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Seroepidemiology, Spatial Distribution, and Risk Factors of *Francisella tularensis* in Jordan

Mohammad M. Obaidat,[1]* Lile Malania,[2] Alaa E. Bani Salman,[1] Ryan J. Arner,[3] and Amira A. Roess[4,5]

[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]*Ryan Arner Science Consulting, LLC, Freeport, Pennsylvania;* [4]*Department of Global Health, Milken Institute School of Public Health, George Washington University, Washington, District of Columbia;* [5]*Department of Global and Community Health, College of Health and Human Services, George Mason University, Fairfax, Virginia*

Abstract. There is a paucity of data on *Francisella tularensis* in the Middle East and North Africa. This is the first countrywide study to determine the seroprevalence, spatial distribution, and risk factors for *F. tularensis* in Jordan. A total of 828 Jordanians were serologically tested for *F. tularensis* by ELISA. These individuals filled out a self-administered questionnaire to collect demographic and risk factor information. Bivariate and multivariate logistic regressions were performed to determine which variables are associated with seropositivity. The overall seroprevalence of *F. tularensis* was 7.7% (95% CI: 6.10–9.75). The bivariate analyses showed that age, region of residence, small ruminant ownership, and practicing horticulture were significantly associated with seropositivity, and these variables were controlled for in the multivariate analysis. The multivariate analysis showed an increased odds of seropositivity among individuals living in northern desert, middle, and northern highland areas, compared with individuals living in the drier southern area, as 7.27 (95% CI: 2.49–21.19), 3.79 (95% CI: 1.53–9.39), and 3.52 (95% CI: 1.45–388.55), respectively. Individuals owning a small ruminant had 1.86 (95% CI: 1.02–3.40) greater odds for seropositivity than individuals who do not own a small ruminant. Individuals practicing horticulture had 2.10 (95% CI: 1.20–3.66) greater odds for seropositivity than individuals who do not practice horticulture. This is the first study to address the seroprevalence of *F. tularensis* in Jordan and the Middle East. Further research is needed to identify clinical cases of tularemia in Jordan and to determine the circulating *F. tularensis* subspecies.

INTRODUCTION

Francisella tularensis is a Gram-negative intracellular coccobacillus. Two of the four subspecies of *F. tularensis*, namely, *tularensis* and *holarctica*, cause disease in humans.[1] The pathogen survives for months in soil, water, and dead animals but is easily killed by heat and water chlorination. *Francisella tularensis* has a broad range of hosts including birds, and domestic and wild mammals[2] and can be transmitted by several species of ticks, flies, and mosquitoes.[3,4] In addition, *F. tularensis* can be transmitted by consuming undercooked infected meat (e.g., rabbits), drinking contaminated water, and inhaling contaminated hay, grain, and soil dust.[5] Following 1–14 days of incubation, the disease, tularemia, can present in six different forms: glandular, ulceroglandular, oculoglandular, oropharyngeal, typhoidal, and pneumonic.[5]

Tularemia has been reported in several countries, mainly in the Northern Hemisphere, such as in the United States,[6] Europe,[2] the Republic of Georgia,[7] Turkey,[8] Japan,[9] and China.[10] Meanwhile, there is a paucity of data on the disease in the Middle East–North Africa region. However, the disease has been reported in Iran.[11]

The lack of the reports about tularemia in different countries might be attributed to the fact that this rare disease presents with a broad spectrum of clinical signs and often goes undiagnosed. For example, a study in Kenya found 3.7% of febrile illnesses tested positive for *F. tularensis* antibodies, although none of the providers suspected tularemia as a potential diagnosis.[12] This scenario was also reported in the United States, where more than half of the confirmed tularemia cases were not initially suspected until the incidental isolation of the *F. tularensis*.[6] This study aimed to determine the seroprevalence, spatial distribution, and risk factors for *F. tularensis* in Jordan.

MATERIALS AND METHODS

Setting and participants. This was a cross-sectional study carried out between November 2015 and May 2016. This study recruited participants from 11 of the 12 governorates in Jordan. Jordan is an upper-middle–income country of 9.7 million people located in the Middle East and Northern Africa.[13] Participants were Jordanian citizens who accompanied relatives who attended local health centers for general health examinations. From each governorate, two to six health centers were randomly selected from the Ministry of Health center directory for inclusion in the study. Participants were recruited by registered nurses for participation in the study and briefed about the purpose of the study. Blood samples were collected from the participants by registered nurses. Serum was harvested from the samples by centrifugation at 3,000 rpm for 10 minutes and stored at the health centers until they were shipped to the Food Safety and Zoonotic Diseases Laboratory at the Jordan University of Science and Technology (JUST). The harvested sera were stored in aliquots (*ca*. 200 μL each) at –20°C until analyses. All sera were documented in the inventory and labeled properly with a unique identifier that included the governorate, health center name, and the number of the sample. Samples were tested within 4 weeks of storage.

Sample size. There are no data on the seroprevalence of *F. tularensis* in Jordan; thus, we calculated the largest needed sample size (n) of 384 to detect a seroprevalence rate of 0.5 ± 0.05. However, sera of 828 participants were tested to increase the power of the analysis.

Laboratory analysis. The serum samples were tested for IgG antibodies to lipopolysaccharides of *F. tularensis* using Serion ELISA classic *F. tularensis* IgG (Virion\Serion GmbH, Würzburg, Germany) in accordance with the manufacturer's

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

instructions. The kit showed 96.3% sensitivity and 96.8% specificity.[14] Antibody titers > 15 U/mL were reported as positive as recommended by the manufacturer. Positive samples were tested by Rose Bengal (Vircell, Granada, Spain) to investigate the possibility of a cross-reaction with *Brucella* spp.

Questionnaire data. A pretested and validated questionnaire was self-administered by participants in Arabic and information collected on demographic, environmental, and zoonotic risk factor information. The questionnaire was pretested by 40 individuals, and follow-up interviews were conducted with them to validate the instrument.

Ethics statement. The Institutional Research Bioethics Committee of JUST approved this study (Institutional Research Bioethics policy # 7601). The bioethics committee of the Jordanian Ministry of Health also approved the study and granted permission to access the government health centers for sample collection. Signed informed consent from adult participants and parental consent for children were obtained before data and sample collection. All data were collected and stored confidentially and accessed only by the research team.

Statistical analyses. The *F. tularensis* seroprevalence status and demographic and risk factor information for each participant were entered into a Microsoft Excel sheet (Microsoft, Redmond, WA), which was then imported into Stata version 14.2 (StataCorp, College Station, TX) for analysis. Bivariate analyses were conducted to analyze the relationship between *F. tularensis* seropositivity and a number of demographic, zoonotic, and environmental variables, including ownership of various animals (cow, goat, sheep, camel, cats, and dogs). A final logistic regression was run to include variables found to be significant at a P-value < 0.05 in the bivariate analysis and variables reported to be risk factors for *F. tularensis* seropositivity in the literature (gender). Results with $P < 0.05$ were considered significant.

RESULTS

Of the 828 people included in the study, 64 (7.7%) were seropositive for *F. tularensis*. The governorates with the highest seroprevalence were Irbid (15.2%), Mafraq (14.9%), and Balqa (11%) (Figure 1). The lowest seroprevalence was reported in Ma'an (1.5%) and Tafilah (2.7%) (Figure 1).

The bivariate analyses showed that age, region, small ruminant ownership, and practicing horticulture were significantly associated with seropositivity (Tables 1 and 2). Significantly higher seroprevalence was found in those aged ≥ 50 years (10.5%) than those aged ≤ 30 (5.4%) (Table 1). Individuals living in the northern desert (Mafraq), northern highland (Ajloun, Irbid, and Jerash), and middle area (Amman, Zarqa, and Balqa) had

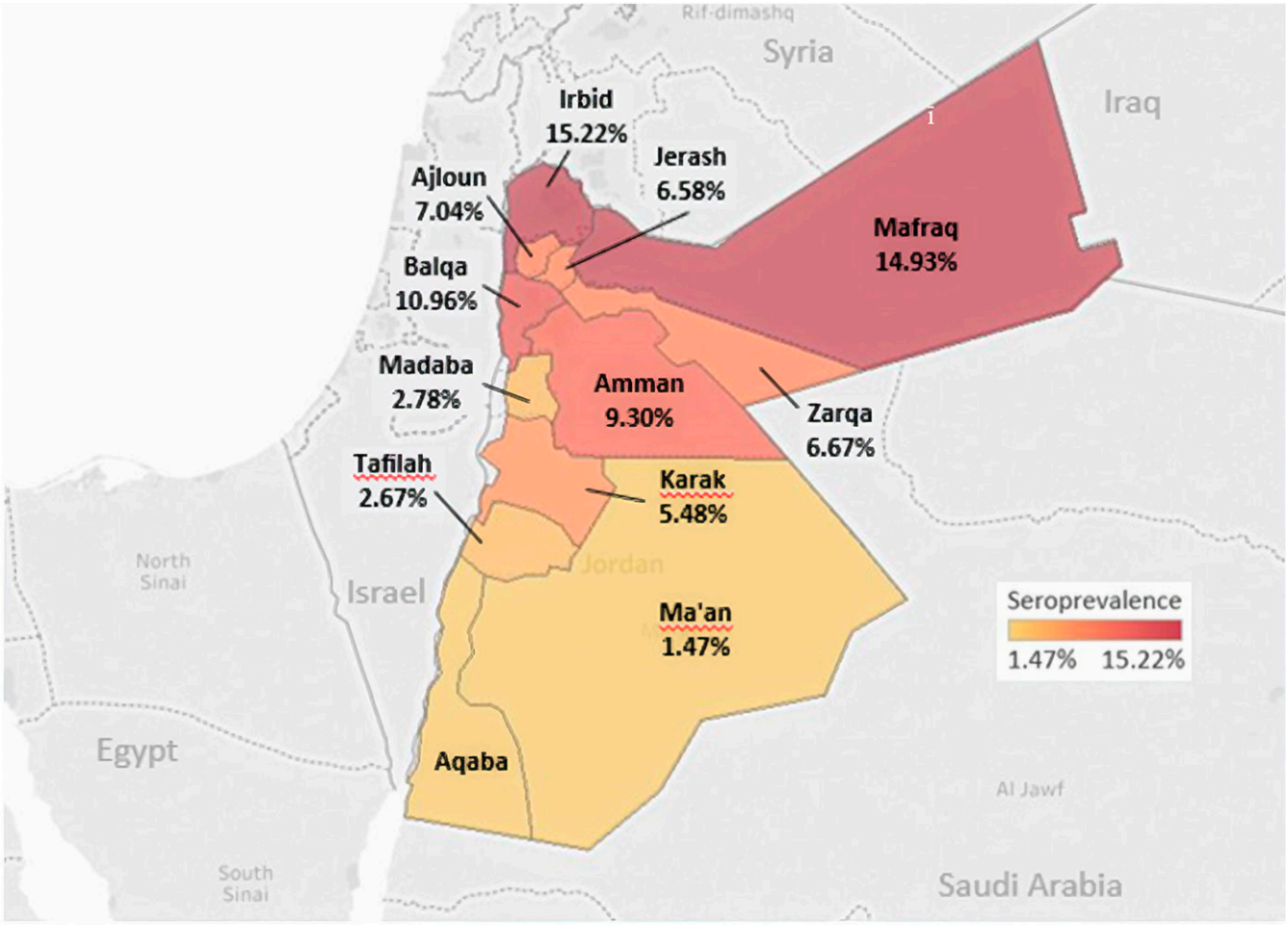

FIGURE 1. Spatial distribution of *Francisella tularensis* seropositivity in Jordan population, 2015–2016. This figure appears in color at www.ajtmh.org.

TABLE 1

Descriptive statistics, seroprevalence, and unadjusted odds ratios for demographic variables associated with *Francisella tularensis* seropositivity in Jordan, 2015–2016 (n = 828)

Variable	# seropositive/# tested (% seropositive)	Unadjusted OR	*P*-value
Seropositive	64/828 (7.7%)	–	–
Age (years)			
< 30	16/296 (5.4%)	1	–
30–49	24/304 (7.9%)	1.5 (0.78–2.88)	0.224
50+	24/228 (10.5%)	2.06 (1.07–3.97)	**0.031**
Gender			
Male	33/339 (9.7%)	1.59 (0.96–2.66)	0.074
Female	31/489 (6.3%)	1	–
Region			
Northern desert (Mafraq)	10/67 (14.9%)	5.24 (1.91–14.37)	**0.001**
Northern highland (Ajloun, Irbid, and Jerash)	24/239 (10.0%)	3.33 (1.41–7.90)	**0.006**
Middle area (Amman, Zarqa, and Balqa)	21/234 (9%)	2.94 (1.22–7.07)	**0.016**
Southern area (Karak, Tafilah, and Ma'an)	7/216 (3.2%)	1	–
Dead Sea plateau (Madaba)	2/72 (2.8%)	0.85 (0.17–4.20)	0.845
Education level			
No education	19/239 (9%)	1	–
Any education	45/589 (7.6%)	0.96 (0.55–1.67)	0.880
Place of residence			
Village or badia	41/457 (9%)	1	–
City	23/371 (6.2%)	0.67 (0.39–1.14)	0.140
Housing type			
Apartment	17/246 (6.9%)	1	–
House	47/582 (8.1%)	1.18 (0.66–2.10)	0.567
Household income			
More than 750 USD	21/247 (8.5%)	1	–
Less than 750 USD	43/581 (7.4%)	1.16 (0.67–2.00)	0.588
Did you live outside Jordan?			
Yes	9/126 (7.1%)	1.11 (0.53–2.30)	0.789
No	55/702 (7.8%)	1	–

significantly higher ($P < 0.05$) seroprevalence than individuals living in the southern area (Karak, Tafilah, and Ma'an) (Table 1). Individuals who own a small ruminant had significantly higher (12.6%) seropositivity than those who do not own a small ruminant (6.4%) (Table 2). Individuals who practice horticulture had significantly higher seropositivity (13.8%) than individuals who do not practice horticulture (5.6%) (Table 2).

There was no significant association between *F. tularensis* seropositivity and gender, education level, place of residence (village versus city), housing type (house versus apartment), and income level (Table 1). Ownership of cows, camels, dogs, and cats was not associated with seropositivity (Table 2). In addition, consumption of raw milk, undercooked meat, or wild traditional herbs and the source of drinking water were not associated with seropositivity (Table 2). Having a home backyard garden and growing vegetables in the backyard were also not associated with seropositivity (Table 2).

The final multivariate regression model included gender, age, region, small ruminant ownership, and practicing horticulture (Table 3). This analysis showed that region, small ruminant ownership, and practicing horticulture were significantly associated with *F. tularensis* seropositivity. Compared with individuals living in the southern area, individuals living in northern desert, middle area, and northern highland had greater odds of seropositivity 7.27 (95% CI: 2.49–21.19), 3.79 (95% CI: 1.53–9.39), and 3.52 (95% CI: 1.45–8.55), respectively. Individuals owning a small ruminant had 1.86 (95% CI: 1.02–3.40) higher odds for seropositivity than individuals who do not own a small ruminant. Individuals practicing horticulture had 2.10 (95% CI: 1.20–3.66) higher odds of seropositivity than individuals who do not practice horticulture (Table 3).

DISCUSSION

This study provides an insight into the seroprevalence of *F. tularensis* in Jordan and found that 7.7% of the study population was seropositive for *F. tularensis*. Lower seroprevalence was reported in endemic countries such as Germany (2% in hunters),[15] Finland (2.0%),[16] Belgium (2.0%),[17] Turkey (0.3–2.1%),[18,19] and Austria (0.5%),[20] whereas higher seroprevalence was reported in the rural population in northern Azerbaijan (15.5%)[21] and in the western (14.4%),[22] southeastern (6.5%), and southwestern (6%) parts of Iran.[11] These comparisons are somewhat limited because different tests were used. Nevertheless, these comparisons indicate varying regional differences that could be explained by varying exposures.

The bivariate and multivariate analyses show that region, small ruminant ownership, and practicing horticulture were significantly associated with seropositivity. Age was associated with seropositivity in the univariate but not the multivariate analyses. Other factors were not associated with seropositivity such as gender; education level; place of residence; housing type; income level; cows' and pets' ownership; consumption of raw milk, undercooked meat, and wild traditional herbs; and the source of drinking. In addition, having a home backyard garden was not associated with seropositivity.

The multivariate analysis showed that the seroprevalence in Jordan varies by region. Regional differences within the same country have been reported in Canada,[23] Sweden,[24,25]

TABLE 2

Descriptive statistics, seroprevalence, unadjusted odds ratios for zoonotic and environmental factors with *Francisella tularensis* seropositivity in Jordan, 2015–2016 (n = 828)

Variable	# Positive/# tested (% seropositive)	Unadjusted odds ratio	*P*-value
Cow ownership			
No	56/755 (7.4%)	1	–
Yes	8/73 (11%)	1.54 (0.70–3.36)	0.283
Camel ownership			
No	63/815 (7.7%)	1	–
Yes	1/13 (7.7%)	0.99 (0.13–7.74)	0.996
Small ruminant ownership			
No	41/646 (6.4%)	1	–
Yes	23/182 (12.6%)	2.13 (1.24–3.66)	**0.006**
Cat ownership			
No	58/777 (7.5%)	1	–
Yes	6/51 (11.8%)	1.65 (0.68–4.04)	0.270
Dog ownership			
No	53/739 (7.2%)	1	–
Yes	11/89 (12.4%)	1.83 (0.92–3.64)	0.088
Drinks raw milk			
No	53/738 (7.2%)	1	–
Yes	11/90 (2.2%)	1.80 (0.90–3.59)	0.095
Eats undercooked meat			
No	56/757 (7.4%)	1	–
Yes	8/71 (11.3%)	1.59 (0.73–3.48)	0.247
Eats traditional wild herbs			
No	31/372 (8.3%)	1	–
Yes	33/456 (7.2%)	0.86 (0.52–1.43)	0.557
Source of drinking water*			
Rain collection cistern	10/87 (11.5%)	1.65 (0.81–3.38)	0.168
Filtered water	42/524 (8.02=%)	1.12 (0.65–1.91)	0.686
Municipality water	17/249 (6.83=%)	0.83 (0.47–1.48)	0.524
Spring lakes	5/49 (10.2%)	1.39 (0.53–3.63)	0.504
Has a backyard garden			
No	41/518 (7.9%)	1	–
Yes	23/310 (7.4%)	0.93 (0.55–1.59)	0.796
Grows vegetables in the backyard			
No	46/609 (7.6%)	1	–
Yes	18/219 (8.2%)	1.10 (0.620–1.93)	0.752
Practices horticulture			
No	34/610 (5.6%)	1	–
Yes	30/218 (13.8%)	2.70 (1.61–4.54)	**0.000**

Bold indicates statistically significant values.

* Water sources were not mutually exclusive; some respondents named 2 water sources.

Azerbaijan,[21] and Iran.[11] These difference might be attributed to differences in tick density by region, annual rainfall, and presence of *F. tularensis* reservoirs.

The multivariate analysis showed that individuals who own a small ruminant have 1.86 higher odds of seropositivity than those who do not own a small ruminant. This might be attributed to the possibility that small ruminants can get infected with *F. tularensis*. For example, *F. tularensis* was confirmed as a cause of abortions in sheep in the Unites States.[26] In addition, goats in northwest Tuscany (Italy) and sheep in Bulgaria and Turkey[27] tested positive for *F. tularensis*.[28] Moreover, cases of tularemia transmitted from sheep to humans were reported in Turkey.[29]

Individuals practicing horticulture in Jordan had 2.1 higher odds for seropositivity than individuals who do not practice horticulture, and this is in line with previous reports. For example, a 4.0% seroprevalence of anti–*F. tularensis* IgG was reported in employees of forestry enterprises in Germany[30]

TABLE 3

Final multivariate logistic regression model of *Francisella tularensis* seropositivity in Jordan population, 2015–2016

Variable	Adjusted odds ratio	*P*-value	95% CI
Age (30–49 years)*	1.63	0.158	0.83–3.21
Age (50+ years)*	1.77	0.112	0.88–3.58
Male†	1.55	0.125	0.88–2.73
Northern desert (Mafraq)‡	7.27	**0.000**	2.49–21.19
Northern highland (Ajloun, Irbid, and Jerash)‡	3.52	**0.006**	1.45–8.55
Middle area (Amman, Zarqa, and Balqa)‡	3.79	**0.004**	1.53–9.39
Dead Sea plateau (Madaba)‡	1.09	0.921	0.21–5.48
Own a small ruminant (yes)	1.86	**0.042**	1.02–3.40
Practices horticulture (yes)	2.10	**0.000**	1.20–3.66

* Compared with reference age-group (< 30 years).

† Compared with female.

‡ Compared with southern areas (Karak, Tafilah, and Ma'an).

and among individuals in Finland participating in farming activities (land preparation, cleaning barns, producing silage, and harvesting hay).[31]

Several factors that are associated with *F. tularensis* in the literature were not associated with seropositivity in this study including age, source of drinking water, and contact with cats. For example, age was associated with seropositivity in Canada[23] and Iran.[22] Water was also confirmed as a source of human tularemia in Turkey,[8,32] but there was no association between water source and seropositivity in ours, and this may be due to the nearly ubiquitous access to treated water in Jordan. In addition, contact with cats was linked to several tularemia cases in the United States.[33,34] In Jordan, few households have cats that live in the home. The seroprevalence did not differ between males and females in our study, which is in line with previous reports from Canada[23] and Iran.[22]

This cross-sectional study provided solid initial evidence of *F. tularensis* and its risk factors in Jordan and established an association between seropositivity and small ruminant ownership and practicing horticulture. The nonspecific signs of tularemia including fever and lymphadenopathy might make the diagnosis difficult for general practitioners and can contribute to underreporting. Thus, it is recommended that clinicians consider tularemia as a differential diagnosis for patients presenting with lymphadenopathies and inflammatory neck masses, especially those who are in contact with small ruminants. Further research is needed to identify clinical cases of tularemia in Jordan and to determine the circulating *F. tularensis* subspecies.

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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, National Center for Disease Control and Public Health, Tbilisi, GA, E-mail: malanial@yahoo.com. Ryan J. Arner, Ryan Arner Science Consulting, LLC, Freeport, PA, E-mail: ryan.j.arner@gmail.com. Amira A. Roess, Department of Global and Community Health, College of Health and Human Services, George Mason University, Fairfax, VA, E-mail: aroess@gmu.edu.

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