Hyperendemic Focus of Q Fever Related to Sheep and Wind

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Q fever is a worldwide zoonosis which is caused by *Coxiella burnetii* and presents as both acute or chronic cases. The disease can be transmitted from animal reservoirs to humans by the inhalation of infected aerosols. The authors investigated the epidemiology of Q fever in the Bouches-du-Rhone district of southern France. The study area was centered around the small town of Martigues near the cities of Marseille and Aix-en-Provence, where the incidence of the disease seemed higher than in neighboring areas. Epidemiologic data included sheep breeding and wind. Between 1990 and 1995, Q fever was diagnosed in 289 patients, leading to an incidence rate of 35.4 per 100,000 in the study area (range: 6-132), compared with 6.6 in the area of Marseille, and 11.4 in the area of Aix-en-Provence. There was a graphical and statistical relation between the sheep densities, the incidence of the disease, and the strong, local wind known as the Mistral, which blows from the northwest. Although *Coxiella burnetii* transmission is multifactorial, we may speculate that the high endemicity in the study area is related to a contamination by aerosols because the Mistral blows through the local steppe where 70,000 sheep are bred. This public health problem requires further studies in order to confirm this hypothesis, and to identify more individual and preventable risk factors.


*Q fever is a worldwide zoonosis caused by* *Coxiella burnetii*, an obligate intracellular organism which lives in the phagolysosomes of the host cell. The main characteristic of Q fever is its clinical polymorphism. In acute cases, the most common clinical syndromes are self-limiting, febrile illnesses of unknown origin, granulomatous hepatitis, pneumonia, and meningoencephalitis (1). Moreover, cases of febrile eruption, myocarditis, and pericarditis have been reported. In chronic cases, endocarditis is the main syndrome (2). Osteomyelitis, infections of vascular grafts or aneurisms (3), and infections during pregnancy (4) have also been reported. Such varied clinical presentations mean that serologic confirmation is required for the diagnosis of Q fever.

Throughout the world, the most common reservoirs for *Coxiella burnetii* are cattle, sheep, and goats (5). The bacterium is found in urine, feces, milk, and birth products of infected animals (6). Human infection occurs following inhalation of contaminated aerosols or ingestion of raw milk or fresh goat cheese. *Coxiella burnetii* is ideally suited to this means of transmission, due to its ability to withstand harsh environmental conditions and to its extraordinary virulence (7). It has recently been shown that infected cats (8), rabbits (9) and dogs (10) can transmit *Coxiella burnetii* to humans, and that these animals have been sources of human outbreaks (5).

The geographic distribution of Q fever is wide and *Coxiella burnetii* is endemic in virtually every country in the world, except New Zealand (11). Due to its varied clinical presentations, the prevalence of *Coxiella burnetii* infection in humans is largely unknown and largely depends on either a local physician's interest in the disease or on the presence of a reliable diagnostic laboratory. It has been suggested that the prevalence of Q fever follows the geographic distribution of rickettsiologists (12) in that in places where the infection is extensively studied, the prevalence can be shown to be extremely high. For example, in southern Spain, 30 percent of patients hospitalized for fever that lasted more than 7 days were shown to have Q fever, and in the Basque country about 60 percent of cases of community-acquired pneumonias were due to *Coxiella burnetii* (13, 14). Previous studies have shown a seroprevalence of 4.03 percent among apparently healthy blood donors from Marseille (phase II immunoglobulin G (IgG) ≥50) (1). This led us to predict that annually more than 2,000 people would become infected in Marseille. These results were consistent with other studies conducted in France: 5 percent in a previous

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Abbreviations: CI, confidence interval; IgG, immunoglobulin G; m/s, meters per second.

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study carried out in Marseille (15) and 4.4 percent in the east central France (16). A higher prevalence has been found in the Alps, where 30 percent of a village population was found to have antibodies (17).

In many countries, Q fever is not a reportable disease, and thus it is difficult to know how many cases occur. Furthermore, sporadic cases are rarely identified. France, Spain, Switzerland, Israel, and the United Kingdom have considerable Q fever activity (5), partly due to an active case finding. Two large outbreaks in Britain (18) and Switzerland (19) have been extensively studied and have provided additional information about the epidemiology of Q fever. In the British study (18), residents who lived along a road along which farm vehicles traveled developed Q fever as a result of the exposure to contaminated straw, manure, or dust from those vehicles. In the Swiss study (19), 415 residents who lived along a valley road along which sheep were herded to and from mountain pastures developed Q fever (19).

In France, from 1985 to 1995, 1,018 cases (731 acute and 287 chronic) were diagnosed at the National Reference Center (Annual Report of the Center, 1997). In the area of Marseille, where the Reference Center is located, one small town, Martigues, apparently has more cases than the surrounding towns. We therefore decided to investigate the epidemiologic situation of this town, compared with neighboring areas.

Because infectious particles containing Coxiella burnetii can easily be transported by the wind (5) and the fact that a large number of sheep are located windward of the study area, we wanted to determine whether wind direction and strength, as well as sheep breeding, could be significantly associated with the seasonal distribution of cases that occur in the study area.

MATERIALS AND METHODS

Serologic diagnosis

The serologic diagnosis was performed at the National Reference Center using the immunofluorescence reference technique as previously described (20, 21). The titers of IgG, immunoglobulin M (IgM), and immunoglobulin A (IgA) against phases I and II of Coxiella burnetii were determined. A serum was considered diagnostic of an evolutive Q fever (acute or chronic) when the phase II IgG titer was ≥200 and the phase II IgM titer was ≥50. A diagnosis of chronic Q fever was made when the phase I IgG titer was ≥800 (21).

Demographic, geographic, and meteorologic data

Marseille is a city located in Southern France with 800,000 inhabitants. About 40 km northwest of Marseille is a large, natural lake called the “Etang de Berre.” For our study, we considered all cities and villages included in a circle centered on the lake (diameter = 50 km) as the Etang de Berre area. Northwest of Etang de Berre is a semi-desert plain region called “La Crau,” which is the only steppe in Western Europe. Aix-en-Provence is a city located 30 km north of Marseille with 125,000 inhabitants. For our study, the areas of Marseille and Aix-en-Provence included all towns and villages located less than 20 km from the two cities. The respective populations of the three areas were as follows: Etang de Berre area, 361,562; Marseille area, 836,904; and Aix-en-Provence area, 176,054 (figure 1).

Data on sheep breeding were obtained from the “Chambre d’Agriculture” in Aix-en-Provence. These data included the number of sheep, number of sheep breeders by area, and mean monthly number of sheep births (figure 2).

Data on medical and paramedical occupations were obtained on the Worldwide Web from the French Ministry of Health web page (www.sante.gouv.fr).

Meteorologic data were obtained from Meteo France weather stations at Istres and Salon-de-Provence in the form of monthly compass cards for 1991–1995. Wind speed and direction are measured three times an hour, leading to more than 1,400 data per month. The tables provided by Meteo France show the percent of these measures by direction, in three meters per second (m/s) speed ranges: 2–4, 5–8, and >8. The Mistral, which is the most common and strongest wind, blows from the northwest. We therefore compiled data on directions 30, 32, 34, and 36 (west-northwest, northwest, north-northwest, and north, respectively), giving a crude number of measures per month. For graphic presentation, this number of measures has been divided by the number of days in the considered month, giving a theoretical number of days per month in which the Mistral blew. The Mistral blows through La Crau before reaching the study area (figure 3). The Mistral is always characterized by the same weather conditions, i.e., a strong wind, which blows for several consecutive days, in sunny and dry conditions. As shown by figure 3, winds that blow in other conditions (rainfall, high humidity, etc.) come from other directions (mainly east and south). Therefore, we decided not to study other meteorologic factors.

Patients

Using the serologic criteria described above, Q fever-positive patients were selected from the database of the National Reference Center from 1990 to 1995. All patients had been admitted to hospital, which mini-
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Population: 361,562
Sheep: 47,619
Q fever incidence: 35.4 per 100,000

Population: 176,054
Sheep: 780
Q fever incidence: 11.3 per 100,000

Population: 27,187
Sheep: 68,820
10 km

Population: 836,904
Sheep: 135
Q fever incidence: 6.6 per 100,000

FIGURE 1. Map of the Bouches-du-Rhône district of France, comparing the global incidence rate of Q fever in the study area of Etang de Berre area, and two adjacent areas, the Marseille area and the Aix-en-Provence area, in 1990–1995.

mizes the detection bias related to physicians' awareness of the disease, although it may lower the detection. The patients were selected according to the geographic origin of their sera, which corresponded to the catchment areas for the public hospitals of Martigues, Salon-de-Provence, Aix-en-Provence, and Marseille, and the few private hospitals in the study area. Medical practice in the above centers is to send all sera for Q fever diagnosis to the National Reference Center, or to screen their sera by immunofluorescence using phase II Coxiella burnetii antigen provided by the National Reference Center. All positive sera are then sent to the center for confirmation, so that all diagnoses are made at the National Reference Center using the same reference technique. For each selected patient, a questionnaire was completed from the patient's files, collecting available administrative, epidemiologic, clinical, and biologic data. In regard to the retrospective patient selection, place of residence was the sole data available on their location (address in the hospital files).

Statistical analyses

All data were managed and analyzed using EpiInfo 6 (CDC, Atlanta, Georgia) and SPSS (SPSS, Inc., Chicago, Illinois). Fisher's exact test was used to test association while mean values were compared using Student's t test. Prevalence odds ratios and their 95 percent confidence intervals were calculated to compare prevalences in the different areas. Correlations between wind frequencies and Q fever prevalence were tested using Spearman's rank test.

RESULTS

Q fever incidence

Between 1990 and 1995, 289 patients who had been admitted to hospital with an active Q fever were diagnosed in the study area. Among these 289 patients, 68 lived outside the study area, and the addresses of 18 could not be determined. As a result, 203 patients...
remained to be included in the study. Of these 203 patients, 128 originated from the Etang de Berre area, 55 from the Marseille area, and 20 from the Aix-en-Provence area. Under these conditions, the 5-year incidence of Q fever in the study area of Etang de Berre (35.4 per 100,000 inhabitants) was 3.0 times higher (95 percent confidence interval (CI) 1.95–4.99) than in the Aix-en-Provence area (11.3 per 100,000 inhabitants) and 5.4 times higher (95 percent CI 3.93–7.39) than in the Marseille area (6.6 per 100,000 inhabitants) ($p < 10^{-7}$) (figure 1). In the Etang de Berre area, incidence of Q fever varied from 132 per 100,000 inhabitants in the city of Ensues to 6 per 100,000 in the city of Istres. The incidence by area is represented in figure 3, which shows two high prevalence areas: one to the north of the Etang de Berre (in the areas of Lançon-de-Provence, Cornillon, Coudoux, and La Fare-les-Oliviers) and one located to the south (Ensues). According to the study criteria, the semi-desert plain area of La Crau was not considered to be part of the study area. However, none of the selected patients originated from La Crau.

Case description

Of the 128 cases from the Etang de Berre area, five medical files could not be found. Questionnaires were therefore completed and analyzed for 123 cases. Males represented 74.8 percent (92 of 123) of the cases admitted to hospital. This sex ratio (2.96) was significantly higher than that of the French population (0.96) ($p < 0.001$) but not, however, significantly different from the sex ratio (2.3) observed in our previous study (1). The mean age of the patients was 40 ± 15 years (range: 9–89 years). The yearly distribution of the 123 cases was 5 in 1990 (the selection began in July), 16 in 1991, 37 in 1992, 16 in 1993, 29 in 1994, and 20 in 1995. The seasonal distribution of the 109 acute Q fever cases from 1991 to 1995 showed a significantly increased frequency in May and June ($p < 0.001$).

The epidemiologic, clinical, and biologic data are summarized in table 1. Of the 91 patients whose occupations were known, eight (8.8 percent) were considered to be exposed to *Coxiella burnetii* risk factors (farmers, stock breeders, and truck drivers who transported animals). A medical or paramedical occupation was given by eight patients (6.5 percent of the cases), which was higher than that found in the 1996 Bouches du Rhône population (2.9 percent) ($p = 0.025$). A rural residence was noted for 28 of 60 patients (45.9 percent). Usual contact with animals was reported for 74 files (60 percent), which is higher than that usually

FIGURE 2. Seasonal variation of Q fever incidence, the "Mistral" wind, and sheep births in the Etang de Berre area of France. Cumulated cases for 1990–1995 are plotted 2 months before they occur (incubation and delay before diagnosis) to represent the time of infection. The northwesterly wind (directions 30, 32, 34, and 36) is represented as the mean monthly number of days with wind speed >8 meters per second (m/s).
found in Q fever cases (1). Contact with sheep was identified by seven patients (9.5 percent), with cats by six patients (8.1 percent), with dogs by 15 patients (20.3 percent), and with rabbits by two patients (2.7 percent). Presence or absence of fever was mentioned for 120 patients, 95 of whom (79.2 percent) were febrile (body temperature >38°C). Seventy-nine of these patients presented with hepatitis, 27 with pneumonia, and seven with a clinically isolated fever. Twenty patients had a skin eruption, and 12 had neurologic findings. Nine patients had serologic findings presumptive of chronic Q fever. Six of these patients were pregnant women who had been admitted to hospital for late abortions, of whom five had already undergone an abortion. Three patients (two males and one female) presented with an endocarditis.

**Wind frequency**

We compared the seasonal distribution of cases with the distribution of the mean monthly number of days with a northwest wind speed of >8 m/s (the Mistral) on the same radar figure in the areas of Istres and Salon-de-Provence (figure 2). Cases were considered 2 months after the wind distribution. This period was chosen to account for the 3–4-week incubation period for Q fever (22), and the mean delay between the onset of the disease and serologic diagnosis (21). This figure shows the high correlation between the wind and Q fever cases (Spearman correlation coefficient = 0.57 \( p < 0.05 \)). Strong winds (>8 m/s) are twice as frequent from the northwest than from other directions (figure 3). If we consider the dominant strong winds...
that blow in this area, it may be observed that both areas with a high Q fever prevalence are in the path of the wind which blows from areas with high sheep density (figure 3). It should be noted that the areas with high Q fever prevalence (Sausset, Carry, and Ensues) are more residential, and the inhabitants have to travel daily to their place of work.

Sheep breeding

The total numbers of sheep (and number per 1,000 inhabitants) were as follows: Marseille area, 135 (0.16/1,000); Aix-en-Provence area, 780 (4.43/1,000); Etang de Berre area, 47,619 (131.7/1,000). In La Crau, which has only 27,187 inhabitants, there were 68,820 sheep. The sheep densities for each district in the Etang de Berre area are shown in figure 3. The majority of sheep are located in the areas of Salon-de-Provence, Istres, Grans, Miramas, and Cornillon. The monthly distribution of sheep births is presented in figure 2, showing that the vast majority of these births take place in October. When we compared the maps showing sheep densities and Q fever prevalence, it was obvious that there was no correlation between the sheep density and Q fever prevalence: the highest sheep densities are in Istres (prevalence: 0.06 percent) and Salon-de-Provence (prevalence: 0.35 percent), whereas in the areas with a high Q fever prevalence (≥0.8) the densities of sheep are much lower (<1/km²).

**DISCUSSION**

Case identification was conducted in the same way in the study area and the two comparison areas, i.e., all cases were selected from the database of the National Reference Center having fulfilled the same case definition criteria. Such a selection permitted meaningful comparisons to be made between the three areas, and thus it can be concluded that the Etang de Berre area is highly endemic for Q fever, compared with the other two areas. It is also interesting to note that the incidence rate of chronic cases (three endocarditis cases for 360,000 inhabitants in 5 years, i.e., 1.7 per million per year) also appears to be markedly higher than the national rate of 1 per million per year (5).

Data from a recent survey of the seroprevalence of Q fever in dogs from Southern France and various foreign countries (23) also showed a higher prevalence in our study area (15 positives among 57 dogs (26.3 percent) from Istres and Miramas) than in Aix-en-Provence (1 positive among 17 dogs (5.9 percent)) (p = 0.06).

This study was not a case-control survey to identify individual behavioral risk factors, which have been previously described (5). The epidemiologic findings among the cases were very similar to those observed in our earlier study (1). Various explanations for the over-representation of medical and paramedical occupations may be hypothesized: 1) physicians’ interest in the disease may lead to a more frequent diagnosis; 2) these occupations lead to a higher exposure to the agent; and 3) their socioeconomic conditions lead them to live in or visit more exposed areas.

Contact with animals, especially with sheep, is usually considered to be a major risk factor (5). Sheep breeding is negligible in the Marseille and Aix-en-Provence areas. However, vast numbers of sheep are located in La Crau and in towns in the Etang de Berre area, such as Istres and Salon-de-Provence, which are located near La Crau. These breeding areas were in a clear windward direction of the areas with high incidences of Q fever. It might be interesting to try to understand why areas such as Châteauneuf, Gignac, or Marignane show lower Q fever incidence, although they are located in the path of the Mistral. Châteauneuf and Gignac are mountainous areas, where a vast majority of the inhabitants live in the southern part, close to Ensues and Le Rove. Moreover, this mountain chain might create specific wind conditions (e.g., wind speed tends to increase when blowing downhill). As for Marignane, a large part of this administrative area is occupied by the International Airport of Marseille.

The seasonal distribution of Q fever, showing a peak in late spring, has already been described (1), but has not yet explained. Figure 2 compares the seasonal dis-

**TABLE 1. Epidemiologic, clinical, and laboratory findings among 123 cases of acute Q fever in the area of Martigues, Southern France, 1990–1995**

<table>
<thead>
<tr>
<th>Type of findings</th>
<th>Cases</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidemiologic findings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years) (SD*)</td>
<td>92</td>
<td>75</td>
</tr>
<tr>
<td>Males</td>
<td>52</td>
<td>50</td>
</tr>
<tr>
<td>Exposed occupation</td>
<td>64</td>
<td>62</td>
</tr>
<tr>
<td>Medical occupation</td>
<td>68</td>
<td>58</td>
</tr>
<tr>
<td>Rural existence</td>
<td>41</td>
<td>35</td>
</tr>
<tr>
<td>Contact with animals</td>
<td>33</td>
<td>28</td>
</tr>
<tr>
<td>Clinical findings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever (&gt;38°C)</td>
<td>95</td>
<td>79</td>
</tr>
<tr>
<td>Chills</td>
<td>52</td>
<td>50</td>
</tr>
<tr>
<td>Sweats</td>
<td>37</td>
<td>31</td>
</tr>
<tr>
<td>Headaches</td>
<td>18</td>
<td>17</td>
</tr>
<tr>
<td>Myalgias</td>
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<td>17</td>
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<tr>
<td>Arthralgias</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>Pulmonary syndrome</td>
<td>63</td>
<td>53</td>
</tr>
<tr>
<td>With x-ray abnormality</td>
<td>85</td>
<td>73</td>
</tr>
<tr>
<td>Neurologic findings</td>
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<td>35</td>
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<tr>
<td>Laboratory findings</td>
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<td></td>
</tr>
<tr>
<td>Platelets &lt;150 giga/liter</td>
<td>79</td>
<td>79</td>
</tr>
<tr>
<td>Transaminases &gt;50 U/liter</td>
<td>79</td>
<td>79</td>
</tr>
</tbody>
</table>

* SD, standard deviation.
tribution of the cases (with a 2-month delay) with that of the Mistral in the areas of Istres and Salon-de-Provence. Figure 2 shows the clear correlation between this wind and the number of Q fever cases. The relation can be established using Spearman correlation coefficients. It is interesting to notice that in October the strong winds from the northwest are only half as frequent as during the rest of the year. Conversely, more than 80 percent of the sheep give birth in October, frequently in open fields, thus not correlating with the seasonal distribution of Q fever cases. Another explanation for this late spring peak could be the increased number of lambs slaughtered for Easter, which takes place in March or April. Among Muslim populations, increased contact with sheep occurs during the Aid-el-Khebir religious feast, also called “the sheep feast.” At this time, many uncontrolled sheep are slaughtered, in unhygienic conditions, generally at home or in open fields. It is also interesting to notice that sheep herds are moved by open trucks in June to spend the summer in the Alps. The trucks are driven through the areas of Istres and Salon-de-Provence, where the largest herds are located, then through more northern cities (e.g., Moursies and Avignon), and not through the study area. This sheep transportation in June might also provide one of the explanations for the higher Q fever incidence in late spring and summer.

This study has demonstrated a graphical and statistical association between cases and wind frequencies which blow from areas with high densities of sheep, and confirms in cases the data on clinical presentation and exposure to known risk factors, mainly contact with animals. It thus combines two factors: first, the ecologic factor of the wind, whose effects can be monitored although not controlled; and second, the individual risk factors or practices related to contact with animals, whose effects are difficult to monitor, but might be partly prevented.

In conclusion, there is a highly endemic area close to Marseille, which constitutes a significant public health threat to the population. Over a 5-year period in a population of 300,000 inhabitants, six pregnant women were infected, of whom five abort (24), and three patients presented a potentially fatal endocarditis. Although Coxiella burnetii transmission is multifactorial, we speculate that the higher endemicity in the study area might be related to a contamination by aerosols, because of the Mistral which blows on the local steppe where 70,000 sheep are bred in open fields. Further analysis and epidemiologic studies in this geographic area are required in order to confirm this hypothesis and to identify and quantify more thoroughly individual and preventable risk factors. Such future work will enable health authorities to better oriente future surveillance and possible preventive measures which could be adopted.

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