical values for correlation coefficients, provided in references [7, 13, 24].

In figure 2 the positions of sample distribution spots have been given (X_{mi}, Y_{oi}), extracted from Table 2, including respective lines known as polygonal frequency lines and the positions of lines (1), (2), (3), (4) and (5).

The flow of the observed relative frequency of different farm animals with Q-Fever infection for every region has been illustrated in figure 3.

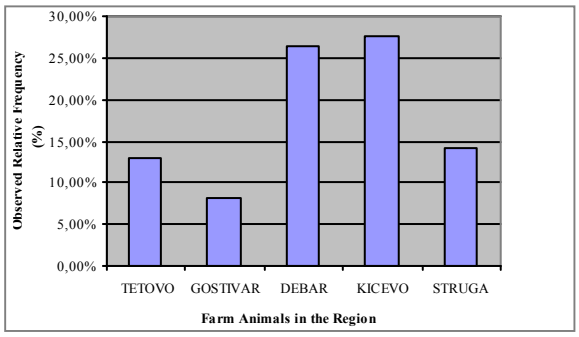

Figure 1. Graphical presentation of observed relative frequency in farm animals with Q-Fever in the work sample

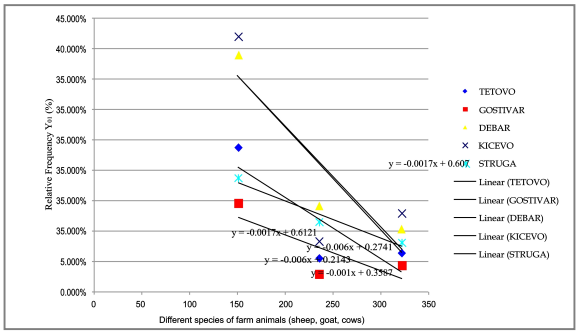

Figure 2. Positions of lines of the linear regression for the expected relative frequencies according to Table 2

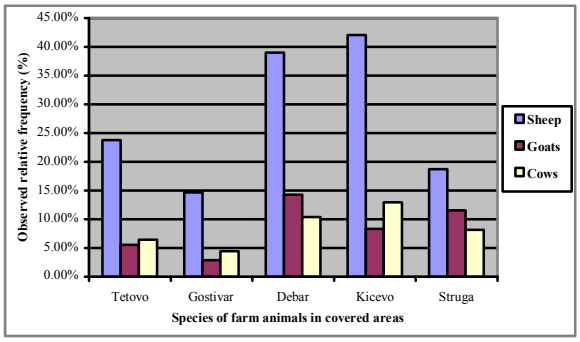

Figure 3. Graphical presentation of the observed relative frequency of farm animals with Q-Fever

DISCUSSIONS

Based on the above-presented data, we can see that the infection with the Q-Fever is present in all regions of Western Macedonia. According to the data from Table 1 and Fig. 1, we can see that the numeric frequency and relative frequency of Q-Fever is higher in the Kicevo region where 46 of 166 (27.71%) farm animals resulted positive; it is followed by the Tetovo region with 42 positive cases out of 322 examined or 13.04%; the region of Debar is next with 40 positive cases out of 151 examined (26.49%); 26 positive cases out of 183 (14.20%) were identified in Struga and finally the Gostivar region was represented with 24 positive cases out of 298 examined farm animals or 8.05%. We can therefore conclude that the observed relative frequency of farm animals with Q-Fever is higher in the Kicevo region and lower in the region of Gostivar.

This infection not only is present in terms of its geographical dissemination, but it has also been noticed in all of the examined species, i.e. sheep, cows and goats. Moreover, as the data in Table 2 show, even within this category, this infection has noticeable differences in various regions. For example, the infection in sheep, as one of the species that influences a lot the transmission of the infection in humans, is at high levels compared to other regions, even at a global level, in proportion with the infection in goats or cows. In this respect, the highest level of the infection has been noticed in the Kicevo region with 42.04%, followed by the Debar region with 39%, Tetovo region with 23.8%, Struga with 18.75% ending up with the region of Gostivar with 14.65%. With the help of simple mathematical calculations, the percentage of the infection in sheep in the overall region of Western Macedonia is 26.37%. This percentage is much higher compared to the one noticed by the authors (Prof. K. Bërxholli and Co., 1995 in Albania – unpublished personal communication material), who have found out that the percentage of the infection in sheep, in Albania, reaches up to 11.24%. In the U.S., for example, this infection in sheep is about 16.5% [35], another big difference compared to the data from Macedonia. In the meantime, according to the data from [36], the level of infection in sheep in Germany e.g. is 8.7% and only 3.5% in the Netherlands. In our opinion, this is due to two main factors: the first is the system of pastures; in Western Macedonia, the system of pastures is almost all natural, i.e. extensive, and different infection factors are more often present throughout the year and therefore their influence is greater in animals in question; the second factor is the lack of measures to be undertaken at failures. Animals fail in stalls, and based on the data we have gathered from their owners, i.e. farmers, it is concluded that by ignoring the causes of failures, we do not undertake measures for dealing with the consequences, favoring thus the further expansion of the infection.

Unlike the high levels of infection in sheep, the infection in goats in this region is quite low. Based on the data from the above-drawn table, we can see that the infection in goats reaches 6.6%; in Albania, this percentage is 12.12%, in Bulgaria 40% and in France 88.1% [36]. In the Netherlands, the level of infection with the Q-Fever in goats reaches 7.8% according to [36].

If we analyze the table more carefully and thoroughly, we will see that, the level of infection, according to regions, is not only different but low too. Therefore, the highest level has been noticed in Debar with 14.28%, followed by Struga with 11.53%, Kicevo with 8.33%, Tetovo with 5.55% and Gostivar with 2.89%. The high level of infection in goats in Debar can somehow be related with the high level of infection in sheep in that region, since, quite often, both sheep and goats are kept together in these regions; however, this is not the case with Kicevo, where there is a huge difference between the level of infection in sheep (42.04%) and the level of infection in goats (8.33%). With these results on table, we are not able to draw any conclusions in terms of these variations in the levels of infection, though we can say that further studies need to be undertaken to clarify this complicated epidemiological situation.

The infection in cows in the region of Western Macedonia is also very low compared to the data provided by various different authors from other European countries. In this respect, the average level of infection in this part of our country is about 7.5% (it has not been presented in the table, but it has been mathematically calculated), and in Albania (Prof. K. Bërxholli and Co., 1995 in Albania – unpublished personal communication material) it is about 10%. In other countries, e.g. in Bulgaria, this percentage reaches 20.8%, in France – 15%, Germany 19.3% and the Netherlands 21% [36]. The highest level of infection with the Q-Fever in the region of Western Macedonia has been noticed in Kicevo with 12.6%, whereas the lowest in the region of Gostivar, with only 4.4%.

In the last column of Table 2 the line equation of linear regression and the correlation coefficient have been presented, wherefrom we are going to identify the dependency, relation, flow and prediction of the spread of Q-Fever frequency in proportion with the number of animals, regardless of their species, for every region separately.

By knowing the fact that the regression shows the average of relationships among phenomena and the movement of individual cases around it, in Graph 2, for every region, we can clearly state that every linear regression line has a negative direction and a weak linear interrelation because the individual cases (three animal species) have been disproportionally distributed further from the line (average) which shows a non-narrow interrelation. This kind of interrelation shows the frequency of the disproportional spread of Q-Fever among the species. The line direction is negative, which means that by continuing the examination of the animals, the infection will spread further, more in the region of Debar and Kicevo and less in Struga and Gostivar.

What seems interesting is the acquired correlation coefficient which is negative for every region but high – the highest in the region of Struga (-0.97), and the lowest in the region of Gostivar and Kicevo (-0.79). In other words, this means that with the continuation of the examination of the animals, the frequency will increase in every region – a conclusion that was also proven by the regression line, i.e. it was verified above with the correlation coefficient.

Based on Graph 3, we can again note the comparative conclusion from above, when we said that the frequency of the spread of the Q-Fever is disproportional among the species, i.e. sheep were the most affected in every region separately.

Regardless of these somewhat complex epidemiological data, we can say that we have noticed the presence of the Q-Fever for the first time in this region in animals and other species. The registration of this infection is a sign not only for the veterinary services, but people in general, since this infection is zoonotic and can cause a precedent for epidemics in humans, as were the cases in the Netherlands and Germany. This is the reason why we should turn to the so-called "forgotten infections" and be more aware of their presence and the consequences they may bear.

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