Epidemiology of Human Leptospirosis in French Guiana (2007–2014): A Retrospective Study

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Abstract. Leptospirosis is a worldwide zoonotic bacterial infection with a rising incidence. French Guiana is mostly covered by Amazonian rain forest. Despite a potentially favorable environment, leptospirosis has been barely studied in French Guiana. The objective of this study was to describe the current trends of leptospirosis epidemiology in French Guiana. A cross-sectional study was performed in the two main hospitals of French Guiana. Cases of leptospirosis from 2007 to 2014 were retrospectively identified with a systematic screening of serological and polymerase chain reaction results to classify them as confirmed, probable, or excluded cases. Medical files were reviewed to collect epidemiological data. Among the 72 included patients, 55 (76.4%) cases were confirmed and 17 (23.6%) were probable. The median age was 39 years (range: 16–82 years) and the M/F sex ratio 6.2. Sixty-two (86.1%) patients required hospitalization, including 12 (16.7%) in the intensive care unit. Three (4.2%) patients died. The monthly distribution of cases was correlated with rainfall ($P = 0.004$) and moisture ($P = 0.038$). Professional exposure was frequently identified (especially gold mining and construction). Among 16 different serogroups identified by microagglutination test, Icterohaemorrhagiae was the most frequent (38.0%). This study revealed an epidemiology close to that observed in Brazilian regions, and professional and climatic risk factors. The high diversity of serogroups may reveal a complex environmental reservoir requiring further investigations. Only 20% of leptospirosis patients were suspected as such on hospital admission, thus emphasizing the need to inform local physicians.

INTRODUCTION

Leptospirosis is a worldwide zoonotic disease caused by *Leptospira* spp. Its world annual incidence is estimated around 1,000,000 cases with 60,000 deaths. The burden of leptospirosis is particularly high in tropical areas.¹ In mainland France, according to the French National Reference Center for Leptospirosis (NRCL), leptospirosis incidence is increasing with 0.9/100,000 and 0.6/100,000 in 2014 and 2015, respectively.² Incidence in the French overseas departments and territories located in the Pacific and Indian oceans and the Caribbean (Martinique and Guadeloupe) is much higher, up to 36/100,000.^{3,4} French Guiana is a French overseas territory located on the northern coast of South America. More than 95% of its surface is Amazonian rain forest. The animal and plant biodiversity is one of the highest in the world. Until recently, leptospirosis was thought to be rare in the region. However, leptospirosis publications are scarce and outdated, only relating case reports or case series.^{5,6} Between 1939 and 1995, only 72 cases have been reported in French Guiana. Because the determinants of leptospirosis are hardly known, we aimed to improve the knowledge on this infectious disease in the region.

The primary objective of this study was to describe the epidemiologic features of human leptospirosis in French Guiana. The secondary objective was to search for environmental risk factors by studying the correlation between climatic variables and the occurrence of cases.

MATERIAL AND METHODS

Study design and population. An ecological cross-sectional study was conducted among patients with a suspected case of leptospirosis admitted to the two main hospitals of French Guiana, Center Hospitalier Andrée Rosemon in Cayenne and the Center Hospitalier de l'Ouest Guyanais in Saint Laurent du Maroni from January 1, 2007 to September 30, 2014. Cases of leptospirosis were identified with the positive results of leptospirosis diagnostic tests performed in instance of routine suspicion. Results were extracted from the NRCL database (Pasteur Institute, Paris, France) and the private laboratory, Laboratoire Cerba (Cergy-Pontoise, France) database.

Biological diagnosis of leptospirosis in French Guiana.

The choice of the diagnostic technique was left to the discretion of the physician. The biological diagnosis relied on real-time polymerase chain reaction (PCR) during the acute phase, for example, day 0 to day 10 after the onset of symptoms and on serodiagnosis from day 7, roughly. All PCRs were performed by Laboratoire Cerba in mainland France. DNA extraction was performed with Easymag (bioMérieux, France) and amplification was performed on Lightcycler 480. The test was an in-house real-time PCR based on a previous study and was equipped with an internal control added at the extraction step to detect inhibitors.⁷ Polymerase chain reaction data were available for the 2010–2014 period.

Serologic screening of immunoglobulin M (IgM) antibodies against *Leptospira* was performed by one of two laboratories: Laboratoire Cerba or the Pasteur Institute in French Guiana. In Laboratoire Cerba, the IgM test was based on an enzyme immuno-assay technique (Serion, Germany). The test was considered negative if the antibody level was lower than 15 UI/mL, equivocal if it comprised between 15 and 20 UI/mL, and positive

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if it was greater than 20 UI/mL. Serum samples were analyzed earlier with RF absorbent to avoid cross-reaction with rheumatoid factors. Both internal quality controls (with known leptospirosis cases sera) and external quality controls (with samples furnished by the Royal College of Pathologists of Australasia) were performed. In the Pasteur Institute in French Guiana, the anti-*Leptospira* IgM detection test was based on a different kit (Panbio, Australia) with a threshold of nine arbitrary units. When equivocal or positive reactions were detected with anti-*Leptospira* IgM tests, serum samples were sent to the NRCL in Paris to perform microscopic agglutination test (MAT) to confirm the diagnosis and determine the presumptive infecting serogroup. In the NRCL, MAT was considered positive if ≥ 100 .^{2,8} Until 2012, fourteen serogroups were routinely tested in MAT in NRCL. In 2012, seven additional serogroups were added to the antigen panel.⁸ After 2009, the NRCL also performed an “in-house” ELISA IgM test.⁹ Serologic data were available for the 2007–2014 period.

Inclusion criteria and case definition. Included patients met the following criteria.

A confirmed leptospirosis case was defined as having

- positive PCR in blood, urine, or CSF
- and/or a MAT seroconversion with a MAT titer ≥ 200
- and/or a 4-fold increase in MAT titers on two consecutive sera samples
- and/or a MAT titer ≥ 400 .

A probable leptospirosis case did not match the previous criteria but had

- MAT seroconversion with low titer (MAT = 100)
- and/or a MAT titer = 200 without seroconversion
- and/or a positive MAT titer with IgM seroconversion or IgM elevated titer at NRCL.

The presumptive infecting serogroup was defined by the highest MAT titer detectable in the latest serum sample. If MAT titers were equal for different serogroups (coagglutinins), presumptive infecting serogroup was undetermined.

Patients with no available clinical information were not included. Pediatric cases (age < 15 years) were excluded.

Data collection and definition. Patients' medical charts were retrospectively reviewed to collect demographic, exposure, clinical, biological, radiological, microbiological, and outcome data in anonymized and standardized forms. Leptospirosis initial suspicion was considered if written in the medical chart at the hospital admission of the patient. Severe forms of leptospirosis were defined by the use of vasopressor agents for hemodynamic support and/or dialysis for acute kidney injury and/or mechanical ventilation for respiratory distress and/or death.^{10,11} Climatic data of the study period (2007–2014) of the meteorological station of the Félix Eboué airport, provided by Météo France, such as cumulative daily rainfall, daily average temperature under shelter (24 observations), and daily and average humidity, were obtained.

STATISTICAL METHODS

Epidemiologic data. Quantitative variables were described with mean and standard deviation or median and 25–75 interquartile range (IQR), depending on the variable distribution, and qualitative variables were described with percentages.

Climatic data. Bivariate Poisson regressions were performed to identify potential correlations between climatic measurements and the occurrence of cases. A *P* value < 0.05 was considered significant.

Ethics. The study was approved by the ethic committee of the Cayenne hospital. The collected database was declared to the National Commission on Informatics and Liberty, number 2068308.

RESULTS

Demographic and outcome results. During the 8-year study period, 72 patients were included, among whom 55 (76.4%) were confirmed cases and 17 (23.6%) were probable cases (Figure 1). Although the NRCL provided exhaustive data from French Guiana, patients exclusively originated from both hospital, Cayenne (*N* = 69) and Saint Laurent du Maroni (*N* = 3). The median number of cases per year was eight cases (IQR: 5.5–12.5). The median age was 39 years (IQR: 29–50, range 16–82 years). The age category 20–49 years represented 63.9% of patients (Table 1). The M/F sex ratio was 6.2. Twelve patients (15.9%) had comorbidities. Almost two-thirds of the patients were born in a foreign country (60.6%), mainly Brazil (39.4%). Exposure data were scarce, but when so, an occupational exposure factor was identified for 64.6% (31/48) of patients. Gold mining and construction were most frequently reported in, respectively, 25.0% (12/48) and 14.6% (7/48) of patients. The other main nonprofessional exposure factors were forest stays, river swimming, and proximity to rodents. Sixty-two (86.1%) patients were hospitalized at least one night, and 12 (16.7%) were admitted to the intensive care unit (ICU). For ICU patients, severity criteria were as follows: need for vasopressor agents in 10 patients, dialysis in seven patients, and mechanical ventilation in nine patients.

Eighty-one percent (56/69, missing data *N* = 3) of patients received an initial empirical antibiotic regimen although only 19.4% (14/72) were suspected as leptospirosis on admission to the emergency ward. There were three in-hospital deaths (lethality rate = 4.2%, 95% confidence interval: 1.4–11.6).

Biological diagnosis of leptospirosis in the study patients. A positive MAT was present for 63 included patients (87.5%). Coagglutinins were found in 13 cases of positive MAT. Among patients with identification of presumptive infective serogroup (*N* = 50/72, 69.4%), 16 different serogroups were found (Table 2). The main identified serogroup was Icterohaemorrhagiae in 19/50 (38.0%) cases, followed by Australis, Ballum, Canicola, and Tarassovi with 4 (8.0%) cases for each one. The following serogroups were also identified: Louisiana, Sejroe, Cynopteri, Panama, Pomona, Sarmin, Bataviae, Celledoni, Djasiman, Hebdomadis, and Mini. Nine patients (12.5%) were included because of an isolated positive PCR without positive MAT. They all had an IgM test: six were negative (all performed before the 10th day after symptoms onset), one was equivocal (day 12), and two were positive (day 5 for each). Polymerase chain reaction was not performed in most of the study patients (55.6%).

ENVIRONMENTAL RESULTS

Location of the cases. Among the 72 patients, 69 reported living in French Guiana and three abroad (two in Suriname and one in Brazil) (Figure 2). Among those living in French Guiana,

IgM = immunoglobulin M by ELISA, MAT = microscopic agglutination test, PR = polymerase chain reaction

* Inclusion criteria : MAT seroconversion, significant increase of MAT titers on two consecutive sera samples, elevated MAT titer or a positive MAT titer with IgM seroconversion or IgM elevated titer at NRCL.

FIGURE 1. Flowchart of the study. IgM = immunoglobulin M by ELISA; MAT = microscopic agglutination test.

places of residence were scattered throughout French Guiana: 45 (65.2%) were living in Cayenne or its surroundings, 8 (11.6%) in Maripasoula, and 4 (5.8%) in Saint Laurent du Maroni.

Climatic variables. The monthly distribution of cases was positively correlated with rainfall and moisture ($P = 0.004$ and $P = 0.038$, respectively) and negatively correlated with temperature ($P = 0.0002$) (Figure 3). A higher number of leptospirosis cases was observed during the long rainy season between May and July with 43.1% ($N = 31$) of cases and the short rainy season between January and February with 19.4% ($N = 14$).

DISCUSSION

This is the largest study about confirmed human leptospirosis ever published on the Guiana Shield, which ranges from the eastern part of Venezuela, Guyana, Suriname, and French Guiana to the State of Amapá in Northern Brazil. Previous publications are scarce and old in the region and few of the reported cases were confirmed with MAT positive results.⁵

The epidemiological profile of our patients was quite common and comparable with other studies in the region and worldwide: mostly young, active males.^{1,12} There were 16.7%

of severe cases and 4.2% of lethality. In Brazilian states near French Guiana, the reported lethality rate was heterogeneous: 0.7%, 2.6%, and 10.3% in one study in Macapá (Amapá), and in two studies in Manaus, Amazonas, respectively.¹² Nevertheless, comparison with Brazilian studies is difficult because of heterogeneity of biological diagnostic criteria, differences in access to care, and lack of identification of the benign forms of the disease misdiagnosed as dengue fever during epidemics.^{13,14}

Risk factors for leptospirosis correspond to direct or indirect contact, through contaminated environment, with animals that carry *Leptospira* pathogenic strains.¹⁵ In the present study, 65% of patients with available data had a possible occupational exposure, especially gold mining. In gold mining camps, risk factors for leptospirosis are common such as poor resources, lack of hygiene and soiled water are frequent, and waterborne diseases have already been described.¹⁶ The illegal situation of these gold miners, mainly originating from the poorest regions of northern Brazil, hampers access to care with potentially aggravated outcomes and underreporting of diseases.¹⁷ Outdoor leisure activities such as forest hiking and river bathing were also reported in this study but less frequently than professional exposure.

There was an association between climatic data and occurrence of cases. Cases occurred more frequently during the

TABLE 1

Characteristics of the 72 included patients with leptospirosis

Variable	Details	Results, N (%)
Age (years) (N = 72)	Median (interquartile)	39 (29–50.3)
	Range	16–82
Age categories (N = 72)	10–19 yo	4 (5.6%)
	20–29 yo	15 (20.8%)
	30–39 yo	17 (23.6%)
	40–49 yo	14 (19.4%)
	50–59 yo	13 (18.0%)
	> 60 yo	9 (12.5%)
Case type (N = 72)	Confirmed	55 (76.4%)
	Probable	17 (23.6%)
Gender (N = 72)	M	62 (86.1%)
	M/F gender ratio	6.2
Place of birth (N = 66)	Brazil	24 (36.4%)
	French Guiana	13 (19.7%)
	Mainland France	9 (13.6%)
	Haiti	7 (10.6%)
	Suriname	6 (9.1%)
	French overseas territories	4 (6.1%)
	Guyana	2 (3.0%)
	Guinea-Bissau	1 (1.5%)
Underlying condition* (N = 69)	Yes	11 (15.9%)
Occupational activity (N = 48)	Gold mining	12 (25.0%)
	Building	7 (14.6%)
	Other at-risk profession	12 (25%)
	Unemployed	17 (35.4)
At-risk activity	Forest hiking	23/29 (79.3)
	River bathing	13/16 (81.3)
	Gardening	7/9 (77.7%)
	Rodent seen near home	13/20 (65.0%)
Initial suspicion of leptospirosis written in medical chart (N = 72)	Yes	14 (19.4)
Empiric antibiotic regimen (N = 69)	Yes	56 (81.2)
Patients' support (N = 72)	Outpatients	10 (13.9)
	Ward	50 (69.4)
Severe cases (N = 72)	Vasopressive drugs	10 (13.9)
	Dialysis	7 (9.7)
	Mechanical ventilation	9 (12.5)
	Death	3 (4.9)

Yo = years old.

* Several underlying conditions possible in one patient: diabetes mellitus (N = 2), epilepsy (N = 2), high blood pressure (N = 4), HIV infection (N = 1), immunosuppressive or corticosteroid treatment (N = 3), hemolytic anemia (N = 1). Alcohol, drug, and tobacco use were not considered as comorbidities.

rainy seasons. A strong link between rain and leptospirosis rates is a well-known phenomenon in tropical regions including South America.¹⁸ During rainy periods, physicians' suspicion toward leptospirosis should be increased in case of compatible symptoms.

The Icterohaemorrhagiae serogroup represented 79% of the human cases of leptospirosis between 1939 and 1995, compiling the sparse data available in the literature. Among 16 different presumptive infecting serogroups identified in the study, Icterohaemorrhagiae represented 38% of cases. This rate was similar to the results of NRCL since 1996.⁵ The rising diversity of serogroups may reflect a change in the pattern of infecting strains but this is difficult to ascertain, notably because of the higher number of strains included in the MAT panel test of the NRCL in the last decades. In the present study, a high diversity of implicated serogroups was noted and

TABLE 2

Distribution of the presumptive infecting serogroups of *Leptospira*, 2007–2014

Serogroup*	N	%
Icterohaemorrhagiae	19	30.2
Australis, Ballum, Canicola, and Tarassovi	4†	6.3†
Cynopteri, Sejroe, Lousiana, and Panama	2†	3.2†
Bataviae, Celledoni, Djasiman, Hebdomadis, Mini, Pomona, and Sarmin	1†	1.6†
Coagulglutinins	13	20.6

* The presumptive infecting serogroup was defined by the highest microscopic agglutination test (MAT) titer detectable in the latest sample among the included patients with MAT inclusion criteria (N = 63). If MAT titers were equal for different serogroups, presumptive infecting was considered undetermined (coagulglutinins).

† Per each serogroup.

could reveal multiple animal *Leptospira* hosts. Similar studies have been performed in Brazilian states close to French Guiana, namely, Amazonas and Para, that showed heterogeneous results and a high number of serogroups.^{19,20}

The most common reservoir for *Leptospira* is *Rattus norvegicus*.¹⁵ In our study, when the information was available (N = 20), a contact with rodents was reported in 65% but because of the retrospective design of the study, the exposure rate remains uncertain. A wide variety of domestic animals can be found as *Leptospira* reservoirs, as demonstrated in many South American countries.²¹ Nevertheless, no survey exists concerning leptospirosis in household animals or cattle in French Guiana to assess their role in human transmission. A few studies reported the presence of *Leptospira* spp. in animals in French Guiana.^{22,23} In French Guiana, forest exposure can lead to a possible contact with *Leptospira* through an environment contaminated by urine from the wildlife and could play a significant role in leptospirosis. Some studies reported that leptospirosis exists in numerous wild and domestic mammals present in French Guiana, so wildlife might promote *Leptospira* persistence and be implicated in transmission to humans.²⁴ As with other endemic pathogens such as *Toxoplasma gondii* and *Coxiella burnetii*, research is ongoing to assess the role of wildlife in leptospirosis transmission. Studies are currently evaluating whether captured wild rodents—among other species—harbor *Leptospira* spp. in French Guiana. Besides, animal serological surveys and *Leptospira* isolation should be performed to investigate the role played by domestic animals.

Leptospirosis diagnosis can be challenging. Repeated samples are required to study the evolution of antibody titers (IgM and MAT) when PCR is negative or not tested. Positive anti-*Leptospira* IgM detection is an early marker of the disease but has a limited specificity.²⁵ Indeed, serological cross-reactions have been described with common infections in French Guiana such as acute Q fever or dengue fever.^{26–28} Eventually, authors assumed that exposure to French Guiana environment could be responsible for the detection of IgM antibodies against *Leptospira* (including nonpathogenic strains).⁸ Therefore, to avoid the inclusion of patients with false positive results and differential diagnoses, it was chosen not to include patients with isolated positive IgM. However, those strict biological criteria could be criticized for several reasons. The main limitation was the noninclusion of authentic leptospirosis cases in initial stages of the disease with positive IgM antibodies as the only criteria. This may have lowered the number of cases identified in this study compared with the NRCL report.² The number of leptospirosis cases in French

FIGURE 2. Residence location of the 72 patients with leptospirosis, 2007–2014.

Guiana was relatively stable between 1996 and 2011.⁵ The trend of increasing reported cases of leptospirosis after 2011 raises the following explanatory hypotheses: a real emergence or an improvement in the access to biological diagnosis. Contrary to the present study, the detection by the NRCL of IgM antibodies with their “in-house” technique is sufficient to consider a case of leptospirosis whatever MAT or PCR results.⁹ Interestingly, the existence of patients with symptoms compatible with the diagnosis of leptospirosis and elevated titers of NRCL “in-house” IgM tests, whose delayed MAT results remained negative (unpublished NRCL data), could suggest the existence of untested serogroups in the MAT panel and therefore possibly new species, as previously reported by others.²⁹ Unfortunately, we were unable to test this hypothesis because all patients included in our study

through a positive PCR only had one negative early MAT. To ascertain this hypothesis, culture and isolation of pathogenic *Leptospira* strains in those patients would have been necessary. Further research using genotyping techniques could be considered based on obtained positive PCR samples.

For most of the patients (80%), leptospirosis was not suspected on hospital admission. This apparent lack of concern could be caused by the presence of other endemic diseases such as malaria, Q fever, Amazonian toxoplasmosis, or dengue fever.^{1,20,27,30} Thus, patients with mild form of the disease could be overlooked, leading to an underestimated burden of leptospirosis.

In the French Caribbean, prospective studies have revealed a higher level of incidence of leptospirosis than previously known.^{2–4,31} They led health authorities to implant local

FIGURE 3. Monthly distribution of the cases compared with average daily rainfall (A), average temperature (B), and average humidity (C). Aggregate data on 1 year. Months 12, 1, and 2: small rainy season; Month 3: small dry season; Months 4–6: big rainy season; Months 7–11: big dry season.

surveillance network and on-site efficient diagnostic tools and increased local physicians' awareness toward leptospirosis.

CONCLUSION

We present here the largest study on confirmed leptospirosis ever performed in the Guiana Shield. It demonstrates that leptospirosis is increasingly prominent in our region with severe cases, refuting the long-held assumption that it was a rare disease. It revealed epidemiological features close to Brazilian regions and an association with rainfall. Because of a possible underestimation, prospective studies are needed to assess the real burden of leptospirosis in the region. Moreover, field investigations are necessary to confirm the high diversity of involved serogroups and assess the role of a possibly complex environmental reservoir.

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