Role of Sex, Age, Previous Valve Lesion, and Pregnancy in the Clinical Expression and Outcome of Q Fever after a Large Outbreak

Hervé Tissot-Dupont,1 Véronique Vaillant,2 Sylvie Rey,3 and Didier Raoult1

1Unité des Rickettsies, Unité Mixte de Recherche 6020, Université de la Méditerranée, Marseille, 2Institut de Veille Sanitaire, Saint-Maurice, and 3Cellule d’Intervention Régionale en Épidémiologie Rhône-Alpes, Drass Rhône-Alpes, Lyon, France

Background. Q fever is a zoonosis caused by Coxiella burnetii. After a large outbreak occurred in the Chamonix Valley in the French Alps in 2002, an extensive surveillance was conducted, to describe the variations in the clinical expression of acute Q fever according to host factors, as well as to monitor the risk of evolution of acute Q fever to chronic Q fever in patients at risk.

Methods. Three groups of patients with risk factors for evolution of acute Q fever to chronic Q fever were considered: 376 pregnant women, 19 immunocompromised patients, and 91 patients with valvular or vascular abnormalities. A group of 578 people without risk factors for evolution of acute Q fever to chronic Q fever was also tested. Diagnosis of Q fever was based on serologic testing by immunofluorescence assay.

Results. Between 30 August 2002 and 31 July 2003, a total of 1946 serum samples obtained from 1064 persons were tested. A total of 101 patients (9.3%) had acute Q fever diagnosed, and 5 patients (0.5%) had chronic Q fever diagnosed. A diagnosis of acute Q fever was established for 11 pregnant women (2.6% of 379 pregnancies), 5 patients with valvular disease (5.5%), and 85 people without risk factors (14.7%) (71 [27.9%] of 254 symptomatic patients and 14 [4.3%] of 324 asymptomatic patients). A new pregnancy in a woman with negative results of serologic tests for Q fever exposes the woman to a new risk for acute Q fever able to evolve to chronic Q fever. The rates of clinical expression were 90.6% in adult men, 75% in adult women, and 33.3% in children, and they were significantly lower (9.1%) in pregnant women. Evolution to chronic Q fever was observed in 5 patients.

Conclusion. This study emphasizes the importance of active surveillance in postepidemic conditions, especially among patients at risk, as well as the importance of systematic serologic testing during pregnancy.

Q fever is a worldwide zoonosis due to Coxiella burnetii, an obligate intracellular bacterium. The main characteristic of Q fever is its clinical polymorphism [1]. In acute cases, the most common clinical syndromes are fever, granulomatous hepatitis, and pneumonia. In chronic cases, endocarditis is the main syndrome [1]. Osteomyelitis, infections of vascular grafts or aneurysms, and infections occurring during pregnancy [2] are also reported. The usual reservoirs for C. burnetii are cattle, sheep, and goats [3], which shed the bacterium in urine, feces, milk, and birth products [1]. Infected pets, such as cats [4], rabbits [1], and dogs [5], have been sources of outbreaks in humans [3]. Human infection mainly occurs after inhalation of contaminated aerosols. The diagnosis of Q fever is based on specific serologic findings. The reference technique is indirect immunofluorescence assay [6].

Various factors influence the clinical expression and outcome of the disease [7]. C. burnetii itself plays a role in the intensity of the clinical expression of acute Q fever: in animal models, the Nine Mile strain is associated with more active disease than is the Priscilla strain [8]. Some genotypes are rarely isolated from patients with acute infections, but all have been found in patients with chronic endocarditis [9]. The route of infection and inoculum size are also involved [10, 11]. However, the main factors able to influence the clinical expression of acute Q fever, as well as its evolution to
chronic Q fever, are host factors [7]: immunocompromised patients present more often with pneumonia, and they are likely to experience relapse. Approximately 40% of persons with acute Q fever and valvular disease, which may be mild or undiagnosed but is present before the onset of acute Q fever, will develop chronic endocarditis. Acute Q fever in pregnant women, whether symptomatic or not, may result in abortion, prematurity, or a low birth weight. Q fever may evolve to chronic Q fever after delivery and may be associated with recurrence of miscarriage [12]. Age is a risk factor: at comparable exposure levels and seroconversion rates, symptomatic Q fever is 5 times more likely to be diagnosed in people ≥15 years of age than in younger people. [7]. Sex is also a risk factor: at comparable levels of exposure and seroprevalence, the ratio of male to female subjects is 2.45 among adults in France. The predisposition for infection in men is explained by the protective role of female sex hormones [13].

During the summer of 2002, a large outbreak of Q fever occurred in the Chamonix Valley in the French Alps. Because of the large proportion of asymptomatic cases, and because of the high risk of chronicity among at-risk patients (i.e., pregnant women, patients with a valvular or vascular abnormality, and immunocompromised patients), we decided to perform serologic surveillance for 1 year. The goals of this surveillance were (1) to describe the variations in the clinical expression of acute Q fever depending on host factors, and (2) to monitor the risk of evolution of acute Q fever to chronic Q fever in patients at risk.

**MATERIALS AND METHODS**

**The Chamonix Valley.** Chamonix is a city (altitude, 1050 m) located at the foot of Mont Blanc in the French Alps. Its population is 9829 inhabitants. The valley is 27 km long, with a south-north orientation. The population of the whole valley includes 12,927 inhabitants (49.4% of whom are male, and 50.6% of whom are female) and thousands of tourists.

**Surveillance modalities.** As soon as the outbreak was investigated, the surveillance was started. All the physicians were informed about Q fever and the outbreak investigation. Several groups of patients were considered. Systematic serologic testing was proposed for patients known to be at risk for developing chronic Q fever—that is, pregnant women, patients with any valvular or vascular abnormality, and immunocompromised patients (those with HIV infection or cancer and those receiving corticosteroid therapy). Serologic testing for Q fever was also performed for patients with clinical symptoms evocative of Q fever (e.g., fever with or without headaches, flu-like syndrome, myalgia, arthralgia, and liver involvement). Moreover, any person wishing to be tested for any reason could be sampled, and any physician could recommend serologic testing if he or she believed it was necessary.

Blood samples were drawn in private laboratories, and every couple of days, they were sent to the National Reference Center for Rickettsial Diseases in Marseille, France. The epidemiological and clinical data that were collected and sent to the National Center for Rickettsial Diseases included data on sex, date of birth, term of pregnancy, symptomatology (and date of onset), the physician, and hospitalization.

During the case-control study, 111 control subjects were tested. These control subjects were randomly selected from nonfebrile persons who were present in the Chamonix Valley during the period of the outbreak exposure. Thus, all of them can be considered to be asymptomatic.

**Serologic tests.** Because of the frequency of asymptomatic infections (60%) [1], which lead to such patients having similar risks of evolution to chronic Q fever, the case definitions were based on results of serologic tests. Indirect immunofluorescence assays were performed as described elsewhere [6]. Under the usual diagnostic conditions, in our hands, a serum sample is considered to be diagnostic of evolutive Q fever (acute or chronic) when the phase II IgG titer is ≥200 and the phase II IgM titer is ≥50, or when seroconversion has been noted. In the context of an epidemic, when the positive predictive value was increased, it was important to enhance the sensitivity of serologic testing. Therefore, a cutoff value that was 1 dilution lower (i.e., a phase II IgG titer ≥100 and/or a phase II IgM titer ≥25) was considered for the diagnosis of acute cases. A diagnosis of chronic Q fever is considered when the phase II IgG titer is ≥800 [6].

**Statistical analysis.** Frequencies of qualitative data were compared using Pearson’s χ² test or Fisher’s exact test with the use of EpiInfo software, version 6.04fr (Centers for Disease Control and Prevention and EpiConcept). A difference was considered to be statistically significant when P < .05.

**RESULTS**

**Physician participation.** A total of 73 different physicians sent to the laboratory serum samples that were obtained from their patients. Twenty-three local physicians had testing performed for >10 patients. The 2 obstetricians sent serum samples obtained from 219 and 101 pregnant women; the cardiologist sent serum samples obtained from 40 patients; and the 9 most active general practitioners sent serum samples obtained from 31 to 53 patients.

From 30 August 2002 through 31 July 2003, a total of 1946 serum samples obtained from 1089 persons underwent testing. A total of 101 cases of acute Q fever (9.3%) and 5 cases of chronic Q fever (0.5%) were diagnosed (table 1).

**Pregnant women.** A total of 891 serum samples, obtained from 376 pregnant women, were tested during pregnancy. Of the women, 350 had ongoing pregnancies, 11 had testing per-
formed shortly after normal delivery, and 18 had testing performed after spontaneous abortion. A total of 379 pregnancies were considered, because 2 women had 2 normal consecutive pregnancies during the surveillance and 1 woman had a normal pregnancy after abortion. The mean age (± SD) of these women was 31 ± 7 years. One hundred eighty-eight women had a single serum sample tested, 77 women had 2 serum samples tested, and 111 women had ≥3 serum samples tested.

The results of serologic tests were negative for 343 (90.5%) of 379 pregnancies, for 317 (90.6%) of 350 ongoing pregnancies, and for 18 (100%) of 18 abortions, as well as for 8 (72.7%) of 11 women after delivery. Acute Q fever was diagnosed in 11 women (2.6% of 379 pregnancies), one of whom later developed a profile of chronic infection. The results also showed residual antibodies (phase II IgG without IgM) in association with 21 (5.5%) of 379 pregnancies (in 19 [5.4%] of 350 ongoing pregnancies and in 2 [18.2%] of 11 women after delivery). For 4 pregnancies, the data were not sufficient to draw conclusions (i.e., a single serum sample had IgG and/or IgM titers below the cutoff value).

Most (371 of 376) of these pregnant women were asymptomatic, whereas 5 (1.3%) had fever, 1 complained of headache, and 1 had fatigue. One woman who had testing performed had a suspected diagnosis of pericarditis. Four of these symptomatic women had negative test results.

All 11 women who had positive test results were treated according to our protocols (with trimethoprim-sulfamethoxazole, 160 mg/800 mg twice daily until delivery [12]) and were carefully monitored. One of them seroconverted and then exhibited antibodies typical of chronic infection at month 8 of pregnancy. After delivery, this patient received treatment, as for any patient with chronic Q fever, according to our protocols (i.e., doxycycline plus hydroxychloroquine sulfate [14]).

**Persons with cardiac involvement.** A total of 177 serum samples that were obtained from 91 persons with cardiac abnormalities were tested. Seventy-four patients had a known valvular abnormality, 6 had cardiopathy, 1 had myocarditis, 1 had pericarditis, and 3 had a coronary vascular graft. The 6 remaining persons had a nonspecified "cardiologic problem."

The mean age (± SD) of the study participants with cardiac involvement was 65 ± 17 years of age. The ratio of male to female subjects was 0.91 (43 male and 47 female subjects). Sixty-two persons had a single serum sample tested, 14 persons had 2 serum samples tested, and 15 persons had ≥3 serum samples tested.

A total of 5 persons (5.5%) had acute Q fever diagnosed; one of these persons later experienced endocarditis. Seven persons had residual antibodies. Most (74 of 91) of the patients were asymptomatic. Of the 6 patients who experienced fever, 2 had negative test results, 3 were considered to have acute Q fever (one case of which became chronic), and 1 had residual antibodies.

Of the 5 patients who had acute Q fever diagnosed, 4 could be treated with doxycycline plus hydroxychloroquine sulfate and monitored for 1 year according to our protocols. Unfortunately, and as expected, the patient who was not treated later had a chronic form of Q fever develop.

**Persons with immunodeficiencies.** A total of 27 serum samples obtained from 19 persons (5 male and 14 female subjects; mean age [± SD], 58 ± 20 years) were tested. The reported causes of immune suppression were as follows: solid or hematologic cancer (n = 14), immunosuppressive treatment (n = 2), HIV infection (n = 2), and an unspecified cause (n = 1). Four (21.1%) of 19 patients were symptomatic; 3 of the 4 patients had fever (which was associated with nausea in one patient and with sore throat in 1 patient). One patient complained of fatigue. None of these patients had positive test results.

**Patients without known risk factors.** A total of 812 serum samples were obtained from this group of 578 patients and were tested; 461 (79.8%) of these patients had negative test
results, 85 (14.7%) had acute Q fever, and 31 (5.4%) had residual antibodies. Three patients with acute Q fever were later found to have antibodies compatible with the presence of chronic infection. Data were not sufficient to draw conclusions for one patient.

One group of 254 patients had a clinical presentation compatible with a diagnosis of acute Q fever. Of these patients, 169 (66.5%) had negative test results, 11 (4.3%) had residual antibodies, and 71 (27.9%) had acute Q fever. Three of these 71 patients had Q fever that eventually become chronic. The first of these 3 patients was a 36-year-old man who was symptomatic in July 2002 and who was considered to have endocarditis because he had an aortic insufficiency, with no vegetation noted on ultrasound examination. The second patient was a 78-year-old woman who had a history of pulmonary tuberculosis. She was symptomatic in July 2002. Findings of cardiac ultrasonography were normal. A thoracic CT scan demonstrated a residual pulmonary opacity. The third patient was a 44-year-old man who was symptomatic in July 2002 and who experienced relapse in August 2002. His first serum sample (obtained on 13 August 2002) had a negative test result, and the result for his second sample (obtained on 31 December 2002) demonstrated a chronic profile. No clinical and evolutive data were available.

The second group of 324 patients was asymptomatic. Of those patients, 290 (89.5%) had negative test results, 14 (4.3%) had recently been exposed to C. burnetii, and 20 (6.2%) had received a positive serologic test result, although it was below the cutoff for diagnosis of evolutive disease.

When we compare these 2 groups by use of the $\chi^2$ test, the rate of positive results was higher among the group of symptomatic patients (27.9%) than among the group of asymptomatic patients (4.3%) (OR, 8.59; 95% CI, 4.6–16.9; P <.001).

Serum samples for which data were not available. Thirty-six serum samples for which data were not available were sent to the laboratory. All samples tested negative, except for those obtained from 3 patients who exhibited low titers of phase II IgG, without IgM.

Control subjects. Of the 111 asymptomatic control subjects who underwent testing, 1 (0.9%) had serologic titers (phase II IgG, 50; phase II IgM, 25) corresponding to our definition of acute Q fever.

Comparisons between groups. For this comparison, we considered the groups as previously defined: pregnant women (n = 11); patients with cardiac involvement (n = 5); patients with immunodeficiency (n = 0); and patients without known risk factors, who were known as “other” patients (n = 85); and control subjects (n = 1). We considered the patients who met the case definition to be symptomatic.

Under these conditions, pregnant women were less often symptomatic (1 of 11 such patients was symptomatic) than were patients with cardiac involvement (3 of 5 such patients were symptomatic) (OR, 0.07; 95% CI, 0–1.61; P = .029). They were also less often symptomatic than the other patients (71 of 85 such patients were symptomatic) (OR, 0.02; 95% CI, 0–0.17; P <.001). Pregnant women were also less often symptomatic than nonpregnant women (48 of 54 nonpregnant women with a diagnosis of acute Q fever [in other groups]) (OR, 0, 95% CI, 0–0.07; P <.001).

Incidence of acute Q fever, by sex, age, and patient group. Table 2 shows the comparison of cases of acute Q fever among the previously defined patient groups, according to sex. A difference was found when all patients were compared: more cases of acute Q fever were diagnosed among 307 male subjects (17.6%) than among 380 female subjects (9.5%) (OR, 0.4; 95% CI, 0.14–1.08; P = .002). A difference was also noted in the group of subjects without known risk factors: more cases were diagnosed among 259 males (19.7%) than among 319 females (10.5%) (OR, 2.06; 95% CI, 1.25–3.39; P = .002). In the subgroup of symptomatic patients, more cases were also diagnosed among 142 males (34.5%) than among 112 females (21.4%) (OR, 1.9; 95% CI, 1.06–3.58; P = .02).

Of the group of people without known risk factors, 23 children <15 years of age were tested. Of these children, 11 were boys and 12 were girls. Nine (5 boys and 4 girls) reported symptoms that included fever. Three (13.04%) of the 23 children had acute Q fever diagnosed, and 2 of these children were symptomatic (i.e., they had fever).

Table 3 summarizes the data on age and sex for patients with serologically defined cases of acute Q fever: pregnant women were the patients who were less often symptomatic (9.1%), whereas the rate of symptomatic cases was slightly higher (33.3%) among children and was much higher among adult nonpregnant females and males >14 years of age (75% and 90.6%, respectively). The statistical comparison shows a significant difference between pregnant women and adult males (OR, 96; 95% CI, 9.1–4244; P <.001), between pregnant women and adult females (OR, 22; 95% CI, 2.1–223; P =.003), and between pregnant women and pregnant men (OR, 3.7; 95% CI, 0.94–14.6; P =.06).

<table>
<thead>
<tr>
<th>Patient group, by presentation and risk factor</th>
<th>Patients with Q fever, n/N (%)a</th>
<th>Male</th>
<th>Female</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No known risk factor</td>
<td>51/259 (19.7)</td>
<td>34/319 (10.5)</td>
<td>.002</td>
<td></td>
</tr>
<tr>
<td>Symptomatic</td>
<td>49/142 (34.5)</td>
<td>24/112 (21.4)</td>
<td>.02</td>
<td></td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>2/117 (1.7)</td>
<td>10/207 (4.8)</td>
<td>.15</td>
<td></td>
</tr>
<tr>
<td>Cardiac abnormality</td>
<td>3/43 (6.9)</td>
<td>2/47 (4.2)</td>
<td>.57</td>
<td></td>
</tr>
<tr>
<td>Immunodeficiency</td>
<td>0/5 (0)</td>
<td>0/14 (0)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>54/307 (17.6)</td>
<td>30/380 (9.5)</td>
<td>.002</td>
<td></td>
</tr>
</tbody>
</table>

a Data are no. of patients with Q fever/total no. of patients tested (% of patients with Q fever).

Clinical Expression of Q Fever • CID 2007:44 (15 January) • 235
and nonpregnant women (OR, 40; 95% CI, 4.2–1787; P < .001), and between adult males and children (OR, 19.2; 95% CI, 0.78–1154; P = .038). The small number of cases did not permit demonstration of the differences between pregnant women and children (P = .09), between males >14 years of age and nonpregnant women (P = .054), and between adults and children (P = .07).

DISCUSSION

Knowledge regarding Q fever in humans has widely increased during the past decade, mainly in terms of understanding its pathophysiology [7, 8], the clinical presentations of acute [1, 15–17] and chronic cases [7], and the specific populations at risk for chronic infection (e.g., people with valvular disease, pregnant women [18], immunocompromised hosts [1, 15], and children [19, 20]). Diagnosis of Q fever has been improved in terms of molecular testing, by use of real-time PCR [21, 22]. Treatment strategies, including drug testing and monitoring, have been proposed for acute [1] and chronic [14] cases, as well as for specific hosts, such as pregnant women [12] or patients with valvular damages.

To our knowledge, the present study reports, for the very first time, active serologic surveillance of Q fever in humans, for 1 year after a large outbreak that occurred in a tourist area and for which there was no removable source of Coxiella burnetii. This surveillance has demonstrated its feasibility. The efficiency of the surveillance was also demonstrated, because a total of 101 patients with acute Q fever and 5 with chronic Q fever had Q fever diagnosed and then were monitored. Moreover, this is the first outbreak in which asymptomatic, acute, and chronic infections were diagnosed. We also confirmed that 1 patient can have acute Q fever evolve to chronic Q fever.

In terms of knowledge of Q fever, we have been able to show a difference in the clinical expression of Q fever, according to sex and age: although not statistically significant, because of the small number of cases, a higher rate of symptomatic cases may be confirmed among adult males (91%) than among females (75%), as described in most of epidemiological studies [1, 7], and as explained in animal models by the protective role of 17β-estradiol, the adult female hormone, which could also explain why the sex ratio is biased only after puberty [13]. Maltezou et al. [19, 20] have shown that the clinical expression of Q fever in children <14 years of age was much lower than that in adults. Again, although nonsignificant, clinical expression was 2.6 times lower in children (33%) than in adults of both sexes (85%). We were able to show a significant difference between men and children.

We demonstrated that pregnant women were less symptomatic than other women and other patients. Q fever during pregnancy was known to be likely asymptomatic [12], which was the case in our series, because only 1 of the 11 pregnant women who had Q fever diagnosed was symptomatic. The conditions of the surveillance among pregnant women (involving 2 concerned obstetricians who tested all pregnant women they monitored) can be considered to be the conditions of a survey. Under these conditions, 11 cases have been diagnosed among 379 nonselected pregnancies (with 1 case developing per 34 pregnancies), which is much more common, under this epidemiologic conditions, than was estimated in Martigues, France, an area of high endemicity (where 1 case developed per 415 pregnancies) [23].

The present study also let us observe an evolution from acute to chronic Q fever in 5 patients: a pregnant woman and a patient with valvular abnormalities (who both refused the antibiotic prophylaxis), as well as 3 patients without known risk factors. The necessity of systematic follow-up of acute cases after such an outbreak has recently been emphasized [24], as has the importance of the detection of minimal valvular diseases among patients with acute Q fever [25].

In conclusion, to our knowledge, this was the very first time that such a surveillance was conducted during and after the epidemic, showing its feasibility and usefulness. Thus, under epidemic conditions (when >5 grouped cases are noted within 1 month), our advice is to test (once) any person considered to be at risk (as defined above). This surveillance was especially active among pregnant women, demonstrating that such women are less symptomatic than any other patients with acute Q fever. This enhances the importance of systematic testing during pregnancy in areas where Q fever is prevalent: under standard conditions, a pregnant woman should be tested when febrile or after any abnormal delivery. Under epidemic conditions, or in populations with frequent animal contacts, our advice is to test any pregnant woman. Those with positive test results should be treated and monitored. Pregnant women with negative test results should be tested every month until delivery.

Acknowledgments

Potential conflicts of interest. All authors: no conflicts.
References