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**Tularemia: a case series of patients diagnosed at the National Reference Center for rickettsioses from 2008 to 2017.**

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**Summary of the article main point:**

This case series presents 177 patients with tularemia in France between 2008 and 2017: Glandular and ulcero-glandular forms were the most frequent. Two aortitis, an infectious endocarditis, a myocarditis, an osteoarticular infection and a splenic hematoma were diagnosed.

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## Abstract

**INTRODUCTION:** We describe the epidemiological, clinical and prognostic aspects of 177 tularemia cases diagnosed at the National Reference Center for rickettsioses, coxiellosis and bartonellosis between 2008 and 2017.

**METHODS:** All patients with a microbiological diagnosis of tularemia made in the laboratory were included. Clinical-epidemiological data were collected retrospectively from clinicians in charge of patients using a standardized questionnaire. Diagnostic methods used were indirect immunofluorescence serology, real-time polymerase chain reaction and universal PCR targeting the 16S rRNA gene.

**RESULTS:** The series included 54 females and 123 males (sex ratio 2.28, mean age 47.38 years). Eighty-nine (50.2%) were confirmed as having tularemia on the basis of a positive *F. tularensis* PCR or seroconversion, and 88 (49.8%) were considered as probable due to a single positive serum. The regions of France that were most affected included Pays de la Loire (22% of cases), Nouvelle Aquitaine (18.6% of cases) and Grand-Est (12.4% of cases). Patients became infected mainly through contact with rodents or game (38 cases, 21.4%), through tick-bites (23 cases, 12.9%) or during outdoor leisure activities (37 cases, 20.9%). Glandular and ulcero-glandular forms were the most frequent (109 cases, 61.5%). Two aortitis, an infectious endocarditis, a myocarditis, an osteoarticular infection and a splenic hematoma were also diagnosed. Tularemia was discovered incidentally in 54.8% of cases. Seventy-eight patients were hospitalized, no deaths were reported.

**DISCUSSION:** Our data suggest that in an endemic area and/or in certain epidemiological contexts, tularemia should be sought in order to allow an optimized antibiotic therapy and a faster recovery.

**Key Words:** Tularemia; *Francisella tularensis*; case series; France; diagnosis

## Introduction

Tularemia is a zoonotic disease caused by *Francisella tularensis*. This facultative intracellular Gram-negative bacillus was isolated for the first time from flying squirrels in Tulare County in the USA by Mac Coy and Chapin<sup>1</sup>. Tularemia is endemic in North America<sup>2</sup>, Asia<sup>3</sup> and Europe<sup>4-8</sup>.

*Francisella tularensis* subspecies *tularensis* (type A), almost restricted to North America, is responsible for the most severe diseases. The lethality may be as high as 30% in untreated pulmonary forms<sup>9</sup>. In contrast, *F. tularensis* subspecies *holarctica* (type B) is widely distributed in the Northern Hemisphere, but also in southern Australia, and associated with a lethality rate < 1%. Clinical signs vary according to the geographical area, season and thus mode of contamination<sup>6,7,10-13</sup>. Six clinical forms are classically recognized: the ulceroglandular (ulcer associated with lymphadenopathy) and glandular (lymphadenopathy) forms, upon skin inoculation after animal contact (most often lagomorphs or small rodents) or by arthropod bite; the oculoglandular (conjunctivitis) form after conjunctival inoculation; the oropharyngeal (sore throat) form upon ingestion of contaminated water or food<sup>14</sup>; and two systemic diseases, including the pneumonic (pneumonia) and the typhoidal forms (mimicking symptoms of typhoid). Frequent complications of lymphadenopathies are suppurations and even skin fistulas. Other complications such as sepsis or meningitis<sup>15</sup> are more rarely reported and usually occur in patients with comorbidities and/or immunosuppression.

Current knowledge of tularemia comes from data reported in highly endemic areas such as North America<sup>11,16</sup> and Northern Europe<sup>10</sup>. In contrast, few data exist for Western Europe<sup>17-19</sup>.

Here, we present the epidemiological, clinical, diagnostic and treatment data of 177 patients diagnosed with tularemia in the French reference center for rickettsioses, coxiellosis and bartonellosis in Marseille, France, from January 1, 2008 to December 31, 2017.

## Methods

### Definition of tularemia cases:

All patients with a suspected diagnosis of tularemia were considered as confirmed when they exhibited compatible clinical findings and at least: (1) a positive real-time PCR (RT-PCR) and/or 16S rRNA PCR for *F. tularensis*; (2) seroconversion; or (3) a four-fold increase in immunofluorescence serological titers, as previously described<sup>20</sup>. Culture was carried out only on PCR-positive samples.

Patients with compatible clinical findings and a single positive serological test were considered probable cases.

### Patients and clinical samples:

The present study is a retrospective analysis of epidemiological and clinical data from patients with tularemia. Data had been prospectively collected since 2008 using an anonymized and standardized questionnaire and stored on a secured computer by the French reference center for tularemia.

### Patient Consent Statement

The present study was validated by the Ethics Committee of the “Institut hospitalo-universitaire” (IHU) Méditerranée Infection under reference 2017-029.

The consent form to be signed by patients was sent to the clinicians, who obtained the signature before transmitting the data.

### Mode of transmission:

We assigned the most likely source of contamination according to the scheme already used by Maille *et al.*<sup>18</sup>:

- Any patient infected with *F. tularensis* who reported direct contact with hares during the month before the onset of symptoms would have been infected by this exposure;

- A tick bite reported during the month before the onset of symptoms would be the route of contamination for any patient unless the patient also reported direct contact with hares;
- An occupational exposure during the month before the onset of symptoms would constitute a circumstance of contamination unless the patient also reported direct contact with hares or a tick bite;
- Recreational activities resulting in exposure to aerosols or dust in the forest during the month before the onset of symptoms would be circumstances of contamination unless the patient reported direct contact with hares, tick bite or occupational exposure.

### Laboratory diagnosis

Serology was performed using indirect immunofluorescence. Immunoglobulin G and M titers were measured. For this purpose, a formalin-inactivated antigen prepared in-house from a biovar I strain of *F. tularensis* subspecies *holarctica* was used as previously described<sup>20</sup>.

When lymph node biopsy specimens were available, a *F. tularensis*-specific RT-PCR assay targeting the *yqaB* gene (Ftul0541F, Ftul0541R and Ftul0541P), was also used for the detection of the bacterium, as previously described<sup>22</sup>. In addition, a patient with hip arthritis was detected positive using a broad range PCR assay followed by sequencing the 16S RNA gene with the fd1 and rP2 primers was used<sup>22</sup>.

### Outcome

Therapeutic success was defined as the resolution of symptoms (fever, abscess) one month after appropriate antibiotics (fluoroquinolone, tetracycline, or aminoglycoside) had been discontinued.

We considered as therapeutic failure the persistence of symptoms and/or the occurrence of complication(s) despite appropriate antibiotic.

Surgery was performed either as a diagnostic and/or a curative procedure. Diagnostic surgery was performed in patients presenting with enlarged lymph nodes of unknown or uncertain etiology.

Curative surgery was performed in patients with a complicated form such as abscess, prosthesis infection, aortitis.

### Statistics

The Fisher's exact test was used to compare the number of therapeutic failures with doxycycline and fluoroquinolones, and assess the correlation between immunosuppression and the need for surgical treatment as well as the correlation between immunosuppression and the occurrence of therapeutic failure.

An ANOVA test was carried out to investigate statistical correlations between the occurrence of therapeutic failure or the need for surgical treatment and the time between the onset of symptoms and effective antibiotic therapy.

### **Results:**

Confirmed and probable cases (Supplementary Figure1):

A total of 251 patients were included. For 68 patients, the laboratory criteria were not fulfilled. Another six patients that had been infected abroad were excluded. Overall, 89 confirmed and 88 probable cases (total 177 patients) were included in the study.

### Epidemiological data:

The male-female sex ratio was 2.28 (54 female and 123 male). The mean age of patients was 47.38 +/- 17.8 years (range 2 to 89 years).

A total of 173 cases were sporadic, and four cases were clustered in two groups: two were household cases, and two were patients infected during an orientation race in a forest. The geographical distribution of infected patients is depicted in Figure 1.

Exposure factors are detailed in Figure 2. The most common risk factor was a contact with hares, game (including boar, deer and doe) or rodents (21.5%), followed by exposure to aerosols (20.9%). No specific exposure factor was identified in 18 patients.

Contact with hares, game or rodents occurred more often in the winter season, while tick-bites were mostly reported in Summer (Supplementary Figure 2).

#### Clinical data (Tables 1 and 2):

##### Significant background:

Thirteen of 142 patients (9.15%) were immunocompromised: eight patients had diabetes (one type I and seven type II). Four patients were on immunosuppressive therapy: one on mycophenolate mofetil, one on methotrexate, and two on anti-TNF $\alpha$ . The thirteenth patient suffered from liver cirrhosis. One patient had a vascular prosthesis.

The average incubation time of tularemia, calculated from 49 patients' data, was 9.28 $\pm$  9.7 days (range 1 to 43 days). Supplementary Figure 3 represents the distribution of the incubation times, which mostly ranged from one to five days. In our series, 7 patients exhibited unusually long incubation delays, ranging from 16 to 43 days.

##### Clinical forms:

Sixty-one (34.5%), 48 (27.1%), 32 (18%), 14 (7.9%), nine (5.0%) and four (2.3%) patients presented with an ulceroglandular, glandular, pleuropulmonary, typhoidal, oropharyngeal, or oculoglandular forms, respectively. We identified nine (5.1%) atypical forms which are presented in Supplementary Tables 1 and 2: a combined oculoglandular and ulceroglandular form, a pre-thyroid abscess, an ulceroglandular form associated with aortitis, a pleuropulmonary form associated with aortitis, a pleuropulmonary form associated with myocarditis, an aortic endocarditis, a total hip prosthesis infection, a pleuropulmonary form complicated by a splenic hematoma, and a pleuropulmonary form complicated by pericarditis.

The hip prosthesis infection occurred in a 49-year-old immunocompromised patient with cirrhosis. While drunk and walking outside, this male patient fell and suffered both femoral neck fracture and skin lacerations. He had a total hip replacement. In addition to hepato-renal decompensation of his cirrhosis with hepatic encephalopathy, the immediate aftermath of surgery was complicated by a

hematoma of the hip that had to be surgically drained. 16S rRNA PCR testing of a hematoma sample revealed the presence of *F. tularensis*. No culture was performed. The evolution of the illness was favorable with a three-month treatment with doxycycline followed by a one-stage exchange arthroplasty and additional antibiotic therapy with ciprofloxacin and gentamicin for three months.

The case of splenic hematoma occurred in a 73-year-old male with a pleuropulmonary form of tularemia. This non-immunocompromised patient had a history of pericarditis, hypothyroidism and coronary stent placement. The diagnosis of tularemia was confirmed by PCR-detection of *F. tularensis* DNA in a mediastinal lymph node. A spontaneous splenic hematoma developed during hospitalization for tularemia as a complication of a moderate splenomegaly. The evolution of the illness was favorable after 21 days of doxycycline treatment.

We also diagnosed tularemia in a patient who developed a pre-thyroid lodge abscess without having any evident history of exposure to *F. tularensis*. While performing a mediastinoscopy for a mediastinal lymph node biopsy, the surgeon unexpectedly drained an abscess from the pre-thyroid chamber. The diagnosis of tularemia was made by *F. tularensis*-specific PCR from the abscess pus. The evolution of the illness was favorable after surgical drainage and doxycycline therapy.

### Symptoms

The patients' symptoms are summarized in Table 2. The main symptoms included fever (85.0%), general impairment, (33.3%), chills (26.4%), myalgia (25.5%), sweats (25.0%) and arthralgia (21.2%).

### Location of lymphadenopathies:

The upper limbs were the most frequent location, in 56 patients (31.6%), followed by the chest (46, 30.0%), lower limbs (38, 21.4%), neck (31, 17.5%) and abdomen (2, 1.1%). Twenty-nine patients (16.4%) had enlarged nodes in various anatomical sites.

Inoculation skin lesions:

Twenty-nine patients (17.0%) exhibited an inoculation lesion on the upper limbs, 23 (13.5%) on the lower limbs, five (2.9%) on the trunk, three (1.7%) on the scalp, and one (0.6%) patient had both upper limb and facial ulcers.

Secondary dermatological lesions (all dermatological manifestations following the initial inoculation ulcer):

Nineteen patients had secondary dermatological lesions, including seven with lymphangitis ranging from the primary skin lesion to an adenopathy, five had a rash (location and type not specified), three had nodosum, one had cellulitis, one had erythema multiforme, one had pustules, and one had livedo reticularis.

#### Microbiological results

Initial presumed diagnosis:

For 67/148 patients (45.2%) for whom a suspected diagnosis was specified, tularemia was the main diagnostic request. In the other cases, the main suspected etiologies were: cat-scratch disease (44, 27.7%), Q fever (19, 12.8%), rickettsiosis (12, 7.9%), Whipple's disease (3, 2.0%), ehrlichiosis (2, 1.3%) and anaplasmosis (1, 0.7%).

Confirmation of tularemia diagnosis:

Six cases (6.9%) were confirmed by seroconversion and five (5.8%) by a four-fold rise in antibody titers between two serum samples.

Confirmed diagnosis of tularemia was obtained in 78 patients (86%) by PCR testing of lymph node (64), skin (6), lung (3) or aorta biopsies (2), bronchoalveolar lavage (1) and joint (1) fluid.

In addition, *F. tularensis* was identified by 16S rRNA PCR-sequencing of a bacterial strain that could not be routinely identified.

Cultures were performed for 59 of the 78 PCR-proven specimens, and 6 (1%) were positive.

Blood tests:

Blood test results are summarized in Supplementary Table 3. Twenty-two out of 91 (24.1%) patients had leukocytosis, 1.1% had leukopenia, 31.3% had liver cytolysis, 6.7% had thrombocytopenia, and 4.0% had thrombocytosis. The mean CRP rate was 81.6 +/- 60.5 mg/L (range 4 to 248).

Evolution:

Seventy-eight (53.4%) patients were hospitalized. Sixty (40.5%) developed complications, including lymph node abscesses (39), fistulizations (14), persistent asthenia (2), aortitis (2), and one case each of myocarditis, pericarditis and splenic hematoma.

Antibiotic therapy:

One hundred and seventy-two patients received an antibiotic therapy active against *F. tularensis*, including 118 who received one antibiotic. The most commonly prescribed antibiotics were doxycycline (106 patients) and an oral fluoroquinolone (42). Two patients were administered a fluoroquinolone and doxycycline. Table 3 and Supplementary Table 4 specify the effectiveness of treatments known to be active against tularemia. The mean duration of antibiotic therapy was 16 (min 7, max 28, SD 4.5) days for doxycycline, and 21 (min 7, max 84, SD 18.3) for fluoroquinolones. There were more therapeutic failures for fluoroquinolones (ciprofloxacin, levofloxacin, ofloxacin and unspecified fluoroquinolones, 14/43 [33%]) than for doxycycline (9/91 [9.9%],  $p=0.02$ ). The mean duration between the onset of symptoms and the onset of effective antibiotics was 38.6 days (range 5 to 71, SD 16.7) for patients who presented with a therapeutic failure, *versus* 42.5 days (range 1 to 175, SD 33.4) for patients who recovered ( $p=0.64$ ).

In contrast, 13 patients recovered without any effective antibiotic therapy, including four who benefited from lymph node excision, six who received an ineffective empirical antibiotic treatment, and three who neither received antibiotics nor underwent surgery. Their characteristics are specified in Supplementary Table 5. None of the thirteen patients was immunocompromised. There were four

pleuropulmonary forms, three oropharyngeal forms, three glandular forms, two typhoidal forms and one oculoglandular form.

Surgery (Supplementary Table 4):

Eighty patients (51.6%) underwent surgery: 31 (20%) had a lymph node puncture, 47 had lymph node removal (30.3%), 1 (0.6%) had an aortic allograft, and 1 (0.6%) had a total hip prosthesis replacement.

Thirty-four patients (21.9%) underwent surgery before effective antibiotic therapy, seventeen (10.9) after, eight (5.1%) at the same time. For twenty-one patients, the date of surgery was unknown. No data about surgery was available for 22 patients.

For patients who underwent surgery, the mean delay between onset of symptoms and effective antibiotic therapy was longer (52.1 days, range 7 to 175, SD 37.9) than for those who did not have surgery (mean 32.1 days, range 1 to 87 SD 19.5,  $p=0.006$ ). In immunocompromised patients, 5/13 patients (38.5%) benefited from surgery, compared to 21/127 (16.6%) in immunocompetent patients ( $p=0.06$ ).

## Discussion

We describe 177 cases of tularemia diagnosed in the French reference center for rickettsioses, coxiellosis and bartonellosis from January 1<sup>st</sup>, 2008 to December 31<sup>st</sup>, 2017. During this period, the French reference center for tularemia in Grenoble recorded 317 cases, and Santé Publique France 611 cases. Among our 177 cases, three were previously described in a published series by the French reference center for tularemia<sup>19</sup> and 44 cases included in a study published by Santé Publique France, the French national public health agency<sup>18</sup>. Table 1 compares these three French series.

The most affected regions were “Nouvelle Aquitaine”, “Pays de la Loire” and “Grand Est” (Figure 1), as previously described<sup>18,19</sup>. The annual distribution of cases is similar to that described in the literature<sup>19</sup>: tick-borne contamination occurred more often in Summer, while contamination during hunting or contact with infected animals occurred more often in Winter. The mean incubation time

was 9.28 days, which is longer than that usually described (3 to 5 days<sup>16</sup>). As expected, the most common forms were ulceroglandular (34.5%) and glandular (27.1%). These forms had a significantly higher therapeutic failure rate than the other forms (19.2% versus 7.6%,  $p < 10^{-2}$ ). We also diagnosed rare forms (Supplementary Tables 1 and 4), including one case each of hip prosthesis infection, splenic hematoma and pre-thyroid lodge abscess. To date, few cases of joint prosthetic infections have been reported, affecting the knees<sup>23,24</sup> or hips<sup>25</sup>. We assume that the hip prosthesis infection complicated a skin wound contamination with *F. tularensis*. In contrast, we could not find any previous case of spontaneous splenic hematoma complicating a splenomegaly, or pre-thyroid abscess, in the course of tularemia. However, a case of parapharyngeal abscess was reported in the literature<sup>26</sup>.

In addition, we diagnosed two cases of *F. tularensis* aortitis, one of which had previously been published<sup>27</sup>, and a case of pericarditis complicating a pleuropulmonary form. Other cases of pericarditis have been described in the literature<sup>28</sup>, including one previously diagnosed in our laboratory in 2007<sup>29</sup>. We also diagnosed a case of *F. tularensis* aortic endocarditis<sup>30</sup>. Only four confirmed cases of *F. tularensis* endocarditis have been described to date<sup>30-32</sup>. We also described a probable case of myocarditis complicating a pleuropulmonary form. Indeed, the diagnosis was made on the basis of a positive serology and histological findings observed in a mediastinal lymphadenopathy biopsy. To date, only two cases of *F. tularensis* myocarditis have been described in the literature<sup>33, 34</sup>.

Seventy-eight of the 177 patients (53.4%) required hospitalization. The clinical signs exhibited by patients were not specific (Table 2). In our series, the majority of patients had fever (85%), lymphadenopathy (72.2%) and inoculation lesions (36%). During our study, we did not find a statistical relationship between the time to introduce effective treatment and the occurrence of therapeutic failures. The diagnosis was obtained in 99 patients (56%) by serology, and in 78 patients (44%) by PCR.

The antibiotic that was most commonly used in our series was doxycycline (administered 106 times as monotherapy), followed by a fluoroquinolone alone (42 patients). In our series, the observed

therapeutic failure rates for doxycycline and fluoroquinolones (9.9% and 32.5%, respectively) were high. It was previously demonstrated that the earlier effective antibiotic therapy is administered to tularemia patients, the less often therapeutic failure occurs<sup>35,36</sup>. We observed long delays prior to antibiotic therapy onset, which may explain such high therapeutic failure rates. However, the therapeutic failure rate was significantly higher for fluoroquinolones ( $p = 0.002$ ), which are currently recommended with doxycycline as first line treatment in the less severe cases<sup>37</sup> by the World Health Organization (WHO)<sup>38</sup>. In their series, Rojas-Moreno described in their retrospective analysis of 17 patients no case of therapeutic failure under doxycycline for a mean duration of 21 days in addition to surgical treatment<sup>39</sup>. Castrillon et al. and Eliasson et al. both described more therapeutic failures with doxycycline than with fluoroquinolones (42.8% and 3% therapeutic failures with doxycycline, respectively, and 4.5% and no therapeutic failure with fluoroquinolones<sup>7,10</sup>). In our series, among the 42 patients on fluoroquinolone alone, only 11 patients received ciprofloxacin 500mg 2 times per day (Table 3). We acknowledge the fact that the high failure rate observed for fluoroquinolones may at least in part be explained by the heterogeneity in molecule, dosage and treatment duration used.

Due to its clinical and pathological presentation, tularemia can be confused with cat-scratch disease or tuberculosis<sup>40,41</sup>. In our series, the suspected diagnosis by clinicians was tularemia in only 67 patients (45.2%), and *Bartonella* infection in 44 patients (27.7%). Our data suggest that tularemia is probably underdiagnosed in France due to its unspecific clinical presentation and insufficient knowledge of the disease by clinicians. We suggest that tularemia should systematically be considered among the differential diagnoses of enlarged lymph nodes or prolonged fever in patients with outdoor activities.

## Conclusion

Tularemia is endemic in France in the Nouvelle Aquitaine, Grand Est and Pays de la Loire regions. This infection is probably underdiagnosed. Although the ulceroglandular form was the most common, we identified rare forms of the disease such as splenic hematoma and osteoarticular infection. In endemic areas and in a consistent epidemiological context, diagnosing this disease allows optimized patient management.

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## **AUTHOR'S CONTRIBUTION:**

Anne Darmon-Curti and Pierre-Edouard Fournier analyzed the data;

Anne Darmon-Curti and Pierre-Edouard Fournier wrote the manuscript;

François Darmon performed the statistical analysis;

Aurélie Hennebique, Max Maurin, Thomas Guimard, Guillaume Martin-Blondel, Timothée Klopfenstein, and Jean-Philippe Talarmin provided information on many patients;

Sophie Edouard and Didier Raoult critically revised the manuscript.

## **Potential conflicts of interest.**

The authors of this manuscript have no conflicts of interest related to the work presented. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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**Table 1:** Comparison of the data in our series with 2 other French series

	<b>Maurin et al.<sup>19</sup></b>	<b>Mailles et al.<sup>18</sup></b>	<b>Our series</b>
Number of patients included	101	433	177
Mean age	51.7	49	47.38
Sex ratio	1.2	1.8	2.28
Hunters	16 (15.8%)	52 (12%)	39 (21.7)
Incubation time (days)	5.5	NR	9.28
Glandular forms	24 (23.7%)	200 (46%)	48 (27.1%)
Ulceroglandular forms	34 (33.7%)	113 (26%)	61 (34.5%)
Pleuropulmonary forms	10 (10%)	42 (10%)	32 (18%)
Oropharyngeal forms	17 (16.8%)	25 (6%)	9 (5.0%)
Oculoglandular forms	4 (4%)	8 (2%)	4 (2.3%)
Typhoidal forms	9 (8.9%)	45 (10%)	14 (7.9%)
Hospitalization	30 (29.7%)	188 (43%)	78 (53.4%)
Complications	NR	20	60 (40.8)
Death	1	2	0
Confirmed cases	94	130	89

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Strain isolation	16	30	0
PCR	39	75	78
Serologies (seroconversion, titer x4)	39	11	11
Probable cases	7	303	88
Cases in common with our series	3	63	

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**Table 2:** Clinical data of 177 patients in France (2008-2017): Comparison with data from 5 previously reported case series<sup>A</sup>

	Ref <sup>11</sup>	Ref <sup>8</sup>	Ref <sup>40</sup>	Ref <sup>7</sup>	Ref <sup>19</sup>	Our study
Country	USA	Sweden	Turkey	Spain	France	France
Number of patients (M/F)	88 (3.5)	234 (1.05)	205 (0.55)	142 (0.59)	101 (1.37)	177 (2.28)
Study period	1949-1979	2000-2004	1988-1998	1997-1998	2006-2010	2008-2017
Age ranges (means)	2-82 (NI)	1-88 (48.3)	5-75 (NI)	14-82 (52)	5-95 (52)	2-89 (47.4)
Main sources of infection	Hares	Mosquitos	Water	Hares	Hares	Hares
Fever	85	83	66	90.8	67.3	85.0
Headache	45	32	15	9.9	NA	13.4
Myalgia	31	NA	6	25.4	20.8	25.5
Arthralgia	15	NA	NA	14.8	16.8	21.2
Cough	38	25	NA	24	5.9	9.2
Sore throat	15	3	58.5	16.9	15.8	7.0
Nausea and/or vomiting	17	23	NA	24	5.9	2.8
Diarrhea	10	9	NA	2.1	3.9	6.4
Inoculation lesion	59	88	NA	61.4	31.7	35.6
Secondary	5.7	29.9	14	17.6	2.9	11.9

dermatological lesion						
Lymphadenopathy	86	91.9	85	69.7	69.3	87.8
Pharyngitis	23.8	NA	29	16.2	19.8	4.2
Conjunctivitis	NA	NA	2	NA	2.9	3.5
Hepatosplenomegaly	16	NA	2	NA	2.9	5.6
Worsening of condition	NA	NA	NA	38.7	3.9	33.8

M/F: Male/female sex ratio, NA: no data available

<sup>A</sup>: All data are given as percentages unless otherwise specified.

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**Table 3:** Antibiotic therapy administered and therapeutic failure rates

Antibiotic therapy <sup>1</sup>	Total number of patients on antibiotic therapy	
	N (%)	TF /* (%)
Doxycycline, 200 mg/d	104 (59)	9 /91 (9.9)
Ciprofloxacin, 500 mg X2/d	21 (12)	7/21 (33)
Unspecified fluoroquinolone and dosage	11(6.2)	4/9 (44)
Ofloxacin, 200 mg X2/d	5 (2.8)	1/5 (20)
Levofloxacin, 500 mg/d	4 (2.3)	2/4 (50)
Doxycycline, 200mg/d + IV amikacin	2 (1.1)	0/2 (0)
Ciprofloxacin, 750mg X2/d + IV gentamicin + doxycycline, 200mg/d	1 (0.56)	0 /1(0)
Unspecified fluoroquinolone + IV gentamicin	1 (0.60)	0 (0)
Levofloxacin, 500mg X2/d + doxycycline, 200mg/d	1 (0.60)	0/1 (0)
Ofloxacin, 400 mg X2/d	1 (0.60)	0/1(0)
IV amikacin	1 (0.60)	0/1 (0)

IV gentamicin	1 (0.60)	0/1 (0)
No antibiotic active on <i>Francisella tularensis</i>	13 (7.3)	0/12(0)
No data	11 (6.2)	0/1 (0)

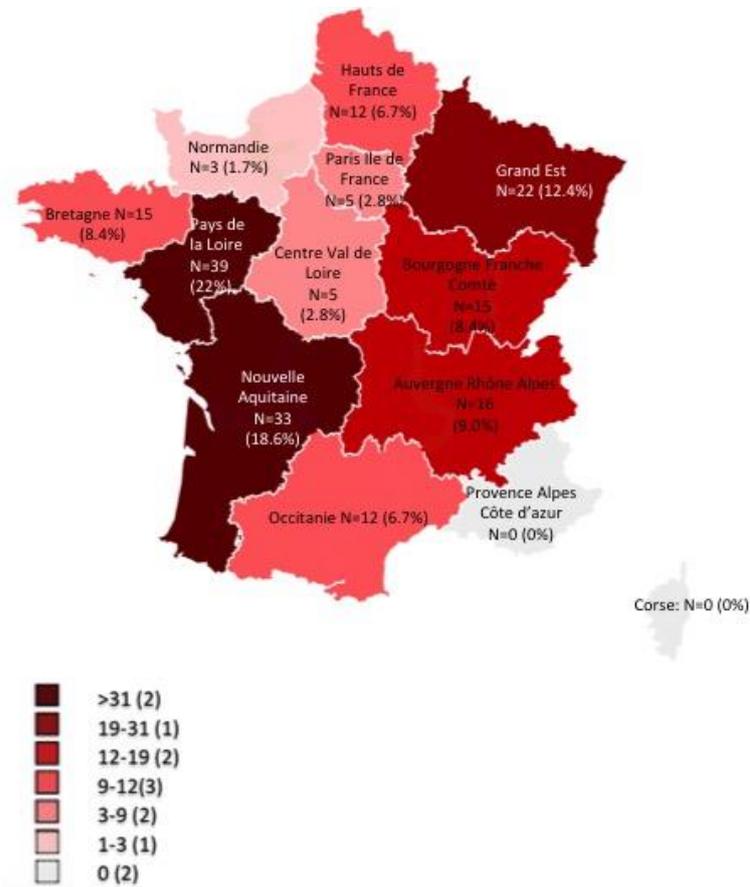
N = number of patients; TF = therapeutic failure; \* = number of patients for whom data is available;  
 mg/d = milligram/day; X2/d = two times per day; IV = intravenous

<sup>1</sup> If not specified, antibiotics were administered orally.

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## FIGURE TABLE AND GRAPHICS

**Figure 1:** Geographical distribution of tularemia cases



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**Figure 2:** Source of exposure (game include boar, deer and doe)

