

What do we know about Q fever in Mexico?

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ABSTRACT

In Mexico, Q fever is considered a rare disease among humans and animals. From March to May of 2008, three patients were referred, from the state of Hidalgo to a tertiary-care center in Mexico City, with an acute febrile illness that was diagnosed as Q fever. We decided to undertake a cross sectional pilot study to identify cases of acute disease in this particular region and to determine the seroprevalence of *Coxiella burnetii* among healthy individuals with known risk factors for infection with this bacteria. Q fever was defined according to the Centers for Disease Control and Prevention criteria. All subjects were interviewed for signs and symptoms of the disease, demographic and household characteristics and occupational exposure to cattle. Blood samples were taken from hospitalized and outpatients with symptoms suggestive of Q fever, as well as from asymptomatic individuals with direct and daily exposure to cattle (slaughterers, butchers, farmers, shepherds and veterinarians) in the five municipalities. We report the occurrence of 17 cases with positive antibodies against *C. burnetii* in a rural area of central Mexico; eight cases had clinical criteria of acute Q fever disease. Results from this pilot study underscore the need for active surveillance programs and comprehensive studies to further define the prevalence and risk factors associated with the disease in Mexico, to know more about its clinical presentation and to characterize bacterial factors involved in its pathogenesis.

Key words. Q fever. *Coxiella burnetii*. Exotic diseases in Mexico. Infections in the rural area. Zoonosis.

INTRODUCTION

Q fever is a zoonotic disease caused by *Coxiella burnetii*, a species of bacteria with a worldwide distribution.¹ The primary reservoirs of *C. burnetii* are cattle, sheep and goats. *C. burnetii* is excreted

¿Qué sabemos acerca de la fiebre Q en México?

RESUMEN

En México la fiebre Q se considera una enfermedad rara entre los humanos y los animales. Sin embargo, entre marzo y mayo 2008 tres pacientes del estado de Hidalgo fueron referidos a un hospital de tercer nivel en la Ciudad de México por una enfermedad febril aguda y fueron diagnosticados con fiebre Q. Se decidió llevar a cabo un estudio piloto para identificar casos de enfermedad aguda en esa región y determinar la prevalencia serológica de *Coxiella burnetii* en individuos sanos con factores de riesgo conocidos. Se definió fiebre Q conforme a los criterios de los Centros de Control y Prevención de Enfermedades (CDC). Todos los sujetos en estudio fueron entrevistados para detectar signos y síntomas de la enfermedad, características demográficas y de la vivienda y exposición ocupacional a ganado. Se tomaron muestras sanguíneas a los pacientes hospitalizados y externos con síntomas sugerentes de fiebre Q, así como a individuos asintomáticos con exposición directa y cotidiana con ganado (granjeros, carniceros, pastores y veterinarios). Se reportaron 17 casos con anticuerpos positivos contra *C. burnetii* en esta área rural; ocho casos cumplieron con los criterios de enfermedad aguda. Los resultados subrayan la necesidad de llevar a cabo programas de vigilancia activa y la realización de estudios prospectivos poblacionales para definir la prevalencia y factores de riesgo de la enfermedad en México, así como para caracterizar mejor la presentación clínica y los factores asociados con la patogenicidad de la bacteria.

Palabras clave. Fiebre Q. *Coxiella burnetii*. Enfermedades exóticas en México. Infecciones en el área rural. Zoonosis.

in milk, urine and feces of infected animals and most importantly, during birthing the bacteria is shed in high numbers within the amniotic fluids and the placenta. The organisms are resistant to heat, drying and many common disinfectants, features that enable the bacteria to survive for long

periods in the environment. Infection of humans usually occurs after inhalation of aerosols from contaminated barnyards dust, excreta and direct contact with birth fluids of infected herd animals. The disease has also been described in abattoir workers.² Only about 40% of all people infected with *C. burnetii* develop clinical disease and in certain risk groups (immunocompromised hosts) the infection (symptomatic or not) may result in chronic disease (2% of cases).³⁻⁵

Since 1994, Q fever is a notifiable disease in Mexico.⁶ Due to the lack of specific signs and symptoms and to the difficulties of making an accurate diagnosis without appropriate laboratory testing, Q fever is underreported and it is commonly referred as a rare, exotic disease in both, humans and animals. Interestingly, the seroprevalence of Q fever reported in the United States during the National Health and Nutrition Examination Survey (NHANES 2003-2004), was higher for subjects of Mexican-American origin than that reported in the non-Hispanic American populations. This study suggested differences in geographical or occupational exposure, but we could not identify the source of the infection.⁷

MATERIAL AND METHODS

From March to May 2008, three patients were referred to this tertiary-care hospital located in Mexico City, with persistent high fever, chills, malaise and mild hepatitis. Serologic assessment of the three patients revealed positive antibodies against *C. burnetii* and in two, a liver biopsy showed the classical granulomatous hepatitis. All of them were residents of a farming region in the state of Hidalgo, Mexico. We decided to undertake a cross sectional pilot study to identify cases of acute disease in this particular region and to determine the seroprevalence of *C. burnetii* among healthy individuals with known risk factors for infection with this bacteria. From June through August 2009, this pilot study was conducted in collaboration with the jurisdictional health authorities of five municipalities in the state of Hidalgo. Q fever was defined according to the Centers for Disease Control and Prevention (CDC) criteria.⁸ All subjects were interviewed for signs and symptoms of the disease, demographic and household characteristics and occupational exposure to cattle. Blood samples were taken from hospitalized and outpatients with symptoms suggestive of Q fever, as well as from asymptomatic individuals with direct and daily exposure to cattle (slaughterers, butchers, farmers, shepherds and veterinarians)

in the five municipalities. Serologic assessment for specific antiphase II *C. burnetii* antigen type IgG antibodies was performed using an ELISA test (Phase II IgG, Virion/Serion®, Würzburg, Germany); positive results were confirmed using an indirect immunofluorescence assay (IFA) (BioMerieux®, Marcy l'Etoile, France). Infection with *C. burnetii* was considered positive by either an antiphase II *C. burnetii* antigen IgG titer > 200 IU/mL or antiphase II *C. burnetii* antigen IgM titer > 50 IU/mL in a single serum sample. Statistical analyses were performed using the STATA software® version 8:0 (College Station, Texas, USA). Measures of central tendency and dispersion, frequency and proportions, chi-square test or Fisher's exact test were used as appropriate to describe the data and to determine the significance of associations between study variables. Odds ratios and corresponding 95% Confidence Intervals (95% CI) were calculated using logistic regression methods. A two-tailed *p* value ≤ 0.05 was considered as statistically significant. The Institutional Review Board approved the study, and all subjects signed informed consent.

RESULTS

A total of 159 subjects were included in the study (Figure 1). Twenty three subjects reported a history of prolonged fever during the prior year or presented with acute symptoms: the three initial symptomatic patients, five more cases of acute Q fever detected during the study and three of 15 subjects with a history of prolonged fever had > 200 IU/mL titers of anti-phase II *C. burnetii* antigen IgG antibodies. Among the 136 asymptomatic subjects, 6 (4.4%) subjects were infected, and 3 of them had serologic evidence of acute infection with *C. burnetii* (specific IgG antibody titers ≥ 1:256 by IFA). The median age of the 8 acutely ill subjects was 44 years, all had acute fever, chills, headache, fatigue, myalgias and arthralgias; mild hepatitis was detected in 6 cases, and only 3 had daily exposure to cattle. None developed pneumonia, endocarditis or endovascular infections. All patients with suspected or confirmed diagnosis of Q fever were treated and all had complete resolution of symptoms. Table 1 shows the demographic characteristics and antibody titers of the 17 (10.7%) subjects with confirmed *C. burnetii* infection.

Univariate analysis including the 159 subjects in the study showed that male gender (OR 6.2, 95% CI: 0.8 to 48.88, *p* = 0.08) and living in Huichapan/Tezcoautla (OR 6.7; 95% CI: 1.47, 30.38, *p* = 0.014),

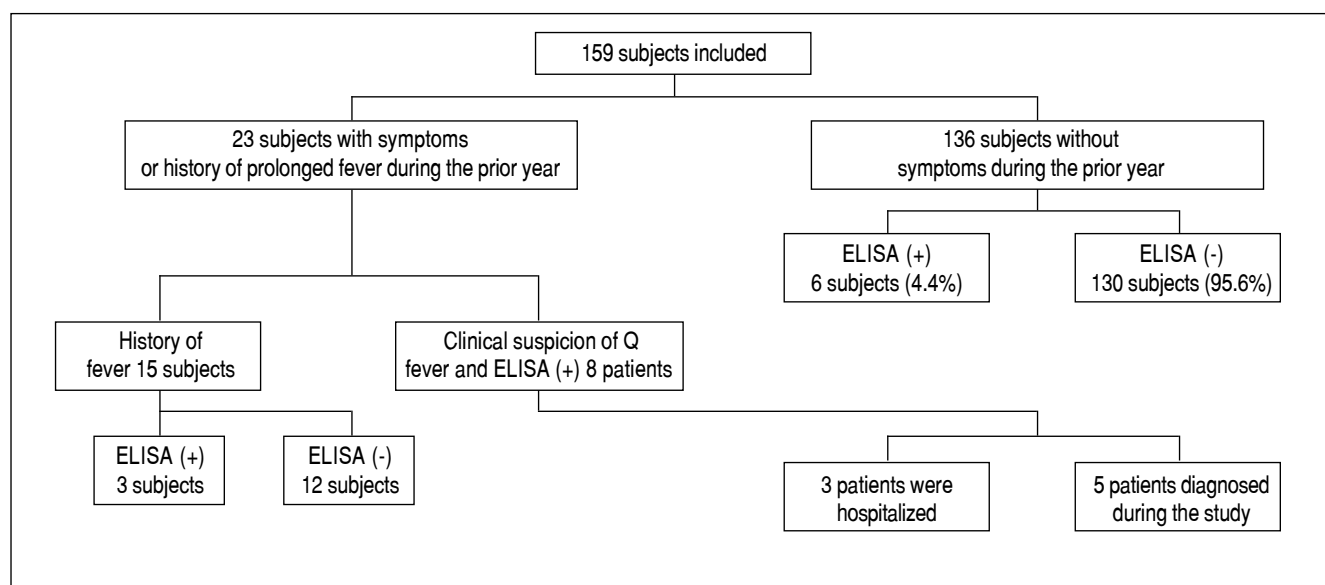


Figure 1. Population included in the study and prevalence of infection by *Coxiella burnetii*: 159 subjects were included in the study, 23 reported a current or previous history of fever and 136 more asymptomatic.

Table 1. Description of the 17 subjects with antibodies against specific antiphase II *Coxiella burnetii* antigen.

Patient	Age (years) and gender	Occupation	Residence	ELISA	Immunofluorescence titer			
				Antiphase II IgG antibodies (UI/mL)	Antiphase I IgG antibodies	Antiphase II IgG antibodies	Antiphase I IgM antibodies	Antiphase II IgM antibodies
1	30, M	Shepherd	Huichapan	> 200	1:256	≥ 1:1024	≥ 1:1024	≥ 1:1024
2	42, M	Slaughterman	Tecozautla	> 200	1:512	≥ 1:1024	≥ 1:1024	≥ 1:1024
3	55, M	Contractor	Huichapan	> 200	≥ 1:1,024	≥ 1:1024	≥ 1:1024	≥ 1:1024
4	47, M	Physician	Huichapan	> 200	1:256	1:256	Negative	1:64
5	42, M	Mechanic	Huichapan	> 200	1:512	≥ 1:1024	1:256	1:512
6	39, M	Mechanic	Huichapan	> 200	Negative	≥ 1:1024	1:128	≥ 1:1024
7	70, M	Farmer	Nopala	> 200	≥ 1:1024	≥ 1:1024	Negative	Negative
8	48, F	Housewife	Tecozautla	> 200	≥ 1:1024	≥ 1:1024	≥ 1:1024	1:256
9	20, M	Slaughterman	Tecozautla	50	1:128	1:256	Negative	Negative
10	26, M	Slaughterman	Tecozautla	88	Negative	≥ 1:1024	1:256	≥ 1:1024
11	43, M	Veterinarian	Huichapan	95	1:512	1:512	Negative	Negative
12	61, M	Slaughterman	Huichapan	55	1:128	1:128	Negative	Negative
13	39, M	Slaughterman	Huichapan	39	1:16	1:256	Negative	Negative
14	30, M	Slaughterman	Huichapan	110	1:128	1:512	1:32	1:16
15	25, M	Butcher	Huichapan	62	1:128	1:128	1:32	Negative
16	59, M	Farmer	Huichapan	122	1:256	1:512	Negative	Negative
17	49, M	Butcher	Alfajayucan*	70	1:128	1:128	Negative	1:16

*Cases 1-3 were the initial febrile patients referred to INCMNSZ due to persistent fever; cases 4-8 were diagnosed as having a recent episode of high fever during the cross-sectional study; cases 9-11 were subjects with history of fever during the prior year and evidence of acute infection by serology, and cases 12-17 were detected among the asymptomatic subjects included in the study.

two of the five municipalities of the health jurisdiction, had higher risks for infection with *C. burnetii* than female subjects and subjects living in other municipalities. Male gender, age ≥ 40 years old and living

in Huichapan/Tecozautla increased the risk of infection with *C. burnetii* after adjusting for other study variables in multivariate analysis (Log likelihood χ^2 (3) = 19.8; p = 0.0002) (Table 2).

Table 2. Demographic factors associated with risk of infection with *Coxiella burnetii* in 159 subjects from a rural area of the state of Hidalgo.

Variable	Serology		Univariate analysis		p	Multivariate analysis*		p
	Positive	Negative	Odds ratio	95% CI		Odds ratio	95% CI	
• Gender								
Male	16	102	6.2	0.80, 48.8	0.80	5.99	0.73, 48.7	0.09
Female	1	40	1.0			1.0		
• Age								
< 40 years	10	60	1.95	0.70, 5.42	0.20	4.22	1.35, 13.2	0.01
≥ 40 years	7	82	1.0			1.0		
• Occupation								
High risk	12	119	0.27	0.13, 1.85	0.17			
Lower risk	5	23	1.0					
• Residence								
Huichapan/Tecozautla	15	75	6.7	1.47, 30.4	0.14	11.63	2.33, 57.9	0.003
Other	2	67	1.0			1.0		

*Log likelihood = -44.15; χ^2 (3) = 19.83; p = 0.0002.

DISCUSSION

This study confirms the presence of *C. burnetii* in Mexico and discards the notion of Q fever as an exotic disease in this region of the world. The state of Hidalgo occupies the second place in the activity of raising sheep in Mexico. The municipalities of Huichapan and Tecozautla harbor the biggest slaughter houses in the region; about 80% of the land assessed is referred to as cattle area (National Institute of Statistics and Geographical Information, 2002). To our knowledge, this is the first study that demonstrates the endemic presence of *C. burnetii* in Mexico. All previous reports had been limited to sporadic case reports.⁹⁻¹² The overall seropositivity of 11% indicates a significant rate of infection in a small sample of the population with occupational risk and environmental exposure. It is noteworthy that 5 of the 8 symptomatic patients with confirmed *C. burnetii* infection had no exposure to livestock; this is not surprising, since incidental infection has been well documented.³

Q fever is a worldwide emerging disease. Currently, the Netherlands is experiencing an epidemic of disproportionate magnitude^{13,14} and this fact reflects the need to better understand the occurrence of *C. burnetii* infection in populations living in high-risk conditions. Results from this pilot study underscore the need for active surveillance programs and comprehensive studies to further define the prevalence and risk factors associated with the disease in Mexico, to know more about its clinical presentation and to characterize bacterial factors involved in its

pathogenesis. As Dr. Raoult, an expert on rickettsial diseases has expressed: “Once you start looking for Q fever, you will find more and more”.¹⁵

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