Comparison between Emerging Q Fever in French Guiana and Endemic Q fever in Marseille, France

Sophie Edouard,† Aba Mahamat,† Magalie Demar, Philippe Abboud, Felix Djossou, and Didier Raoult*

Aix Marseille Université, Marseille, France; Department of Infectious and Tropical Disease, Centre Hospitalier
Andrée Rosemon, Cayenne, French Guiana

Abstract. Q fever is an emergent disease in French Guiana. We compared the incidence clinical and serologic profiles between patients from Cayenne, French Guiana and Marseille in metropolitan France during a four-year period. The annual incidence of diagnosed acute Q fever was significantly higher in Cayenne (17.5/100,000) than in Marseille (1.9/100,000) ($P = 0.0004$), but not the annual incidence of endocarditis (1.29 versus 0.34/100,000). Most patients had fever (97%) and pneumonia (83%) in Cayenne versus 81% and 8% in Marseille ($P < 0.0001$ and $P < 0.0001$, respectively) but transaminitis was more common in patients from Marseille (54% versus 32%; $P < 0.0001$). The proportion of patients with cardiovascular infections was significantly lower in Cayenne (7%) than in Marseille (17%) ($P = 0.017$), although they showed a stronger immune response with higher levels of phase I IgG ($P = 0.024$). The differing epidemiology, clinical, and serologic responses of patients from Cayenne and Marseille suggest a different source of infection and a different strain of *Coxiella burnetii*.

INTRODUCTION

Coxiella burnetii is an obligate intracellular bacterium that is responsible for Q fever, a worldwide zoonosis that was first described in Australia in 1935.¹ A wide variety of wild and domestic mammals, birds, and arthropods may be infected by this bacterium.² *Coxiella burnetii* is principally transmitted to humans by aerosols from the parturient fluid of the infected cattle, goats, and sheep that constitute the main reservoir for the bacteria.³ Q fever is characterized by its clinical polymorphisms; this bacterium may cause acute and chronic infections in humans. Acute Q fever occurs during the first infection by *C. burnetii*. Most (60%) cases in described outbreaks are asymptomatic. Isolated fever, atypical pneumonia, and transaminitis, are the most frequently observed symptoms.⁴

The severity of acute Q fever depends on the strain of *C. burnetii* that infects the patient.⁵ In most cases, patients with an acute infection recover spontaneously. However, endocarditis and vascular infections develop in 1–5% of patients; these complications occur most commonly in patients with underlying cardiovascular abnormalities, vascular prosthesis, or immunosuppression.^{6,7} All strains of *C. burnetii* appear to be capable of causing cardiovascular infections, although these subsequent infections are mainly related to host factors and are independent of the clinical manifestations of acute Q fever. Therefore, although the strain influences the severity of acute Q fever, the incidence of diagnosed acute Q fever does not really reflect the incidence of Q fever.⁸ The occurrence of cardiovascular infection may be more indicative of the real incidence of Q fever.

Because *C. burnetii* is a fastidious bacteria, the most commonly used method for the diagnosis of Q fever is serologic analysis.⁹ The phenomenon of phase variation that is exhibited by *C. burnetii* constitutes the basis for the interpretation of serologic test results. The shift from virulent phase I to aviru-

lent phase II is correlated with a partial loss of lipopolysaccharides.² Phase II antibodies have been observed in acute Q fever, and high levels of phase I IgG are observed in patients with cardiovascular infections.⁹

Coxiella burnetii was first identified in French Guiana in 1955.¹⁰ Only sporadic cases were reported until 1996, when three patients with acute respiratory distress syndrome were hospitalized in an intensive care unit.¹¹ One patient died and many cases of Q fever were concurrently diagnosed in the general population. A retrospective seroepidemiologic study showed a significant increase in the incidence rate of *C. burnetii* infection in 1996, particularly in Cayenne, which is the main urban center in which more than half of the population is concentrated.¹² These data are surprising because Q fever occurs more frequently in rural areas, and urban cases are not linked to the classical sources of infection (goats, sheep, and cattle). The low infection rate of livestock in Guiana with *C. burnetii* confirms this particular epidemiology. Another study has confirmed these data; during 1996–2000, 132 cases of *C. burnetii* infection localized around Cayenne were confirmed by serologic analysis.¹³

The emergence of Q fever in Cayenne was sudden. In 1996, the annual incidence of acute Q fever was 37 cases/100,000 inhabitants, and the incidence increased to a peak of 150 cases/100,000 inhabitants in 2005.¹⁴ No link between livestock and infection was found, but other risk factors were reported, including the presence of a forest or wild mammals near the house, exposure to the aerosols generated by earthworks or gardening, and the presence of air conditioning in vehicles (Table 1).¹³ Clinically, the most common presentation of acute Q fever is pneumonia, and *C. burnetii* was present in 24% of community-acquired pneumonia cases in French Guiana.¹⁵ The prevalence of *C. burnetii* in pneumonia in French Guiana was the highest of any country reported worldwide.

In metropolitan France, Q fever is endemic, and patients most commonly have fever and transaminitis (Table 1).² In our laboratory, we tested samples from patients from metropolitan France and French Guiana and observed that for several years, the phase I IgG titers of patients from French Guiana have been more strongly increased, without an increase in the prevalence of cardiovascular infection, than

* Address correspondence to Didier Raoult, Aix Marseille Université, Unité des Rickettsies, Unité de Recherche sur les Maladies Infectieuses et Tropicales Emergentes, UM63, CNRS 7278, IRD198, INSERM 1095, Marseille, France. E-mail: didier.raoult@gmail.com

† These authors contributed equally to this article.

TABLE 1
Epidemiology of Q fever in metropolitan France and French Guiana

Variable	Metropolitan France	Reference	French Guiana	Reference
Male sex, %	66%	28	70%	13
Age (years)	46.2	28	38.6	13
Predominant clinical presentation of acute Q fever	Transaminitis	21	Pneumonia	13,15
Location of cases	Rural area		Urban area	13,29
Annual incidence	1.9/100,000 inhabitants	28	37–150/100,000 inhabitants	14
Seasonality	Spring, summer	28	March/April–August/September	13
Risk factors	Contact with parnutrients of infected livestock; contact with farm animals, raw milk and cheese consumption; and arthropod-borne transmission	2,28	Living near a forest, presence of bats, marsupials, or other wild animals near the residence; terracing and gardening work; and air-conditioned vehicles	13

for patients from metropolitan France. The aim of this study was to compare clinical symptoms, immune responses, and prevalence of cardiovascular infections between patients with Q fever from French Guiana and metropolitan France.

MATERIALS AND METHODS

Study design. As a national reference center for Q fever, our laboratory routinely receives human samples from all parts of France, including French Guiana. We retrospectively compared clinical findings, serological profiles, and prevalence of cardiovascular infection in patients who had been diagnosed with Q fever living in the Cayenne area to similar data from patients living in the Marseille area, in southern France, where our laboratory is located. We also compared *C. burnetii* DNA detection in serum samples from these two groups. The study was approved by the local IFR48 Ethic Committee (no. 13-001).

Inclusion criteria and case definitions. We included all patients from the Cayenne and Marseille areas who had been newly diagnosed with Q fever during January 2008–December 2011 and who had positive serologic results for Q fever in our laboratory. We included patients with phase II antibody titers that were consistent with acute Q fever (IgG II $\geq$ 200 and IgM II $\geq$ 50) or with increased phase I antibody titers (IgGI $\geq$ 800) and patients who seroconverted with a four-fold increase of phase II antibodies.

Clinical data. Clinical data were obtained by phone contact with the physician in charge of the patients who were included in our study. A standardized questionnaire with clinical information, microbiologic findings, treatment data, and echocardiography or positron emission tomography scan results was completed. These data were analyzed retrospectively. Transaminitis was defined as an increase in transaminases (aspartate aminotransferase and alanine aminotransferase) to greater than twice the reference values. Endocarditis and vascular infection were diagnosed according to the new criteria established for Q fever cardiovascular infection.⁷

Serologic analysis. Serologic tests were performed using an indirect immunofluorescent antibody (IFA) assay, which is the reference method for the serodiagnosis of Q fever.⁹ We used reference strains *C. burnetii* Nine Mile I and Nine Mile II as antigens, and antigen preparation and purification was performed as described.⁹ Serum samples were first screened for total immunoglobulin directed against *C. burnetii*. A quantification assay for IgG, IgM, and IgA phases I and II

was performed on the positive serum samples as described.⁹ Serologic screening and quantification for patients from the Marseille area was performed in our laboratory. Screening for Q fever serologic results for the patients from Cayenne was performed at the Pasteur Institute of Cayenne, and phase I and phase II antibody titers for these patients were quantified in our laboratory in Marseille.

Polymerase chain reaction. DNA was extracted by using a QIAamp Tissue Kit (QIAGEN, Hilden, Germany), and quantitative real time PCR (qPCR) was performed in a CFX96 thermocycler (Bio-Rad, Marnes-la-Coquette, France) using primers and probes specific for intergenic sequences IS1111 and IS30a as described.¹⁶ DNA from the *C. burnetii* Nine Mile II strain was used as a positive control and sterile water was used as negative control. The PCR was routinely performed in our laboratory for negative serum samples, and preceding evidence of seroconversion, and on serum samples whose titer of phase I IgG first reached 800; we suspected that these infections were evolving to the chronic form of the disease.

Statistical analysis. The Student's *t*-test, Fisher's exact test, Mann-Whitney test, or chi-square test and standard statistical software (GraphPad Prism 5; GraphPad, San Diego, CA) were used for statistical analyses of the data. A *P* value < 0.05 was considered significant.

RESULTS

In our study, we included 115 patients from the Cayenne area and 182 patients from the Marseille area who had been given a diagnosis of Q fever by an IFA assay during January 2008–December 2011. Based on our data, we estimate that the annual cumulative incidence for acute Q fever in the Cayenne area (17.5 cases/100,000 inhabitants) was significantly higher than that in the Marseille area (1.9 cases/100,000 inhabitants) during these four years ($P = 0.0004$, by chi-square test).

The age and sex of a patient at diagnosis did not differ significantly between these two populations, ($P = 0.7$ and $P = 0.26$, respectively). The mean age of the patients from Cayenne was 48 years (median = 47.1 years, range = 16–97 years), whereas the mean age for patients from the Marseille area was 47 years (median = 48.3 years, range = 4–87 years); 60% of patients in Cayenne and 66% of patients in Marseille were men. Clinical and serologic findings for these two populations are shown in Table 2.

The proportion of patients with fever was higher in Cayenne (97%) than in Marseille (81%) ($P < 0.0001$, by chi-square test).

TABLE 2

Epidemiology of Q fever, clinical symptoms, and serologic results for metropolitan France (Marseille area) and French Guiana (Cayenne area)*

Variable	Total (n = 297)	Cayenne area (n = 115)	Marseille area (n = 182)	P
Age, years, median (IQR)	47.9 (35.0–57.2)	47.1 (35.8–57.3)	48.3 (35.0–56.9)	0.7
Male sex, no. (%)	190 (64)	69 (60)	121 (66)	0.26
Clinical manifestation of acute Q fever, no. (%)				
Fever	259 (87)	112 (97)	148 (81)	0.0001
Transaminitis	136 (46)	37 (32)	99 (54)	0.0001
Acute pneumonia	110 (37)	96 (83)	14 (8)	0.0001
Patients with cardiovascular infection	39 (13)	8 (7)	31 (17)	0.01
Serologic profile				
IgG phase I titer < 800	151 (51)	49 (43)	102 (56)	0.024
IgG phase I titer ≥ 800	146 (49)	66 (57)	80 (44)	0.024

*IQR = interquartile range.

Transaminitis was found in a significantly higher proportion of patients from Marseille (54%) than from Cayenne (32%) ($P < 0.0001$, by chi-square test), in contrast with pneumonia, which was more prevalent in patients from Cayenne (83%) than in patients from Marseille (8%) ($P < 0.0001$, by chi-square test). The proportion of patients with Q fever who had cardiovascular infections was significantly higher in Marseille; 31 patients (17%) had cardiovascular symptoms, including 27 patients with endocarditis and 4 patients with vascular infection, and 8 (7%) patients from Cayenne had endocarditis ($P = 0.01$, by chi-square test). No patients with vascular infections were reported in Cayenne. The annual cumulative incidence during these four years for Q fever–associated endocarditis in the Cayenne area (1.29 cases/100,000 inhabitants) was not significantly different than the incidence in the Marseille area (0.34 cases/100,000 inhabitants) ($P = 0.45$, by chi-square test).

We studied serologic profiles and compared immune responses of these two populations based on the maximal titers of phase I IgG in serum samples that were positive in our laboratory by the IFA assay. We observed that patients from Cayenne had significantly higher phase I IgG titers (57% of patients from Cayenne versus 44% of patients from Marseille had IgG titers ≥ 800; $P = 0.024$, by chi-square test). The median of IgG phase I titers for patients from Cayenne was also significantly higher than for patients from Marseille (800, range = 25–51,200 and 400, range 25–25,600 respectively; $P = 0.0087$, by Mann-Whitney test) (Figure 1). The PCR was performed for serum samples from 92 patients from Cayenne

and 118 from Marseille. We did not observe a difference in the percentage of PCR-positive results for serum samples obtained during the acute form of the disease or for serum samples with phase I IgG titers ≥ 800 (Table 3).

We also compared the positive predictive value (PPV) of the titer of phase I IgG for cardiovascular infection diagnosis in these two populations according to the updated criteria.⁷ Among patients with phase I IgG titers ≥ 800, 1,600, 3,200, and 6,400, the respective numbers of cardiovascular infections were 31, 20, 15, and 11 for patients from Marseille and 8, 8, 6, and 5 for patients from Cayenne. Therefore, the PPVs for the diagnosis of cardiovascular infection according to the IgG phase I titer were 48%, 65%, 88%, and 92% at titers ≥ 800, ≥ 1,600, ≥ 3,200, and ≥ 6,400 in Marseille and were significantly lower, at 12%, 19%, 29%, and 50%, respectively, for patients from Cayenne ($P < 0.0001$, $P = 0.0001$, $P = 0.0002$, and $P = 0.055$, respectively, by chi-square test) (Table 4).

DISCUSSION

Our study provided a clinical and serologic comparison between Q fever in French Guiana and metropolitan France. We chose to compare the epidemiology, clinical findings, and microbiologic results for patients from Cayenne with those of patients from the Marseille area because Marseille is the location of our reference center, and we have a detailed understanding of the epidemiology of Q fever of this area. We tested all of the patients by using the same techniques.

FIGURE 1. **A**, Comparison of Q fever phase I IgG titers in patients from Marseille, France, and from Cayenne, French Guiana. Values are median ± range of phase I IgG titers obtained from patients from Marseille (400, range = 25–25,600) (●) and Cayenne (800, range 25–51,200) (■) ($P = 0.0087$, by Mann-Whitney test). **B**, Distribution of phase I IgG titers in patients from Marseille and Cayenne.

TABLE 3

Results of qPCR performed on serum, according to phase I and phase II immunoglobulin serum levels*

Variable	Cayenne, French Guiana area	Marseille, France area	P
	No. patients/total patients tested (%)	No. patients/total patients tested (%)	
Positive qPCR	7/92 (8)	21/118 (18)	
Acute Q fever	1/41 (2)	5/75 (7)	0.325
IgG phase I $\geq$ 800	6/51 (12)	5/43 (12)	0.983

*qPCR = quantitative polymerase chain reaction.

In our study, we confirmed that diagnosed acute Q fever has a higher incidence in Cayenne than in Marseille, and that the major clinical presentation of Q fever in Cayenne is pneumonia. In a review of 58 Q fever pneumonia radiographic charts in Cayenne, 90% harbored abnormalities. Among these abnormalities, an alveolar syndrome (80%) or an alveolo-interstitial syndrome (20%) with or without opacities may be seen on chest radiographs. The clinical manifestations of acute Q fever reportedly vary from one geographic area to another.² For example, the main manifestation of acute Q fever in the Spanish Basque region,¹⁷ in an outbreak in the Netherlands,¹⁸ in southeast Canada,¹⁹ and in Switzerland²⁰ is pneumonia, in contrast to metropolitan France and southern Spain, where the predominant presentation of Q fever is transaminitis.^{7,21}

We hypothesized that exposure to higher inocula by aerosol or to a particularly virulent strain of *C. burnetii* circulating in Cayenne could explain the observed manifestation of Q fever and severity of the pneumonia in Cayenne. The size of the inoculum can influence the clinical picture and the degree and duration of the clinical response in acute Q fever, as described in several animal models.^{20,22,23} A murine model of aerosol infection has shown that only high inocula of the *C. burnetii* strain Nine Mile I ($> 10^8$ bacteria) cause pneumonia.²² However, different clinical forms of acute Q fever are also dependent on the strain.^{5,22,24,25} In the guinea pig model, severe acute pneumonia developed in animals when they were infected with *C. burnetii* strains harboring the QpH1 plasmid (Nine Mile, African, and Ohio strains), mild to moderate disease when they were infected with plasmid-less *C. burnetii* strains (Q217 and Q212 strains), and were asymptomatic when they were infected with *C. burnetii* strains harboring the QpRS (Priscilla) or QpDG (Dugway) plasmids.²³ Only *C. burnetii* strains carrying the QpH1 or the QpDV plasmid have been associated with acute Q fever in humans.²⁶

Because the clinical picture and severity of acute Q fever is related to the strain, the incidence of diagnosed acute Q fever

does not reflect the actual incidence of Q fever. We observed a higher proportion of asymptomatic cases of acute infection in Europe than has been described in other studies.^{1,8,21} In large studies in Switzerland²⁷ and the Netherlands,⁸ half of the patients with acute infections were asymptomatic, and only 5–20% of acute infections were severe enough to prompt a diagnostic test.^{1,7} In the Marseille area, the annual reported incidence of diagnosed acute Q fever was 1.9 cases/100,000,²⁸ which is 25-fold less than the annual estimated incidence of Q fever, which is 50 cases/100,000.² No annual estimated incidence is available for the Cayenne area, but the incidence of diagnosed acute Q fever in Guiana, which was 37 cases/100,000 in 1996 and increased to 150 cases/100,000 in 2005,¹⁴ is most likely underestimated, despite the severity of the disease. Thus, the number of cases of cardiovascular infection may be indicative of the real incidence of Q fever. Approximately 1–5% of patients who have been diagnosed with acute Q fever develop cardiovascular infection in the Marseille area.² These data are not available for French Guiana. Only one study has identified 22 (2.3%) cases of endocarditis and 933 of acute Q fever during 1990–2006.¹⁴ In our study, we found that compared with Marseille, the annual incidence of acute Q fever increased nine-fold in Cayenne, although the annual incidence of cardiovascular infection increased only four-fold in Cayenne. The fact that we did not find a significant difference in the incidence of Q fever-associated cardiovascular infections between Cayenne and Marseille suggests that the severity of acute Q fever in Cayenne is at least as important in explaining the higher incidence of symptomatic cases of acute Q fever in Cayenne as the exposure risk.

Our data show that patients from Cayenne with Q fever infections had higher levels of phase I IgG without a higher prevalence of cardiovascular infections. In a previous study, Frankel and others showed that an increase in the level of phase I IgG is correlated with higher PPVs for the diagnosis of endocarditis in France.²⁸ The PPVs for possible or definite endocarditis increase with the levels of IgG titer, and we found comparable results in this study for patients from the Marseille area. For patients from the Cayenne area, we could not use the same serological cut-off that is used to diagnose cardiovascular infections in French patients⁷ because the PPV of phase I IgG for patients from this area is much lower. For example, a 56-year-old man with acute Q fever and pneumonia and transaminitis, but no valvulopathy, was identified in Cayenne. The first serum sample, which was obtained concomitantly with the onset of clinical symptoms, exhibited phase I IgG titers of 800 and phase I IgM titers of 1,600. Four

TABLE 4

Positive predictive value (PPV) of Q fever phase I IgG titers for patients with endocarditis or vascular infections from the Marseille, France and Cayenne, French Guiana areas*

Variable	Phase I IgG titer			
	≥ 800	$\geq 1,600$	$\geq 3,200$	$\geq 6,400$
Patients from Marseille area (n = 65)				
Possible or definite endocarditis or vascular infection	31	20	15	11
Total	65	31	17	12
PPV, % (definite or possible endocarditis or vascular infection)	48	65	88	92
Patients from Cayenne area (n = 65)				
Possible or definite endocarditis or vascular infection	8	8	6	5
Total	65	42	21	10
PPV, % (definite or possible endocarditis or vascular infection)	12	19	29	50
P	< 0.0001	0.0001	0.0002	0.055*

*By Fisher exact test.

months later, IgGI titers had increased to 12,800, and IgMI titers had decreased to 100; two months after that, the IgGI titers decreased to 6,400 without treatment. In 27 years at our reference center, we have never observed high IgGI titers in patients who live in the metropolitan area and are infected with *C. burnetii* without endocarditis or vascular infection, and we have never observed patients cured spontaneously.

In conclusion, Q fever in Cayenne presents with a severe form of acute pneumonia and a stronger serologic response than has been observed elsewhere, suggesting exposure to higher bacterial inocula and/or the circulation of a specific strain. Further work is ongoing and should confirm these hypotheses.

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Authors' addresses: Sophie Edouard and Didier Raoult, Aix Marseille Université, Unité des Rickettsies, Unité de Recherche sur les Maladies Infectieuses et Tropicales Emergentes, UM63, CNRS 7278, IRD198, INSERM 1095, Marseille, France, E-mails: soph.edouard@gmail.com and didier.raoult@gmail.com. Aba Mahamat, Magalie Demar, Philippe Abboud, and Felix Djossou, Department of Infectious and Tropical Disease, Centre Hospitalier Andrée Rosemon, Cayenne, French Guiana, E-mails: mahamataba@gmail.com, magalie.demar@ch-cayenne.fr, philippe.abboud@ch-cayenne.fr, and felix.djossou@ch-cayenne.fr.

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