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Lyme disease in France: a primary care-based prospective study

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SUMMARY

To estimate the incidence of Lyme borreliosis in France, describe its clinical presentations, and assess its potential risk factors, we conducted a nationwide prospective study in the French Sentinelles Network, consisting of 1178 general practitioners (GPs). Of these, 875 (74%), i.e. 1·6% of all French GPs, participated in the study from May 1999 to April 2000. Eighty-six cases of Lyme disease were reported and validated, of which 77 (90%) consisted of erythema migrans. At national level, the incidence was estimated at 9·4/100 000 inhabitants. Compared to the French general population, Lyme disease patients were older ($P<10^{-4}$), more were living in rural areas ($P<10^{-3}$), and amongst the working population, more were farmers ($P<10^{-3}$) and fewer, salaried workers ($P<0{\cdot}005$). Cervidae density correlated strongly with the estimated regional incidence of Lyme disease ($r=0{\cdot}82$). Both incidence data and identified risk factors can help to target measures for its prevention and treatment.

INTRODUCTION

Lyme disease is the most common tick-borne infection in both Europe and the United States [1]. In contrast to the United States, where the disease has been surveyed through a federal computerized public health system since 1982, national surveillance data are very scarce across Europe, with some exceptions like in Slovenia [2], and are not available in France. According to the Centers for Disease Control and Prevention, the mean annual incidence was estimated at 6·3 cases per 100 000 inhabitants in 2000 in the United States, ranging from 0 to 111/100 000 according to the state, with almost a twofold increase from 1991 to 2000 and a distribution highly concentrated in the northeastern, mid-Atlantic, and north-central states [3]. In Europe, according to some available estimates, the annual incidence is roughly increasing from Western to Eastern countries, and presumably from south to north, e.g. from 0·3/100 000 in the United Kingdom (unpublished estimate, quoted by O'Connell et al. [1]) or 0·6/100 000 in Ireland [4] to 137/100 000 in Slovenia [2]. The acknowledged causative agents of Lyme disease are spirochetes *Borrelia burgdorferi sensu lato* (*s.l.*): *B. burgdorferi sensu stricto* (*s.s.*) in North America, *B. afzelii*, *B. garinii*, and *B. burgdorferi s.s.* in Europe [5].

Indirect epidemiological methods mainly have been used in the past, including seroprevalence surveys and measurement of the prevalence of ticks (especially *B. burgdorferi*-infected ticks). Moreover, risk factors for the disease, e.g. type of occupation or local density of certain animal species, are not well documented. We, therefore, conducted a nationwide French

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Table 1. *Case definition of Lyme disease used in the study*

Early clinical manifestations, i.e. erythema migrans possibly associated with influenza-like symptoms such as fever, malaise, myalgias, arthralgias or lymphandenopathy, or with conjunctivitis.

To meet the criterion for diagnosis, the erythema migrans lesion had:

- either to reach a diameter of at least 5 cm
  - if it appeared in a period of days to weeks following a tick bite;
  - or without any recent history of tick bite, in case
    - of an exposition possibly at risk in the 30 previous days, because either of a stay at a rural place or in a house with a garden, or of a ride in the country or in woods;
    - or of a positive serological testing.
- Or, if did not reach a diameter of 5 cm
  - to have appeared in the 2–30 days following a tick bite at the same site;
  - and to have presented an expanding feature or to have been associated with a positive serologic testing*.

Secondary clinical manifestations, provided that antibody testing* was positive in any body fluid, including blood serum, spinal and synovial fluids.

The diagnostically significant clinical manifestations according to body systems were the following:

- *Skin*: borrelial lymphocytoma, acrodermatitis chronica atrophicans;
- *Nervous system*: especially meningo-radiculoneuritis, cranial neuritis, radiculoneuritis, meningo-encephalitis;
- *Musculoskeletal*: mono- or oligo-arthritis, chronic arthritis;
- *Cardiovascular*: 2nd- or 3rd-degree atrioventricular block, myopericarditis.

* Positive antibody testing required a high titre of specific antibodies or a rise in specific antibodies, either by enzyme-linked immunosorbent assay (ELISA), indirect immunofluorescence assay (IFA), or even haemagglutination (HA), possibly confirmed by Western immunoblotting.

prospective study in primary care, in order to estimate the incidence of Lyme disease at national and regional levels in France, to describe its clinical presentation, and to assess potential sociodemographic and environmental risk factors.

METHODS

Study design

The study was conducted with doctors from the French communicable disease surveillance system called Sentinel [6], which consists of 1178 general practitioners (GPs) distributed throughout the metropolitan country. Of these, 875 (74·3%), i.e. 1·6% of all French GPs, actually participated in the study, on a voluntary and unpaid basis, as they do for the surveillance scheme. The doctors were asked to report, on a questionnaire, all suspected cases of Lyme disease identified in their practice between May 1999 and April 2000, whether the disease had been diagnosed by themselves or by another physician. Each questionnaire included a reminder of the main epidemiological, clinical and laboratory arguments evocative of the disease. In May 2000, a follow-up letter was sent to the physicians of the Sentinel system who had not returned any completed questionnaires, in order to check whether they actually participated to the study but had not seen any case of Lyme disease in their practice during the past year or not.

Case definition

Cases reported by the GPs were secondarily assessed for inclusion according to diagnostic criteria derived from those used by Centers for Disease Control and Prevention (CDC) [7] and those proposed by the European Union Concerted Action on risk assessment in Lyme Borreliosis (EUCALB) [8]. The case definition was based on epidemiological (e.g. tick bite), clinical (cutaneous, neurological, musculoskeletal, and cardiac manifestations), and laboratory (e.g. antibody testing) criteria (Table 1). The accuracy of these criteria by each reported case was assessed for validation by a group of four physicians, including specialists in general practice, internal medicine, and communicable disease epidemiology.

Data collection

Data on patients included sociodemographic characteristics (age, gender, place of residence, professional occupation), circumstances of transmission (mode, setting, activity, context, time lag before onset of symptoms), detailed clinical manifestations of the disease, and results of the diagnostic investigations (bacteriological, others). Missing data were collected through a phone call to the reporting doctor, or in some cases to a specialist consulted by the patient and indicated by the doctor. The Sentinel system had an agreement with the French National Commission of Informatics and Freedom for conducting this research project.

Sociodemographic data for the French population were obtained from the French Institute of Statistics and Economical Studies (INSEE) [9] and the French Institute of Demographic Studies (INED) [10]. The estimated numbers of Cervidae, i.e. roe deer (*Capreolus capreolus*) and red deer (*Cervus elaphus*), and wild boars (*Sus scrofa*) in each French region were obtained from the French Hunting Office, Ministry of Ecology and Sustainable Development, for the season 1998–1999 [11].

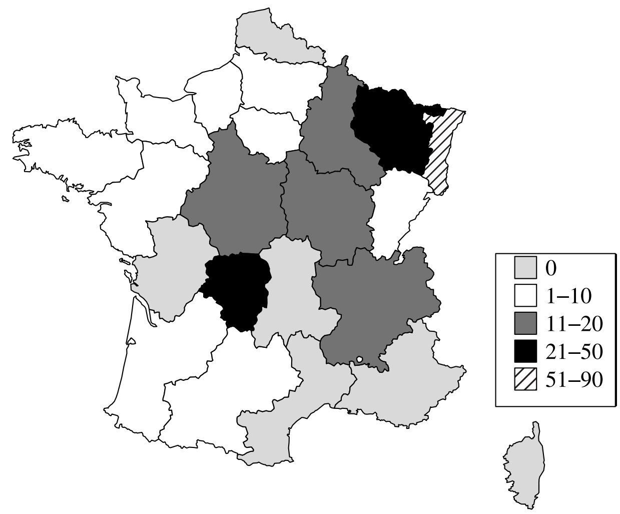

Fig. 1. Estimated regional annual incidence of Lyme disease diagnosed in France in 1999–2000 (per 100 000 inhabitants).

Statistical analysis

The incidence of Lyme disease diagnosed in each of the 20 regions of the French metropolitan country was estimated by extrapolating the observed number of cases in the region. In fact, we multiplied the mean number of cases per participating GP, standardized according to GPs level of participation and geographical representativeness, by the regional number of GPs [12] to obtain the estimated number of cases in each region, and then divided the latter by the size of the regional population [13]. The national incidence of disease was estimated by summing the estimated number of cases in the 20 regions, then dividing by the size of the French population [14]. The incidence of Lyme disease acquired in each region was calculated according to the same model, while extrapolating available data on the location of cases' contamination. For all incidence rates, the 95% confidence intervals (CIs) were derived from the Poisson distribution of events [15].

Patients experiencing Lyme disease were compared with the French general population for sociodemographic characteristics, using Wilcoxon's signed-rank sum test for age and Pearson's χ^2 test for age class, gender, place of residence, type of housing, and professional occupation. We compared the density of both Cervidae and wild boars, expressed as the regional rate of animals per km^2 and human inhabitants, to the incidence of Lyme disease acquired in each region, using the *z* test for correlation.

RESULTS

A total of 109 cases have been reported, of whom 86 (79%) were validated according to the definition criteria. These validated cases had been collected from 69 doctors, whereas 806 did not report any validated case during the study period.

The national annual incidence of borreliosis was estimated at 9·4/100 000 inhabitants (95% CI 7·4–11·4/100 000), which represents around 5500 newly diagnosed cases in France in a year (95% CI 4300–6700). The French regional incidence varied from zero in the Mediterranean coastal areas, e.g. in the Provence–Alpes–Côte d'Azur (PACA) south-eastern region (95% CI 0–7/100 000), to 86/100 000 (95% CI 51–134/100 000) in the Alsace northeastern region (Fig. 1). After exclusion of 11 reported erythema migrans cases of <5 cm in diameter, the national incidence was estimated at 8·2/100 000 inhabitants (95% CI 6·3–10·1/100 000).

Clinical manifestations

Eighty-one patients (95%) presented a single manifestation (Table 2). The main manifestation of disease consisted of erythema migrans (Fig. 2), which was observed in 77 patients (90%). The skin lesion had a median diameter of 10 cm (range 3–50 cm). It was located at a lower limb in 44 patients (57%), at the

Table 2. *Clinical distribution of 86 cases of Lyme disease diagnosed by French GPs between May 1999 and April 2000**

Manifestations	Erythema migrans	Neuro-borreliosis	Arthritis
Erythema migrans	**72**	4	1
Neuroborreliosis	4	**5**	0
Arthritis	1	0	**4**
Total, *n* (%)	77 (90)	9 (10)	5 (6)

* The numbers of cases with only one manifestation of disease are indicated in bold type.

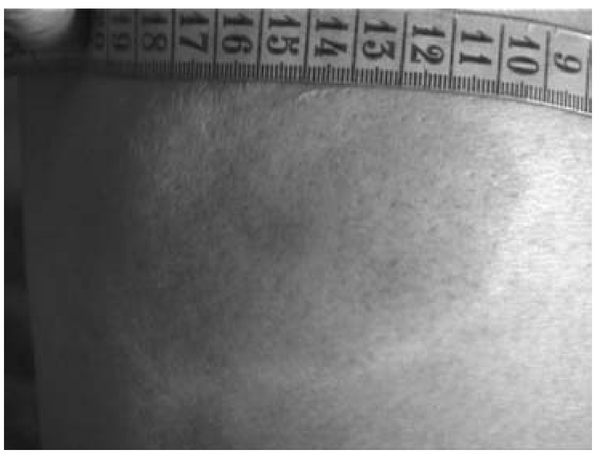

Fig. 2. Erythema migrans located on the thigh (source: Dr Aubry, Schirrhein, France).

trunk in 15 (19%), at an upper limb in 14 (18%), at the neck in three (4%), and at both a lower limb and the trunk in one patient. Only erythema migrans was reported in patients <18 years old (8 cases), which was located at the neck in two of them. In 64 cases (83%) the diagnosis was made between May and September.

Neurological manifestations were observed in nine patients (10%), i.e. meningoradiculitis (3 cases), monoradiculoneuritis (4) and polyradiculoneuritis (2). Radicular signs concerned the lower limbs in seven patients. Musculoskeletal manifestations were observed in five patients (6%), i.e. monoarthritis (4 cases) and oligoarthritis (1). They were restricted to knees and hips. No validated case of cardiological manifestation has been collected. It should be noted that one patient had a first-degree atrioventricular heart block, and was not included in the study (Table 1) [8].

In addition, systemic signs were present in 19 patients (22%), including fatigue (8 cases), fever (8), headache (4), arthralgia (3), myalgia (3), and dyspnoea (1). Other associated manifestations reported were adenopathy (1 case), bilateral conjunctivitis (1), and herpes zoster (1).

Laboratory findings

Overall, a serological testing for IgM and/or IgG antibodies to *B. burgdorferi* was performed in 59 patients out of 86 (69%) for detection, using mostly an enzyme-linked immunosorbent assay (ELISA), and supplemented with Western immunoblotting in nine of these (15%) for confirmation. Among the 72 patients with erythema migrans alone (63%), an initial testing was performed in 45, yielding positive serology in 19 (42%), followed by an iterative testing in 22 (31%), with positive response in nine (41%). Among the 14 patients presenting at least another manifestation, an initial testing was systematically performed, yielding positive serology in 13 (93%) and an equivocal result in one, followed by an iterative testing in seven (50%), always with positive response.

Testing for cerebrospinal fluid antibodies against *B. burgdorferi* was reported for three patients, including one having a meningoradiculitis with a positive result and two having monoarthritis with a negative result. Testing for synovial fluid antibodies against *B. burgdorferi* was reported for one patient having a monoarthritis, yielding a positive result.

No isolation of *B. burgdorferi* from a clinical specimen nor detection by polymerase chain reaction (PCR) was reported.

Circumstances of transmission

Of the 86 patients with Lyme disease, 79 (92%) had been able to report the probable circumstances of their contamination to the doctor. The region of presumed transmission differed from the region where the disease was diagnosed for eight of the 79 patients (10%). For instance, although no reported case was diagnosed in Auvergne (central France) nor in Poitou-Charentes (western France), one transmission originated from each of these regions. A tick bite was recalled by 56 (71%) of these patients and an insect sting by four (5%). The presumed transmission occurred in a country area for 43 patients (54%) and in a forested area for 27 (34%) patients. At that time, 48 of the patients (61%) were walking and 14 (18%) were gardening; 52 (66%) were at recreational

Table 3. *Comparison of Lyme disease cases with the French population for sociodemographic characteristics*

Factor	Lyme disease cases	French population	P
Median age*	56·5 years	36·5 years	$<10^{-4}$
Sex*			
Male	37 (43·0%)	28 839 618 (48·7%)	0·29
Female	49 (57·0%)	30 386 065 (51·3%)	
Place of residence†			
Rural	42 (48·8%)	13 627 000 (23·3%)	$<10^{-3}$
Urban or intermediate	44 (51·2%)	44 891 000 (76·7%)	
Professional occupation‡			
Working population			
Farmers	5 (6·3%)	633 064 (1·3%)	$<10^{-3}$
Salaried workers	3 (3·8%)	72 238 55 (15·1%)	<0·005
Others	27 (34·2%)	18 298 004 (38·3%)	0·45
Non-working population and unemployed persons <60 years	8 (10·1%)	9 437 269 (19·8%)	0·03
Retired people and non-working population ⩾60 years	36 (45·6%)	12 142 509 (25·4%)	$<10^{-3}$

* Population estimates derived from 2000 data.
† Population estimates derived from 1999 data.
‡ Population estimates derived from 2000 data. Data presented only for patients (79) and people aged ⩾15 years.

activities, 10 (13%) on professional occupation, and nine (11%) on holiday. The median time lag between the presumed date of contamination and the onset of symptoms was estimated at 9 days (range 1–92 days, $n=67$) for erythema migrans, 10·5 days (range 1–46 days, $n=16$) for systemic signs, 27·5 days (range 21–184 days, $n=4$) for neurological manifestations, and 65·5 days (range 39–92 days, $n=2$) for musculoskeletal manifestations.

Risk factors

Compared to the French general population (Table 3), patients were older, especially with more patients aged between 45 and 79 years; more were living in rural areas; amongst the working population, more were farmers and fewer were salaried workers; amongst the non-working population, more were ⩾60 years old.

When comparing the density of Cervidae (roe and red deer) and wild boars to the incidence of Lyme disease acquired in each region (data not shown), the correlation coefficient reached significance for Cervidae ($r=0{\cdot}82$, 95% CI 0·61–0·92) but not for wild boars ($r=-0{\cdot}07$, 95% CI $-0{\cdot}48$ to 0·36).

DISCUSSION

From 109 cases prospectively collected from a national primary-care network, we could estimate the annual incidence of Lyme disease in France at 9·4/100 000 inhabitants (95% CI 7·4–11·4/100 000). This rate [especially after exclusion of cases with erythema migrans of <5 cm (8·2/100 000)] is of the same order of magnitude as the US overall estimate in 1999 (6·3/100 000) [3] and lower than that reported in some Eastern European countries, e.g. Sweden (69/100 000 in 1992) [16] or Slovenia (137/100 000 in 1994) [2], placing France at a moderately high risk for Lyme disease. However, US and Slovenian rates may be partly underestimated because they derive from more passive reporting systems, compared to our surveillance network [17].

No evidence for a trend towards increasing incidence

While a major increase in notified Lyme disease incidence has been observed through the notification system in the United States during the 1990s [18], no firm evidence exists for a similar increase in Europe [1]. The increasing trend in the United States probably results on the one hand from a true increase in infection, probably favoured by the rapid increase in the number of white-tailed deer in densely populated areas; on the other hand from enhanced diagnosis and overdiagnosis [18]. A previous national survey performed in 1988 with 480 GPs from the French Sentinel system found an estimate of 16·5 cases per 100 000 inhabitants [19]. Although the use of poorly defined criteria and a possible reporting bias in this study makes the comparison of our results with the latter estimate hazardous, we can reasonably assume that no important increase in incidence occurred in France in the 1990s.

Validity of the study

We cannot exclude that some patients may have been missed in our study, leading to a possible underestimation of the actual rate of infection. First, patients with Lyme disease may have consulted outside primary care without any referral. In our sample, 90% of patients had an erythema migrans, characteristic of early Lyme disease and possibly accompanied by systemic signs, which is consistent with results from several population-based clinical case series [20, 21], but is a little higher than the proportion (77%) reported from a large Swedish study [16]. A few patients with secondary clinical manifestations, e.g. neurological manifestations or even arthritis, may then have been diagnosed by community- or hospital-based specialists, without the knowledge of any GP. Second, despite the case definition included on the questionnaires, non-specific or mild clinical manifestations may not have been recognized, especially in areas of low endemicity, where both the public and doctors may not be sufficiently aware of the disease. While our estimate for the median time lag between the presumed bite and the onset of erythema migrans (9 days) belongs to the typical interval (7–10 days), our estimate for the median time lag before the onset of arthritis ($\sim$2 months) is shorter than the mean reported time (6 months), which may indicate a possible diagnosis bias for muskuloskeletal manifestations, sometimes difficult to attribute to Lyme disease [22]. However, in a population-based study conducted in the south Berry area, central France, the annual clinical incidence was around 50/100 000 inhabitants [23]. Such a rate is consistent with our estimate in Limousin (42/100 000, see black area in Fig. 1), a region which is adjacent to the south Berry area.

Sociodemographic and environmental risk factors

Regional incidences varied widely across France, as 35% of cases were reported from two northeastern regions accounting for only 6·9% of the French population. Such a highly focused distribution of disease incidence has already been reported at county level, e.g. in Wisconsin [24], Austria [4], and Sweden [16].

Risk factors identified in our study included increasing age, rural residence, and farming. Cases roughly displayed a bimodal age distribution, as previously described in the United States [18] and Europe [16, 21], with incidence peaks for children aged 10–14 years and adults aged 60–64 years. However, the median age observed in our study (56·5 years), which is close to the average age in a regional French study (57·8 years) [23], is higher than the median age reported from the United States (39·0 years) [18]. This may be due to the fact that some children are diagnosed by paediatricians and remain ignored by GPs. Whereas several seroepidemiological surveys have suggested an increased risk in forestry workers [25, 26], our study confirms farming occupation [23], and rural residence [27] as risk factors for Lyme disease.

We also showed that the regional distribution of Cervidae strongly correlated with the incidence of Lyme disease across the whole country. A reservoir competence for *B. burgdorferi* is well recognized for small mammals (especially wood mouse, bank vole, common shrew) and also likely for birds and medium-sized animals [28]. Among large mammals, the role of Cervidae (especially roe, red and fallow deer) in the transmission cycle of the infection is not clearly known. According to most authors, Cervidae do not infect feeding ticks with *B. burgdorferi* and are, therefore, not a competent reservoir [28]. The existence of an ecological link between the density of Cervidae (with roe deer accounting for $\sim$88% of them) and the incidence of the disease in our study is consistent with the assumption that deer may operate as an amplifier of feeding tick populations, contributing to the maintenance of the infection within the small mammals' reservoir hosts [29]. Such correlation may just be a reflection of local habitat that is coincidentally favourable for ticks [30]. Conversely, wild boars are unanimously not recognized as competent reservoirs, and the absence of any correlation between their spatial distribution and that of Lyme disease confirms previous findings [31]. According to recent immunological studies, specific binding of factor H to *B. burgdorferi s.s.* outer surface proteins enables the spirochaete to evade complement activation and phagocytosis in various vector and reservoir hosts during the infectious cycle, and contributes to persistent infection [32].

Poor contribution of serological testing at an early stage

In accordance with the definition criteria used in this study, all patients with neurological or musculoskeletal manifestation had a positive serology, yielding a sensitivity of 100%. However, such testing was also performed at least once in 63% of patients with erythema migrans alone, yielding an overall sensivity of only 42%. As recommended by the American College of Physicians, the diagnosis of early Lyme disease, which requires empirical antibiotic therapy, should primarily be based on clinical (erythema migrans) and epidemiological (history of tick bite, or exposure in endemic regions) evidence [33]. Serological testing is usually considered unnecessary and unreliable, due to low sensitivity at this stage (50% in the United States and <50% in Europe), which is confirmed in this study [22]. Indeed, the production of a humoral response to *B. burgdorferi* reaches a sufficient antibody level only several weeks after the onset of the infection [34]. Moreover, the use of Western blotting in our study appeared limited to only 15% of patients previously detected by ELISA or another assay, whereas Western blotting, because of its higher specificity compared to ELISA, has been recommended in the United States as a confirmation test (according to a two-step testing) [35], and suggested at least as a supporting test in Europe [36]. The appropriate use of laboratory tests should, therefore, be promoted through the development of European recommendations for the diagnosis and management of Lyme disease, adapted to the specific clinical spectrum and genetic diversity of *B. burgdorferi* genospecies.

CONCLUSION

Lyme disease has a focal distribution and a moderately high overall incidence in France. Older people, especially farmers, living in rural areas with high Cervidae density are at higher risk to have clinical infection, and constitute a primary target for prevention. Primary-care physicians and the public must be aware of the disease, even in regions where no contamination occurs.

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