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Seroprevalence and Risk Factors for *Coxiella burnetii* in Jordan

Mohammad M. Obaidat,[1]* Lile Malania,[2] Paata Imnadze,[2] Amira A. Roess,[3] Alaa E. Bani Salman,[1] and Ryan J. Arner[4]

[1]*Department of Veterinary Pathology and Public Health, Faculty of Veterinary Medicine, Jordan University of Science and Technology, Irbid, Jordan;* [2]*National Center for Disease Control and Public Health, Tbilisi, Georgia;* [3]*Department of Global Health, Milken Institute School of Public Health, George Washington University, Washington, District of Columbia;* [4]*Ryan Arner Science Consulting, LLC, Freeport, Pennsylvania*

Abstract. This is the first cross-sectional study of the seroprevalence and risk factors for *Coxiella burnetii* in Jordan. A total of 781 individuals from 11 governorates of Jordan were tested by SERION ELISA classic *C. burnetii* IgG Phase 2. A validated and pretested questionnaire was used to collect risk factors and demographic data. The overall seroprevalence for *C. burnetii* was 24.2% (95% CI; 21.3–27.3%). Unadjusted odds ratios showed that governorate of residence, consumption of raw milk, and ownership of sheep, goats, and dogs were significantly ($P \leq 0.05$) associated with *C. burnetii* seropositivity. The multivariate logistic regression showed that individuals who own small ruminants had three times greater odds of seropositivity than those who do not own a small ruminant, after controlling for age, gender, raw milk consumption, and ownership of dogs. In addition, individuals who live in Al-Karak, Az-Zarqa, and Al-Tafilah had significantly greater odds of seropositivity compared with individuals who live in the capital city, Amman (OR = 3.6, 4.8, and 2.7, respectively). This study suggests that preventive measures should be practiced in ruminant farms in Jordan to avoid *C. burnetii* infection. *Coxiella burnetii* should also be considered in the differential diagnosis of febrile-like illnesses in Jordan, especially among farmers and veterinarians.

INTRODUCTION

Coxiella burnetii is an intracellular, gram-negative bacteria, which is very resistant to desiccation, light, and temperature extremes and, thus, can persist in infected animal farms and their surrounding environment for at least 1 year.[1] It is commonly transmitted to humans through inhalation of contaminated aerosols or dust from infected ruminants and their excretions, and a single organism can cause infection when inhaled.[2] Once aerosolized, *C. burnetii* can be widespread and has been found far from the place of origin. Ruminants, cats, and dogs have been noted as reservoirs, and many become infected by tick bites.[3–5]

Coxiella burnetii infection in humans causes the disease Q fever. About 40% of infected individuals develop clinical signs, with 38% exhibiting acute febrile illness and 2% of these cases requiring hospitalization.[6,7] The disease has been reported in many countries around the world but epidemiological data are limited to those generated by outbreak investigations, serosurveys in humans or animals, or data from laboratories, and most data are from the United States and Europe. Q fever has been reported in several countries that share a border with Jordan, including Iraq, Saudi Arabia, and Israel.[3,8–10] A recent study reported an overall *C. burnetii* prevalence of 63% among dairy ruminants (cattle, sheep, and goats) in Jordan.[11] However, there are no data available on seroprevalence and risk factors among humans in Jordan. Thus, this study aimed to fill this knowledge gap through testing a sample of the general population of Jordan for *C. burnetii* seropositivity.

MATERIAL AND METHODS

Study population and sample size. Jordan is located in the Middle East and North Africa region with a GDP of $40.1 billion, a population of 9.7 million, and a life expectancy of 74 years.[12] Sample size was calculated using the formula $n = z^2\, p\, (1 - p)/d^2$ at 95% CI ($z = 1.96$) and expected seroprevalence (p) of 50%, with a precision (d) of 0.05. The minimum required sample size was 384 individuals, but 781 individuals were included for higher precision. Healthy individuals accompanying sick relatives who were seeking care at government human health centers were randomly selected to participate in this study. The health centers were selected from a list provided by the Ministry of Health and the number of health centers, and the target number of individuals from each health center were proportionately selected based on population size from each of the 11 governorates of Jordan.

Setting. This cross-sectional study was conducted from November 2015 to May 2016. All blood samples were collected by registered nurses and medical professionals. At each health center, the sera were harvested from the blood samples by centrifugation at 3,000 rpm for 10 minutes. The sera samples were then placed in Eppendorf tubes and stored at –20°C until shipment to the Food Safety and Zoonotic Diseases Laboratory at Jordan University of Science and Technology (JUST). The samples were transported to the laboratory under cold conditions in ice boxes. Once at the laboratory, aliquots (*ca.* 200 µL each) were made from each serum sample. An inventory was created for all sera samples, and they were properly labeled with governorate name, health center name, and sample number. The samples were stored in racks in the laboratory freezer at –20°C until analyses. The samples were analyzed within 1 month of storage.

Risk factor data collection. A validated questionnaire was used to collect demographic and risk factor data about each participant such as food consumption habits and animal ownership. The questionnaire was tested among 40 individuals, and all needed revisions were made to the final questionnaire. The questionnaire was self-administered in Arabic and returned in a questionnaire collection envelope.

Ethical considerations. This research was approved by the Institutional Research Bioethics Committee of JUST (IRB#7601) and by the Jordanian Ministry of Health. All individuals were briefed about the study objectives, and it was emphasized to all of them that their enrollment is completely voluntary. All data were collected and stored confidentially.

*Address correspondence to Mohammad M. Obaidat, Faculty of Veterinary Medicine, Jordan University of Science and Technology, Irbid 22110, Jordan. E-mail: mmobaidat@just.edu.jo

Laboratory testing. Sera samples were tested for *C. burnetii* IgG antibodies using SERION ELISA classic *C. burnetii* IgG Phase 2 (Institut Virion\Serion GmbH, Würzburg, Germany) following the manufacturer's instructions.

Data management and statistical analyses. The test results and questionnaire data were entered into Microsoft Excel (Redmond, WA) and analyzed using STATA 14.2 (College Station, TX). Frequency distributions were examined to assess the distribution of the data. Simple descriptive statistics and χ^2 statistics were performed where appropriate. Bivariate analyses were conducted to assess associations between seropositivity and each independent variable collected (gender, age, education level, village or city residence, governorate, household income, history of living outside Jordan, consumption of raw meats, consumption of raw milk, and animal ownership [sheep, goats, cattle, camel, dogs, and cats]). Variables associated with the outcome at a *P*-value of ≤ 0.05 were considered significant. The significant variables found in this study and other significant variables reported in literature (such as age) were included in the final logistic regression model after testing for collinearity, variance inflation factors, and Hosmer–Lemeshow goodness-of-fit test.

RESULTS

Overall, the seroprevalence of *C. burnetii* Phase 2 IgG was 24.2% (Table 1). Univariate analysis (unadjusted odds ratios [UOR]) showed higher odds of seropositivity among males (UOR = 1.4, $P = 0.6$ compared with females), and individuals living in the governorates of Az-Zarqa (UOR = 4.0, $P < 0.001$), Tafela (UOR = 2.5, $P = 0.02$), and Al-Karak (UOR = 3.7, $P < 0.001$) compared with those residing in the capital city, Amman. Living in a village and drinking raw milk were also associated with a higher odds of *C. burnetii* seropositivity (Table 1). There was a significantly greater odds of seropositivity among individuals who own any small ruminants (Table 2). Dog ownership was also associated with greater odds of seropositivity (Table 2).

The multivariate logistic regression showed that individuals who own small ruminants had significantly greater odds of seropositivity compared with those who do not own small ruminants (Table 3). In addition, individuals who live in Al-Karak, Az-Zarqa, and Al-Tafilah had significantly greater odds of seropositivity (OR = 3.6, 4.8, and 2.7, respectively) than individuals who live in the capital city, Amman (Table 3).

TABLE 1
Demographic factors and UOR for *Coxiella burnetii* seropositivity in Jordan, 2015–2016; $n = 781$

	No. + /No. tested	% Positive	UOR	*P*-value
Seropositive	189/781	24.2	NA	–
Age (Years)				
< 15	5/18	27.8	1	NA
15–29	54/251	21.5	0.71	0.54
30–49	76/293	25.9	0.91	0.864
50 +	54/219	24.7	0.85	0.77
Gender				
Female	95/440	21.6	1	NA
Male	94/341	27.6	1.38	**0.05**
City or village				
Badia or village	118/438	26.9	1	NA
City	71/343	20.7	0.71	**0.04**
Governorate				
Ma'an	9/69	13.0	0.63	0.34
Irbid	11/70	15.7	0.79	0.60
Jerash	22/87	25.3	1.43	0.36
Al-Karak	34/73	46.6	3.69	**0.001**
Az-Zarqa	38/76	50.0	4.23	**< 0.00**
Al-Tafilah	28/75	37.3	2.52	**0.02**
Al-Balqa	9/74	12.2	0.56	0.26
Amman	13/68	19.1	1	NA
Madaba	13/75	17.3	0.89	0.78
Al-Mafraq	7/57	12.3	0.59	0.30
Ajloun	5/57	8.8	0.41	0.11
Education				
No education	55/203	27.1	1	NA
Any education	134/578	23.2	0.81	0.26
Monthly household income				
Less than 750 USD	127/522	24.3	1	NA
More than 750 USD	62/259	23.9	0.98	0.90
Living Abroad				
Ever lived abroad	26/112	23.2	1	NA
Never lived abroad	163/669	24.4	1.07	0.79
Consumption of undercooked meat				
Yes	17/69	24.6	1.03	0.93
No	172/712	24.2	1	NA
Consumption of raw milk				
Yes	37/110	33.6	1.73	0.01
No	152/671	22.7	1	NA

UOR = unadjusted odds ratios. Values in bold indicate significant association ($P < 0.05$) with seropositivity.

TABLE 2
Animal ownership and UOR for *Coxiella burnetii* seropositivity in Jordan, 2015–2016; $n = 781$

Animal ownership	No. + /No. tested	% Positive	UOR	*P*-value
Camels				
Yes	5/11	45.5	2.65	0.11
No	184/770	23.9	1	NA
Goat				
Yes	72/161	44.7	3.48	**< 0.0001**
No	117/620	18.9	1	NA
Cow				
Yes	13/48	27.1	1.18	0.63
No	176/733	24.0	1	NA
Sheep				
Yes	73/156	46.8	3.86	**< 0.0001**
No	116/625	18.7	1	NA
Small ruminants				
Yes	86/201	42.8	3.46	**< 0.0001**
No	103/580	17.8	1	NA
Cats				
Yes	9/43	20.9	0.82	0.61
No	180/738	24.4	1	NA
Dogs				
Yes	32/93	34.4	1.77	**0.02**
No	157/688	22.8	1	NA

UOR = unadjusted odds ratios. Values in bold indicate significant association ($P < 0.05$) with seropositivity.

DISCUSSION

This study was the first to report evidence of *C. burnetii* infection of humans in Jordan and found an overall seroprevalence of 24.2%, which is higher than the seroprevalence reported in other countries despite the lower sensitivity of the ELISA method used in our study compared with commonly used immunofluorescence assay.[13] Lower seroprevalence was reported in Thailand (12.4%),[14] Northern Ireland (12.8%),[15] and Barcelona, Spain (15.3%),[16] whereas higher seroprevalence was reported in Cyprus (52.7%).[17] Our study also shows that the seroprevalence in small ruminant farmers is 42.8%. In The Netherlands, high seroprevalence was found in dairy sheep (66.7%)[18] and goat (73.5%) farmers.[19]

The dairy cow owners in Jordan are either commercial or subsistence owners, whereas small ruminant owners are primarily subsistence ones with a very short sale chain, primarily to nearby dairy shops. In this study, small ruminant ownership is significantly associated with *C. burnetii* seropositivity. Previous studies in The Netherlands showed that living on a farm increases the odds of seropositivity among veterinary students,[20] and farmers with frequent work or exposure to goats also had a high risk of seropositivity.[18,19] In a study in the United States, farmers who had contact with goats and goat newborns had increased risk of infection during an outbreak associated with abortion storm in a goat farm.[21] The latter study showed that farm visitors also contracted the disease.[21] An outbreak in Germany among residents living in close proximity to a sheep farm was linked to infected sheep birthing.[22,23] Proximity to farm animals and contact with infected animals was also considered as the most important risk factor for infection in other studies from Europe (Germany, France, The Netherlands, and Bulgaria).[24] Another study showed that working with ruminants as laboratory animals doubled the risk for *C. burnetii* seropositivity.[25] The high risk of infection/seropositivity among animal owners is consistent with inhalation being the major transmission route of *C. burnetii* and the ability of the pathogen to travel long distances in air.[26] It has been shown that automatic milking of ruminants and compliance with wearing gloves during and around calving protects farmers against *C. burnetii* infection.[27] Therefore, biosecurity and protective measures are recommended for farmers and veterinarian, especially around calving/lambing seasons. In addition, respiratory protection is recommended during abortion storms in ruminants to protect against *C. burnetii* infection.[26]

TABLE 3
Final multivariate logistic regression model for *Coxiella burnetii* seropositivity in Jordan, 2015–2016

Variable	Adjusted odds ratio	*P*-value	95% CI
Age: 15–29 years*	2.17	0.208	0.65–7.25
Age: 30–49 years*	2.96	0.075	0.90–9.79
Age: 50+ years*	2.58	0.123	0.77–8.63
Male	0.91	0.653	0.62–1.36
Owns small ruminant	3.6	**0.002**	1.59–8.14
Drinks raw milk	1.61	0.066	0.97–2.68
Owns a dog	0.90	0.750	0.49–1.68
Ma'an governorate†	0.67	0.411	0.26–1.74
Irbid governorate†	0.96	0.934	0.39–2.40
Jerash governorate†	0.99	0.980	0.41–2.36
Al-Karak governorate†	**3.60**	**0.002**	1.59–8.14
Az-Zarqa governorate	**4.77**	**0.001**	2.13–10.69
Al-Tafila governorate†	**2.69**	**0.017**	1.19–6.07
Al-Balqa governorate†	0.77	0.597	0.30–2.01
Madaba governorate†	0.87	0.759	0.35–2.15
Al-Mafraq governorate†	0.59	0.313	0.21–1.66
Ajloun governorate†	0.54	0.289	0.18–1.68

Values in bold indicate significant association ($P < 0.05$) with seropositivity.
* Compared with reference age group < 15 years old.
† Compared with the capital city, Amman.

There is a significant difference in the seroprevalence among governorates in Jordan. Individuals who live in Al-Karak, Az-Zarqa, and Al-Tafilah have greater odds of seropositivity compared with individuals who live in the capital city, Amman. Significant differences among regions within the same country have also been reported in Thailand.[14] In addition, two locations were identified with high seroprevalence compared with other locations in Cyprus using geographical information system.[17] Differences among governorates might be explained by differences in rainfall, soil types, moisture, and vegetation density. A recent study showed that vegetation density is negatively associated with Q fever incidence in The Netherlands.[28] Higher soil moisture and open land use is negatively associated with the incidence of Q fever.[28] The large animal populations in Al-Karak, Az-Zarqa, and Al-Tafilah coupled with the low annual rainfall might increase the aerosolization of and infection by *C. burnetii*.

The univariate analysis shows that consumption of raw unpasteurized milk is significantly associated with higher *C. burnetii* seropositivity. However, this association is not significant in the multivariate analysis. A recent risk assessment study in the United Kingdom showed that the risk of drinking raw milk and eating unpasteurized cheese for *C. burnetii* infection exists, but lower than the risk of transmission by aerosol inhalation from parturient products and livestock contact.[29] Moreover, ingestion of *C. burnetii* in raw milk might lead only to seroconversion, not necessarily to clinical disease, and seroconversion might occur from ingesting inactivated *C. burnetii* cells as well as live ones.[30]

In the present study, males have significantly higher seroprevalence compared with females in the univariate analysis, but not in the multivariate one. No significant difference by gender was observed in Thailand,[14] Spain,[16] and The

Netherlands.[19] However, some reported higher anti-*C. burnetii* antibodies in males compared with females and this may be due to males having more contact with livestock in some settings.[31–33]

CONCLUSION

This is the first study to document *C. burnetii* in humans in Jordan and it found that seroprevalence is high. Given that endocarditis has been reported as a chronic complication of Q-fever in several countries such as United States,[34] Canada,[35] and France,[36] it is likely that is also the case in Jordan. Considering Q fever infection in the differential diagnosis of endocarditis could be helpful as this condition can be improved with antibiotic treatment.[37] Q fever should also be considered in the differential diagnosis in febrile-like illnesses in Jordan, especially among farmers, veterinarians, and others with a history of close contact with small ruminants. Future studies of acute or chronic cases of Q fever in Jordan are recommended.

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Authors' addresses: Mohammad M. Obaidat and Alaa E. Bani Salman, Department of Veterinary Pathology and Public Health, Faculty of Veterinary Medicine, Jordan University of Science and Technology, Irbid, Jordan, E-mails: mmobaidat@just.edu.jo and aebanisalman@just.edu.jo. Lile Malania and Paata Imnadze, National Center for Disease Control and Public Health, Tbilisi, GA, E-mails: malanial@yahoo.com and pimnadze@ncdc.ge. Amira A. Roess, Department of Global Health, Milken Institute School of Public Health, George Washington University, Washington, DC, E-mail: aroess@gwu.edu. Ryan J. Arner, Arner Science Consulting, LLC, Freeport, PA, E-mail: ryan.j.arner@gmail.com.

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