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Statistical processing of the data for the presence of Q fever in human population in Western Macedonia

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Abstract

Q fever is an acute and rarely chronic, zoonotic disease. It is caused by *Coxiella burnetii*, an obligate intracellular, pleomorphic coccobacillus. It survives unfavourable conditions in the form of endospores and is extremely resistant to environmental effects. People are usually infected by inhaling the infected aerosol. The aim of study was to examine the frequence of Q fever in the human population in Western Macedonia and determining the statistical trend with descriptive and conclusive statistical methods. The serological test was conducted using the ELISA test kit. The serum isolated from the blood was kept at -30°C until testing. The sera were properly diluted based on therespective protocol using purified antigen of *C. Burnetii.* A total of 520 serums were checked of all ages from people with different epidemiological conditions, of which 114 resulted positive, with positivity rate of about 21.90%.The standard deviation of the infected population in general is 8.53, where in the female gender is higher than the masculine gender, while the age group of the two sexes the standard deviation ranges from 0.84 to 4.98.

The statistical analysis of the data results, prove that there is a connection and similarity among the samples from five regions in terms of the spread of the Q fever infection inhuman population, this is proven by the credibility boundaries with the Kloper-Pirson method. The frequency 78% negative per sample 520 is gained within the median limits from 74% to 86% of the sample.

Keywords: Zoonotic disease, human population, infection, serological test, regions.

1. Introduction

In August 1935, Dr. E. H. Derrick (MD, Melbourne University, 1922), the Director of the Laboratory of Microbiology and Pathology of the Queensland Health Department at Brisbane, Australia, was asked to investigate an outbreak of undiagnosed febrile illness among abattoir workers in Brisbane (10). This illness he named "Q" for "Query" fever. Derrick inoculated guinea pigs with blood or urine from the" fever patients. The guinea pigs became febrile. Derrick was unable to isolate the agent responsible for the fever so he sent a saline emulsion of infected guinea pig liver to Macfarlane Burnet in Melbourne. Burnet was able to isolate organisms which "appeared to be of rickettsial nature" (5). At about the same time Drs. Herald Rea Cox and Gordon Davis at Rocky Mountain Laboratory, Montana were working on the possible vectors of Rocky Mountain spotted fever and tularemia. Davis had ticks (the suspected vectors) feed on guinea pigs; the guinea pigs became ill. In May 1938, Dr. Rolla Dyer, the Director of the National Institute of Health, visited Cox in Montana to challenge Cox's report that he had cultivated rickettsiae in large numbers in embryonated eggs. Ten days later he became ill with retro-orbital pain, fever, chills and sweats. Five mL of his blood drawn on the sixth day of his illness resulted in fever when injected into guinea pigs. Subsequent studies showed that this agent was identical to the Nine Mile agent isolated from ticks. In April 1938, Burnet sent Dyer spleens from mice infected with the Q fever agent, Dyer showed that the Q fever agent was identical to Nine Mile agent (29). Cox named the Nine Mile agent Rickettsia diaporica (diaporica means having the property or ability to pass through) a reference to the filterable property of the agent (8). Meantime in Australia, Derrick proposed the name of

Rickettsia burnetii for the Q fever agent (11). In 1948 Cornelius B. Philip proposed that *R. burnetii* be considered as the single species of a distinct genus since it was now apparent that this organism was unique among the rickettsiae (30). He proposed the name *Coxiella*(30). The Q fever agent is now known as *Coxiella burnetii*.

The initial description of Q fever as an illness occurring among abattoir workers (10) was a strong portender of the epidemiology of this illness. The epidemiology of Q fever in man is linked to the epidemiology of fever in animals. Q fever is a zoonosis. Of all the animals infected by *C. burnetii*, man is the animal to usually develop illness as a result of infection (34). Man becomes infected following inhalation of *C. burnetii*. The desiccation resistant organism is shed from infected animals, usually cattle, sheep, goats or cats, especially at the time of parturition. Air samples are positive for weeks following parturition and viable organisms are present in the soil for periods of up to150 days (40).

Two characteristics of the organism are important in the epidemiology of the disease. These are its ability to withstand harsh environmental conditions, probably as a result of spore formation (28), and its extraordinary virulence for man. A single organism can cause disease in man (9).

Some studies have suggested that ingestion of raw (contaminated) milk is a risk factor for the acquisition of Q fever (16, 27, 22). Seroconversion, but not disease, did occur following ingestion of raw milk (3). It is likely that, in some populations, ingestion of infected material accounts for the high seropositivity rate. Ingestion of *C. burnetii* is probably important in the maintenance of Q fever in the animal population. Cats experimentally infected via the oral route did not become ill, whereas cats infected via the subcutaneous route became febrile and lethargic (14).

Percutaneous infection can occur (12, 13), but accounts for very few cases of Q fever worldwide.

While *C. burnetii* has been isolated from human placentas (35), there is little to suggest that vertical transmission occurs in man.

Person-to-person transmission has been documented but it is very unusual.

Sexual transmission of *C. burnetti* has been demonstrated in mice in the laboratory (38), but whether fever can be transmitted sexually under natural conditions and in other animal species is unknown.

Coxiella burnetii is a highly pleomorphic coccobacillus with a gram-negative cell wall. It measures 0.3 x 1 itm (2); unlike true rickettsiae it enters the cell by a passive mechanism. Within the cell it survives within the phagolysosome - the low pH of this environment is necessary for the metabolic functioning of *C. burnetii*.

Coxiella burnetii undergoes phase variation (21). In nature and laboratory animals it exists in the phase I state. Repeated passage of phase I virulent organisms in embryonated chicken eggs leads to gradual conversion to phase II avirulent forms (2). These two antigenic phases differ in the sugar composition of their lipopolysaccharides (33, 15), in their buoyant density in cesium chloride, and in their affinity for hematoxylin and basic fuchsin dyes. Plasmids have been found in both phase I and phase II cells. There are three different plasmid types varying in length from36 to 45 kilobases (32).

Man is the only animal known to almost always develop illness following infection with *C. burnetii* (1). Several clinical syndromes result from this infection - these are: a self-limited febrile illness, pneumonia, hepatitis, endocarditis, osteomyelitis, Q fever in infancy, neurological manifestations end complications of acute Q fever (25, 24).

While some *C. burnetii* infections are totally asymptomatic (7), the majority are mild self-limited febrile illnesses. It is difficult to know just what proportion of Q fever is truly asymptomatic.

Acute Q fever, which may be manifest as pyrexia of unknown origin, pneumonia or hepatitis, is almost always of abrupt onset. The manifestations of acute Q fever vary from country to country (15). Severe headache is a characteristic feature, so much so that it prompts a lumbar puncture to rule out meningitis in some patients. Headache is more common with Q fever pneumonia than it is in pneumonia due to other agents (23).

Physical examination may be normal apart from an elevated temperature. Hepatomegaly and splenomegaly may be present (6). Uncommon features of acute Q fever include a variety of neurological manifestations: encephalitis, dementia, toxic confusional states, extrapyramidal disease (36), meningoencephalitis (26, 20, 4).

The strains of *C. burnetii* that cause chronic Q fever in man are probably different from those that cause acute disease (31, 39). The major manifestation of chronic Q fever is endocarditis. Another important predisposing factor is paralysis of specific cell-mediated immunity. Lymphocytes from patients with Q fever endocarditis are unresponsive to *C. burnetii* antigens (19) however this may be a secondary rather than a primary phenomenon. Phase I antibodies and antibodies in the IgA fraction predominate in Q fever endocarditis this is not so in acute Q fever.

Acute Q fever is readily treated with tetracycline (37). The treatment of chronic Q fever is difficult. It is probably best to use two antibiotics for at least two years. Some authorities recommend treating chronic fever for life. Strain differences may be very important in the management of chronic Q fever. The Priscilla isolate is less sensitive than the Nine Mile isolate to quinolones and it is resistant to rifampin (41).

Having in consideration that Q fever is a zoonotic disease, the aim of this study was to obtain a clearer picture over the epidemiological situation of the causes of Q fever in Western Macedonia, in relation to the serological presence of the Q fever in people.

2. Material and Methods

The stated study was conducted in the Laboratory of Virology of the Faculty of Veterinary Medicine – Tirana, Albania, using the ELISA Test in humans. The ELISA Kit was imported from the German Firm, SERION. The result‘s aim was to identify the IgG. The blood was taken from people of different pathologies, without any special preferences. It was collected from Gostivar, Tetova, Kercova, Struga and Dibra areas. The number of people tested is 520. The samples were provided in cooperation with the human service. The blood serum is separated by centrifugation at 6000 rpms in 20 minutes. The serum placed in plastic ampoules was kept frozen at -30^{0}C, until its testing. Positivity was based on the cut-off value, which in this case is over 0.5 OD. The sera were diluted before the test at a ratio of 1:400, in two steps. The first dilution was done at a ratio of 1:100, then the stated dilution, at a ratio of 1:4. The test was conducted based on the protocol of Serion Firm. The study‘s aim was to identify the presence of the infection in humans, and not interpret the diagnosis‘ decision. We have also tried to draw a link between human and animal infection by area, as people's blood is picked up at the areas where the blood of the animals was taken, which has resulted in specific seropositivities in the area (17, 18).

Additionally, since the number of serums is based on the minimum required number of serums for statistical processing, the results were processed from a statistical point of view to evaluate the reliability of the outcome that will result from the serological control of the serums in question. Results were processed by using statistical methods, such as the line equation of linear regression and the correlation coefficient.

3. Results and Discussion

In our study, as mentioned above, 520 people are involved. The initial male and female sample data have been separated from region to region (Tetovo, Gostivar, Debar, Kicevo and Struga). To facilitate the study and to assess the level of infection we have made a rough grouping, in terms of age groups: 0-20, 20-40 and over 40 years.

Hence, 520 sera of human were tested, of which 114 of them tested positive and results were processed with statistical methods from which emerged the following results:

Descriptive statistics

The work sample data of farm animals are shown in Table 1.

Table 1. Data of the work sample divided in five regions with men and women of different age groups

i	Xmi(year)		Ni	Yoi(num)	Yoi(%)
Regio	Middle range of age groups of the region		Total number of tested persons	Numerical frecuency of persons positive with Q fever	Relative frequency of persons positive with Q fever
TETOVA	0-20	0,05 – 20,05	46	0	0,00%
	20-40	20,05 – 40,05	34	8	23,52%
	> 40	>40,5	75	21	28,00%
	Total:		**155**	**29**	**18,7**
GOSTIVAR	0-20	0,05 – 20,05	36	1	2,77%
	20-40	20,05 – 40,05	34	2	5,88%
	> 40	>40,5	70	7	10,00%
	Total:		**140**	**10**	**7,14**
DIBRA	0-20	0,05 – 20,05	6	0	0,00%
	20-40	20,05 – 40,05	8	2	25,00%
	> 40	>40,5	50	20	40,00%
	Total:		**64**	**22**	**34,37**
KERÇOVA	0-20	0,05 – 20,05	7	1	14,20%
	20-40	20,05 – 40,05	14	8	57,10%
	> 40	>40,5	53	23	43,30%
	Total:		**74**	**32**	**43,2**
STRUGA	0-20	0,05 – 20,05	47	10	21,20%
	20-40	20,05 – 40,05	14	5	35,70%
	> 40	>40,5	26	6	23,00%
	Total:		**87**	**21**	**24,13%**
	Total amount:		**520**	**114**	**21,90%**

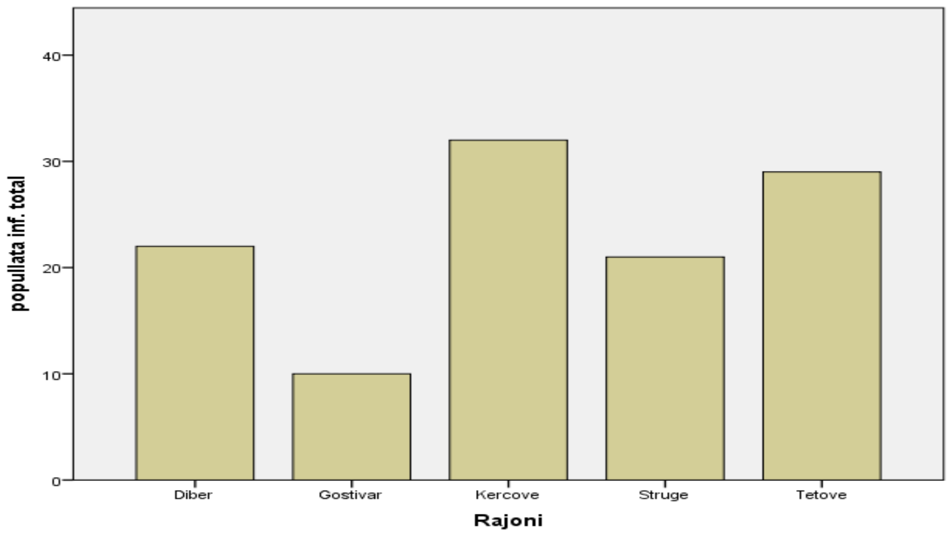


Figure 1. Dissemination of the frequency of infection to the human population

According to the data from Table 1 and Chart 1, where the numerical and relative frequencies are presented for the distribution of Q-affected women and men in the five regions of Western Macedonia (Tetovo, Gostivar, Debar, Kicevo and Struga), we conclude that the Kicevo region has a relatively higher frequency than the other regions, 43.2% of the 74 controlled entities.Positively resulted 32 people and the age group 21-40 is most affected by 57.10% relative frequency and less 0-20 year old age group with 14.20% relative frequency. Then comes the Dibra region with 34.37% relative frequency, where in contrast to the Kicevo region, the most affected here is the age group over 41 with 40.00% relative frequency and no case at the age group 0-20.This follows the region of Struga with 24.13% relative frequency and with the 21-40 age group affected by 35.70%, then Tetovo region with 18.7% and the most affected age group 41 and the last region with less affected by fever Q is the Gostivar region with 7.14% of cases and with the age group over 41 aged most affected. In general, 520 subjects were searched, where 114 subjects or 21.90% of cases were positively reported.

In a more detailed view we can conclude that the age group 0-20 in general for all regions is the least affected group by the Q fever. With simple mathematical calculations, although the table does not present this data, we gain: from a total of 142 controlled heads, 12 resulted positive with Q fever, or relative frequency of 8.45% of cases for the age group 0-20 years. But with the following statistical analysis we will verify this finding.

From Table 2, it is noticed that the standard deviation of the infected population in general is 8.53. Below we have a higher standard deviation of the female infected population than that of the male infected population, which means that the standard error in the calculation will be greater in the infected female population, whereas in the age groups of both genders the standard deviation ranges from 0.84 to 4.98.

Table 2. Descriptive statistics of the spreading of Q-fever

	Mean	Std. Deviation
Total inf. populaiton	22,80	8,526
Infected M	11,00	3,674
Infected F	11,80	5,119
F020 –Infected	1,40	2,608
F2040- Infected	2,80	2,588
F40- Infected	7,60	3,578
M020- Infected	1,00	1,732
M2040- Infected	2,20	,837
M40 –Infected	7,80	4,970

Conclusive statistic on the frequency of Q-fever in the human population

The rate of the frequency of the Q fever in the research regions should be analyzed with the binomial confidence test for each region separately. With the binomial test we obtain very low probability, almost zero for the regions of Tetovo, Gostivar and Struga and 0.018 ($p < 0.05$) for the Dibra region. So the probability for the theoretical frequency 50-50% to occur is very small in these regions. These four regions have a connection between them, which is not the case for the Kicevo region where the probability of occurrence of the theoretical frequency is 0.295 ($p > 0.05$), indicating that in 29% of the cases theoretical frequencies can occur. So this region is distinguished from the other four regions, according to the nature of the spread of the Q fever.

Below are also featured the confidence limits for 95% of the cases in the Tetovo region. The average of 81% of negative cases was obtained between the limits of 74% and 87% of the sample, while for the Kicevo region the average of 43% of positive cases was obtained between the limit of 31% and 35% of the sample.

Table 3. Testing of the hypothesis with the binomial test

Hypothesis Test Summary

	Null Hypothesis	Test	Sig.	Decision
1	The categories defined by EQTE = Jo and Po occur with probabilities 0,5 and 0,5.	One-Sample Binomial Test	,000	Reject the null hypothesis.
2	The categories defined by EQGV = Jo and Po occur with probabilities 0,5 and 0,5.	One-Sample Binomial Test	,000	Reject the null hypothesis.
3	The categories defined by EQDI = Jo and Po occur with probabilities 0,5 and 0,5.	One-Sample Binomial Test	,018	Reject the null hypothesis.
4	The categories defined by EQKE = Po and Jo occur with probabilities 0,5 and 0,5.	One-Sample Binomial Test	,295	Retain the null hypothesis.
5	The categories defined by EQST = Po and Jo occur with probabilities 0,5 and 0,5.	One-Sample Binomial Test	,000	Reject the null hypothesis.

Asymptotic significances are displayed. The significance level is ,05.

Table 4.Clopper -Pearson confidence coefficients

Confidence Interval Summary

Confidence Interval Type	Parameter	Estimate	95% Confidence Interval	
			Lower	Upper
One-Sample Binomial Success Rate (Clopper-Pearson)	Probability (EQTE=Jo).	,813	,742	,871
One-Sample Binomial Success Rate (Clopper-Pearson)	Probability (EQGV=Jo).	,929	,873	,965
One-Sample Binomial Success Rate (Clopper-Pearson)	Probability (EQDI=Jo).	,656	,527	,771
One-Sample Binomial Success Rate (Clopper-Pearson)	Probability (EQKE=Po).	,432	,318	,553
One-Sample Binomial Success Rate (Clopper-Pearson)	Probability (EQST=Po).	,241	,156	,345

Table 5. Chi-square coefficients

Eqnum			
	Observation N	Expetation N	Residual
Negative	406	260.0	146.0
Positive	114	260.0	-146.0
Total	520		

Test statistics	
	Eqnum
Chi-Square	163.969[a]
Df	1
Asymp. Sig.	.000

As in the final statistical analysis of animals (17,18), also in the human population, we will present Ho that has no link between regions for the diffusion of Q fever in the population. H1 has links between the regions, but let's look at the Hi-Square coefficient.

From the first table, the empirical and the theoretical frequency is seen, as well as the residual difference where empirical is 406 negative with Q-fever and 114 positive. While the expectation 260 with 260 cases and the Hi-Square coefficient is greater than zero.The important statistical indicator is 0,000, so the probability is less than 0.05, which is accepted that H1 has links between the regions during the spread of the Q fever in the population, although in the case of region to region analysis there is a difference between the region of Kicevo and the four other regions in the Hi-Square. In all regions, this distinction fades in favor of the other four regions.

Table 6. Statistical indicator of the hypothesis

Hypothesis Test Summary

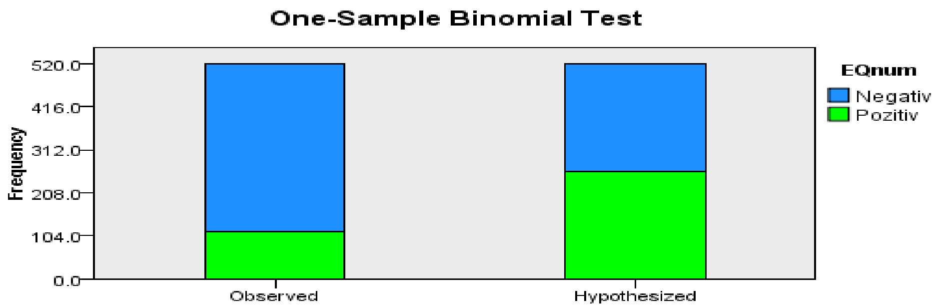
	Null Hypothesis	Test	Sig.	Decision
1	The categories defined by EQnum = Negativ and Pozitiv occur with probabilities 0.5 and 0.5.	One-Sample Binomial Test	.000	Reject the null hypothesis.

Asymptotic significances are displayed. The significance level is .05.

Table 7. The gained coefficients of the credibility of Clopper-Pearson

Confidence Interval Summary

Confidence Interval Type	Parameter	Estimate	95% Confidence Interval	
			Lower	Upper
One-Sample Binomial Success Rate (Clopper-Pearson)	Probability (EQnum=Negativ).	.781	.743	.816



Total N	520
Test Statistic	406.000
Standard Error	11.402
Standardized Test Statistic	12.761
Asymptotic Sig. (2-sided test)	.000

Figure 2. Comparison of our hypothesis with theoretical hypothesis

This finding is also verified by the binomial confidence test for 50-50% probability of the cases, where a 0,000 data is obtained, indicating that our empirical frequency distinguishes from the theoretical 50-50% with a statistically significant difference of 0,000. In the last column, the result of binomial analysis itself says H0 to be thrown and it can be automatically determined that there are links between the regions. Below we also gain the confidence limits with the Clopper-Pearson method. The 78% negative sample rate of 520 is gained within the median limits of 74% to 86% of the sample

From the above results, we conclude that there is a connection between the five regions (Tetovo, Gostivar, Debar, Kicevo and Struga) in the spread of Q fever in the human population, but with a special emphasis, the Kicevo region is distinguished from the other four regions in this connectivity and this phenomenon will be analyzed below with the difference of the differences of averages.

4. Conclusions

The statistical analysis of the data results in the conclusions:

-There is also a connection between the five regions when it comes to the distribution of the Q fever infection in people; however, the region of Kicevo is the most affected compared to the other four.

-Based on the analysis of mean difference, we can conclude that the regions can be divided into three sections depending on the prevalence of the Q fever infection: the Tetovo-Gostivar region is with low prevalence, the Debar-Struga region is with medium prevalence and the region of Kicevo is with high prevalence (based on the criteria obtained from the research results); however, this categorization can change with the increase in samples, due to the difference in the standard deviation for each region separately.

-The difference among mean values shows the distinction in the 40> age group as being the most affected by the Q fever infection, compared to the 20-40 and 0-20 age groups. If there is an increase in the number of examined patients, the difference between this age group and the latter two will also increase, because the standard deviation in calculations is lower in the 40> age group.

-There is a great similarity in terms of the distribution of the Q fever between sexes, which means that this kind of infection does not prefer one sex better than the other.

5. Recommendations

Based on the above-mentioned results, our recommendations are as follows:

Since Q fever is present in Western Macedonia and while the number of cases varies from year to year, veterinarians and physicians must be aware of the epidemiology of this disease. Probably the best approach to management of Q fever is to investigate outbreaks and apply appropriate control measures if necessary. Serological surveys of cattle, sheep and goats should be done periodically to monitor the endemic level of the presence of C. burnetii in a region as measured by seropositivity among the traditional reservoirs of this organism for man. Disease in humans is readily diagnosed as long as the manifestations of the disease and the provincial epidemiology of the disease are known to practicing physicians. Those at high (occupational)risk for this infection should also be aware of its signs and symptoms.

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