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 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. 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).

Since 1994, Q fever is a notifiable disease in Mexico. 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.

**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. 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 IIIgG, Virion/Serion®, Würzbur, 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/Tecozautla (OR 6.7; 95% CI: 1.47, 30.38, *p* = 0.014),
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/Tecozaúltla increased the risk of infection with *C. burnetii* after adjusting for other study variables in multivariate analysis (Log likelihood $\chi^2$ (3) = 19.8; $p = 0.0002$) (Table 2).

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

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

*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.*
DISCUSSION

This study confirms the presence of \textit{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 \textit{C. burnetii} in Mexico. All previous reports had been limited to sporadic case reports\textsuperscript{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 \textit{C. burnetti} infection had no exposure to livestock; this is not surprising, since incidental infection has been well documented\textsuperscript{3}.

Q fever is a worldwide emerging disease. Currently, the Netherlands is experiencing an epidemic of disproportionate magnitude\textsuperscript{13,14} and this fact reflects the need to better understand the occurrence of \textit{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: \textit{“Once you start looking for Q fever, you will find more and more”}\textsuperscript{15}.

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All the authors declare no conflict of interest with the information shown here.

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