

1 **Research article**

2 **Title: Tick-borne lymphadenopathy in northeastern France: A human and**
3 **vector clinical-epidemiological study**

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46 **Abstract** – word count: 168/350 words

47 **Background:** TIBOLA (TICK-BORNE LymphADenopathy) is a tick-borne disease transmitted
48 by *Dermacentor* ticks and is usually caused by *Rickettsia*. In 2021, clinicians in northeastern
49 France reported an increase in TIBOLA cases.

50 **Methods:** This entomo-clinical, multicenter, retrospective, and observational study aimed to
51 describe the evolution of the number of TIBOLA cases between 2016 and 2021 in
52 northeastern France as well as the evolution of the *Dermacentor* tick population.

53 **Results:** A total of 35 cases of TIBOLA were identified, 16 of which occurred in 2021, with
54 clear predominance in April and May. A longitudinal study performed in the Alsace region
55 (endemic for ticks and tick-borne diseases) revealed a peak in tick activity in 2021. A trend
56 toward an increase in TIBOLA cases in 2021 in the northeastern region of France was
57 observed, as was an increase in the *Dermacentor* tick population in some biotopes.

58 **Conclusions:** TIBOLA appears to be an emerging disease that should be monitored, as should
59 the *Dermacentor* population.

60

61 **Keywords:** TIBOLA, DEBONEL, SENLAT, tick-borne disease, rickettsiosis, inoculation
62 eschar, *Dermacentor*.

63

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65

66

67 Text – word count: 3068/5000 words

68 **Background**

69 TIBOLA (Tick BOrne LymphAdenopathy), also called DEBONEL (*DErmacentor* BOrne
70 Necrosis Erythema and Lymphadenopathy) or SENLAT (Scalp Eschar and Neck
71 LymphAdenopathy after Tick bite), is a disease first described in Hungary in 1997 [1]. It is
72 the second most common rickettsial disease in Europe after Mediterranean spotted fever [2].
73 *Rickettsia slovaca* and *R. raoultii* are the main pathogens [3]. Nevertheless, other intracellular
74 bacteria (*Bartonella henselae* [4,5], *Rickettsia massiliae* [6], *Candidatus Rickettsia rioja* [4],
75 and *Francisella tularensis* [7]) have been identified. Symptoms include a necrotic inoculation
76 eschar on the scalp and painful regional lymphadenopathies, as well as more general
77 symptoms (fever, headache, arthromyalgia, and asthenia). This syndrome particularly affects
78 women and children [8,9].

79 Hard ticks in the *Dermacentor* genus transmit *R. slovaca* and *R. raoultii*: *Dermacentor*
80 *marginatus* is found mainly around the Mediterranean area and in North Africa, and
81 *Dermacentor reticulatus* lives mostly in the colder parts of Western Europe [8]. TIBOLA is
82 therefore more frequent during periods of tick activity: spring and autumn [10].

83 Microbiological diagnosis is based on polymerase chain reaction (PCR), skin biopsy,
84 swabs of the inoculation eschar or serology [11]. Unfortunately, these tests often yield false-
85 negatives [8], and the diagnosis is based on a set of arguments (tick bite on the upper part of
86 the body, followed by the apparition of a necrotic eschar and painful regional
87 lymphadenopathies). Systemic complications are rare, but localized alopecia may persist [4].

88 Since some tick-borne diseases are becoming more common in Europe (e.g., tick-
89 borne encephalitis [12] and tularemia [13,14]) and since 2021, clinicians in the northeastern
90 region of France have noticed an unusual number of TIBOLA cases, documenting this clinical

91 observation and comparing it with the presence of *Dermacentor* tick vectors in the
92 environment is important.

93 The primary objective of this study was to describe the evolution of the number of
94 TIBOLA cases between 2016 and 2021 in northeastern France as well as the evolution of the
95 *Dermacentor* tick population. The secondary objectives were to describe the characteristics of
96 the patients.

97 **Methods**

98 **Study design and participants**

99 In accordance with the Strengthening the Reporting of Observational Studies in Epidemiology
100 (STROBE) recommendations, a retrospective, multicenter and observational study was
101 performed. Eighteen hospitals were approached, and 11 ultimately participated. The study
102 included patients from hospitals in Chalon-sur-Saône, Colmar, Dijon, Epinal, Metz,
103 Mulhouse, Nancy, Reims, Sélestat, Strasbourg, and Troyes (northeastern France). Clinicians
104 recorded information on TIBOLA patients diagnosed between January 1st, 2016 and
105 December 31st, 2021. Data collection took place between July 2022 and March 2024. Minors
106 or adult patients who were diagnosed with TIBOLA were eligible.

107 Patients were identified in two complementary ways. First, clinicians from different
108 hospitals were contacted. Furthermore, *Rickettsia* spp. serologies and PCRs performed
109 between 2016 and 2021 in the study centers were extracted from the hospital data. From these
110 positive or negative biological results, the patients' medical files were consulted, and
111 TIBOLA cases were included.

112 The following criteria were used to define probable and certain cases of TIBOLA:

113 - Certain cases: Compatible clinical presentation (inoculation eschar with regional
114 lymphadenopathy, with or without general signs) and possible tick bite and microbiological
115 evidence (positive PCR or serology for a microorganism known to be responsible for
116 TIBOLA). *Rickettsia* serology was considered positive if the antibody titers exceeded 32 for
117 IgM and 64 for IgG or if the IgG levels were four times higher than those in a previous serum
118 sample [15]. The technique used for serology was specific to each center. PCR was
119 considered positive if a pathogen responsible for TIBOLA was identified. Samples from

120 humans (skin biopsy and swabs of the inoculation eschar) were analyzed at the National
121 Reference Center for *Rickettsia* in Marseille [16].

122 - Probable cases: Compatible clinical presentation (inoculation eschar with regional
123 lymphadenopathy with or without general signs) and tick bite observed without
124 microbiological evidence.

125 Case definition is based on TIBOLA syndrome (inoculation eschar associated with regional
126 lymphadenopathy, regardless of the pathogen identified (*Rickettsia*, *Francisella*)).

127

128 **Clinical data**

129 Patient medical records were reviewed by investigators, who used a standardized form to
130 collect various sociodemographic variables (age, sex, place of diagnosis, place of residence,
131 urban or rural home, proximity to forests, fields, waterways, and previous tick bites). The
132 TIBOLA characteristics were collected (date of exposure, date of tick bite, date of tick
133 removal, place of tick bite, symptoms, duration of symptoms and incubation period). The
134 symptom details collected were inoculation eschar (location, pain, and duration),
135 lymphadenopathy (location, number, pain, size, and duration), fever, headache, arthromyalgia,
136 pruritus, rash, facial edema, asthenia and other symptoms. Biological and microbiological
137 data were collected, including serology and PCR data for *Rickettsia* spp. and *F. tularensis* and
138 serology data for *Borrelia*. If available, tick identification and PCR results for the tick were
139 also reported.

140 Details on the antibiotic treatment (molecule, duration and number of antibiotic
141 courses) were also recorded. Based on the French recommendations [17], doxycycline and
142 macrolides were considered appropriate, as was ciprofloxacin if *F. tularensis* was identified

143 as the etiologic agent. Ineffective antibiotics included amoxicillin, amoxicillin/clavulanic
144 acid, pristinamycin and topical fusidic acid.

145

146 **Tick collection and processing**

147 The *Borrelia* National Reference Center has been collecting *Ixodes* and *Dermacentor* ticks as
148 part of its activity since 2014, and these data are presented here.

149 Questing ticks were collected monthly by dragging a white cotton cloth (1 m²) over
150 vegetation as described previously [18] at four different sites in Alsace: two lowland sites
151 (Illkirch and Dannemarie) and two mountain sites (Murbach and Niedermunster) between
152 2014 and 2023. The abundance of ticks by season was also investigated.

153 Tick identification was performed using morphology (by an entomologist), PCR or
154 MALDI–TOF mass spectrometry targeting the cytochrome oxidase I (COI) or 16S rDNA
155 genes as described previously [19]. PCR was performed at the *Rickettsia* National Reference
156 Centre in Marseille, France. Tick identification was performed either in Marseille or at the
157 *Borrelia* French National Reference Centre in Strasbourg, France.

158

159 **Statistical analysis**

160 Patient characteristics are described as frequencies and percentages for categorical variables
161 or medians and interquartile ranges (IQRs) for continuous variables.

162

163 **Results**

164 From *Rickettsia* spp. serologies and PCRs performed between 2016 and 2021, 1096 medical
165 records were screened. Thirty-five certain or probable cases of TIBOLA were included,
166 among which six were certain cases (17%) and 29 were probable cases (83%) (Fig. 1).

167 Among the certain cases, microbiological documentation was obtained by serology
168 (*Rickettsia* in one patient, *F. tularensis* in two patients) and PCR (*Rickettsia* in four patients,
169 *F. tularensis* in one patient). Some patients were both serologically positive and PCR positive.
170 Among the 35 patients, 16 (46%) were reported in 2021, as shown in Fig. 2, which illustrates
171 the steady increase in the number of cases from 2016 to 2021.

172

173 **Population, epidemiology and demography**

174 The study population is predominantly female (sex ratio: 4.8 women to 1 man), young and
175 living in rural areas. Table 1 shows the patients' sociodemographic and exposure
176 characteristics. The spatial distribution of the locations where patients were bitten (or if
177 unavailable, their place of residence) is presented in Fig. 3. Concerning the monthly
178 distribution (Fig. 4), most cases of TIBOLA occurred in April and May.

179

180 **Clinical characteristics**

181 The median incubation period was four days (IQR 2–8). The clinical features and durations of
182 symptoms of the patients are shown in Table 2.

183

184 The inoculation eschar was located primarily on the scalp (86%) and was painful in
185 42% of the cases. Lymphadenopathies were mostly located in the neck but could be
186 associated with other locations (inguinal, axillary, pretragal or retroauricular).

187 Among other symptoms, fever was the most common, affecting more than half of the
188 patients, often between 38 °C and 39 °C. Headache and asthenia were present in more than
189 one-third of the patients, and rash was present in more than one-quarter. Six patients had
190 generalized rash (one certain case with maculopapular exanthema, and among the five
191 probable cases, two with maculopapular exanthema, one with urticaria, one with disseminated
192 vesicles and one with papulovesicular eruption with purpuric rash). Arthromyalgia, neck pain,
193 facial edema and alopecia were also observed.

194 Other symptoms, such as pruritus, scalp hypoesthesia, scalp pain or nodules,
195 subcutaneous collection at the injection site, lymphangitis, nausea and vomiting, diarrhea,
196 anorexia, altered general condition, cough, chest pain and throat pain, were rarely observed.
197 Two patients had complications of fistulation and suppuration of an inguinal
198 lymphadenopathy. One patient had a *F. tularensis*-positive PCR for lymphadenopathy, and the
199 other was a probable case. The latter required hospital care. No other patients were
200 hospitalized. The median duration of symptoms was 17 days (IQR 11–27). One patient
201 experienced asthenia for six months.

202

203 **Biological results**

204 The complete blood counts (CBCs) were mostly normal, and the liver enzymes were not
205 abnormal. C-reactive protein (CRP) levels were measured in 23 patients: the results were
206 <5 mg/L in 13 patients, moderately elevated (between 5 and 30 mg/L) in five patients, and
207 elevated (>30 mg/L) in five patients.

208 *Rickettsia* serology, which was performed in 27 patients, was positive in only one
209 patient 10 days after the onset of symptoms. Among the two PCRs on biopsies performed on
210 the inoculation eschar, one was positive for *R. slovaca*. Among the twelve *Rickettsia* PCRs
211 performed on inoculation eschar swabs, two were positive.

212 Two *Dermacentor marginatus* ticks collected from patients were analyzed using
213 microorganism-targeted PCR, one of which was positive for *R. slovaca*, *R. raoultii*, and
214 *Coxiella-like* bacteria, while the other was positive for *Coxiella-like* bacteria (with negative
215 *Coxiella burnetii*-specific PCR results).

216 Microbiological tests for *F. tularensis* (13 serologies, five PCRs on eschar swabs, one
217 PCR on eschar biopsy and one PCR on lymph node fluid) were performed: two serologies
218 were positive, and one PCR on lymph node fluid was positive.

219

220 **Treatment**

221 A total of 89% of patients received at least one effective treatment, but 34% of patients
222 received two courses of antibiotics, and 14% received three or more (including local
223 antibiotics such as fusidic acid). This led to inappropriate antibiotic therapy in 51% of the
224 patients.

225 The median duration of antibiotic therapy was 15 days (IQR 7–19; data available for
226 30 patients). The median duration of effective antibiotic therapy was 14 days (IQR 6–15; data
227 available for 27 patients). Table 3 shows the details of the nature and duration of treatment.

228

229 ***Dermacentor* density**

230 The annual variation in the *Dermacentor* populations from four sites in the Alsace region was
231 investigated at two mountainous sites (Murbach and Niedermunster) and two lowland sites
232 (Illkirch and Dannemarie), as shown in Fig. 5. For Dannemarie, which is located in an
233 agricultural area that produces corn, the *Dermacentor* population was particularly abundant in
234 2021. The two peaks of tick activity generally occurred from February–March and October–
235 November (data not shown).

236 **Discussion**

237 This study highlights an increase in the number of TIBOLA cases in 2021 in northeastern
238 France as well as an increase in the *Dermacentor* tick population. These results support the
239 view that TIBOLA is a seasonal disease that occurs primarily in the spring [8]. TIBOLA
240 patients are mainly female, young and live in rural areas.

241 TIBOLA is a rare disease that is usually not reported in this region of France. Cases of
242 TIBOLA also appear to have increased in other European countries, as shown in a recent
243 Italian study [20]: the authors described 10 cases based on clinical and epidemiological
244 criteria over a period of 7 years (2015–2022) in Tuscany, a region where TIBOLA was rarely
245 found before.

246 Epidemiological changes also seem to occur in other tick-borne diseases. For example,
247 tick-borne encephalitis, once found almost exclusively in a limited part of northeastern
248 France, now seems to affect a wider area across the eastern half of France [12]. This increase
249 in incidence has also been reported for tularemia by the European Center for Disease
250 Prevention and Control [13,14]. However, the incidence of Lyme borreliosis has been stable
251 in France over the past few years [21,22], and the incidence of Mediterranean spotted fever
252 varies depending on the year [23].

253 The real challenge lies in the current lack of awareness and knowledge about TIBOLA
254 among many physicians and its frequent confusion with Lyme disease [15], leading to
255 inappropriate antibiotic therapy, such as amoxicillin. However, *Rickettsiae* are intracellular
256 bacteria that are naturally resistant to beta-lactams [24]. One of the reasons why doxycycline
257 has become the first-line treatment for Lyme borreliosis since 2018 is that it is effective
258 against other tick-borne diseases [21]. This was confirmed by the 2025 guidelines [25].

259 There are few large-scale studies about TIBOLA in the scientific literature. Several
260 case series, retrospective studies and a few prospective studies can be found. Most of these
261 studies are listed in Table 4. The seasonal fluctuations observed in this work, with the main
262 peak in the spring and a smaller peak in the autumn, are consistent with those reported in
263 previous studies [4,16,20,26–28]. In this study, the median patient age was 32.5 years. In the
264 literature, most patients diagnosed with TIBOLA are younger than 40 years old [3,8,29,30].
265 Individuals who are minors represented a substantial proportion of the patients in the present
266 study (34%), as observed in several other studies [4,31]. There is no convincing
267 pathophysiological hypothesis to explain why children are more affected by TIBOLA than
268 adults are. The same predominance of children can be observed in Lyme borreliosis [32].
269 With respect to clinical features, 17% of patients reported a disseminated skin rash, which is
270 far greater than what has been described in the literature: between 2% [8] and 5% of patients
271 [30]. With respect to fever, the data in the literature are discordant: from 25% [8] to 80% of
272 patients [20]. In the present study, half of the patients reported fever. Fewer cases of alopecia
273 were reported here than in the literature: 14%, while previous studies reported 19% [8]. This
274 finding could be explained by the retrospective design of this study, with a lack of
275 standardized follow-up.

276 The TIBOLA diagnostic criteria are not well defined. Some studies are based on
277 clinical signs following a tick bite [27], whereas others require microbiological
278 documentation [3]. In the present study, certain and probable cases of TIBOLA were
279 distinguished. In most cases, a TIBOLA diagnosis is based on a combination of demographic,
280 epidemiological and clinical factors. Microbiological documentation is particularly difficult
281 and frequently not essential, especially in primary care units, where biological analyses are
282 usually not performed. The absence of microbiological documentation is frequent in the
283 literature, as was the case in the present study. Studies performed in National Reference

284 Centers (Marseille in France, La Rioja in Spain), which routinely perform specific *Rickettsia*
285 serology and PCR, have a higher microbiological documentation rate [3,4,26,27,30] since
286 they include referred patients with a higher probability of TIBOLA.

287 TIBOLA is a local or regional disease with an inconsistent blood phase; this may
288 explain why the serology is often negative, with a sensitivity of 12% [26]. Furthermore,
289 recommendations suggest that serological tests should be repeated to observe seroconversion,
290 which was rarely performed in the present study [17]. In addition, *R. raoultii* is difficult to
291 identify in humans. Some studies suggest that *D. reticulatus* primarily harbors *R. raoultii* and
292 that *D. marginatus* harbors *R. slovaca* [10,33]. *Dermacentor reticulatus* is predominant in
293 northeastern France [8]; this could explain the low proportion of microbiologically confirmed
294 cases in this study.

295 A question arises as to the factors determining the possible expansion of TIBOLA.
296 Global warming could be one of the causes of this increase via a change in the geographical
297 and seasonal distribution of *Dermacentor* ticks, as evidenced by the detection of this tick as
298 early as January [34,35]. Global warming could also induce behavioral changes in hosts,
299 including humans, increasing their outdoor activities and potentially their exposure to
300 arthropod bites. Human activities impacting tick biotopes are also likely to favor vector
301 expansion [18] through the evolution of agriculture over recent decades, through the
302 reforestation and importation of animals, and through a reduction in the use of pesticides
303 (even if this behavior change could have other advantages for human health). In Germany, a
304 participatory citizen study (ticks sent by citizens, collection of geographical information)
305 performed from 2020–2021 revealed the spatial spread of *Dermacentor* [36]. Entomological
306 studies are currently being conducted to document the spread of *Dermacentor* ticks in nature
307 and to explain the determining factors (*Borrelia* National Reference Center, Strasbourg,

308 France). Preliminary data show that in northeastern France, 19% of *D. reticulatus* are infected
309 by *R. raoultii*, whereas *R. slovaca* is rarely detected (1%). Interannual variations rather than
310 real increases in *Dermacentor* were observed, and these ticks are present in specific
311 ecosystems (N. Boulanger—personal communication).

312 Furthermore, a greater number of TIBOLA might not only be a consequence of an
313 emergence but also of a better awareness of tick-borne diseases by medical professionals in
314 France.

315 This study combining human and tick epidemiological data is original but has several
316 limitations linked to its retrospective design, particularly missing data and memory bias
317 among clinicians. To control these biases, microbiological data were extracted to identify
318 cases that the clinicians could not remember. Wide screening based on prescribed tests and
319 careful examination of medical files helped to contain them. This strategy led to the inclusion
320 of several types of tularemia. This disease matches the predefined inclusion criteria:
321 inoculation eschar with regional lymphadenopathy after a tick bite. Hence, a question arises
322 about whether TIBOLA is a disease or a syndrome.

323 TIBOLA is benign and usually has no systemic complications. In most cases, patients
324 do not seek specialized hospital care. This study estimated the number of cases of TIBOLA
325 diagnosed in hospitals in northeastern France, but most of the cases were probably met in
326 primary care, resulting in selection bias. Thus, the number of cases must have been
327 underestimated. The inclusion of outpatients is methodologically and financially complex,
328 and most of the time, patients seen in primary care units do not have microbiological tests.
329 Thus, in an outpatient study, the microbiological documentation rate would have been even
330 lower. Another limitation is that the screening was performed in a limited number of
331 hospitals. In addition, two cases were diagnosed in northeastern France after a tick bite in

332 another region. In terms of entomological data, there were only 4 collection sites in Alsace, a
333 region that is nevertheless endemic for ticks and tick-borne diseases, whereas the clinical
334 inclusion zone was wider in northeastern France. Work is in progress to complete vector
335 epidemiology.

336

337 **Conclusions**

338 This study confirms that TIBOLA is a benign, rare and difficult-to-diagnose disease. These
339 results suggest that TIBOLA could become an emerging disease in northeastern France if
340 environmental conditions favor the development of the vector and its contact with humans.

341

342 **Abbreviations**

343 CBC: Complete blood count

344 °C: Degree Celsius

345 COI: Cytochrome oxidase I gene

346 CRP: C-reactive protein

347 DEBONEL: *DErmacentor* BOrne Necrosis Erythema and Lymphadenopathy

348 IgG: Immunoglobulin G

349 IgM: Immunoglobulin M

350 IQR: Interquartile range

351 MALDI-TOF: Matrix-assisted Laser Desorption Ionization – Time of Flight

352 mg/L: Milligrams per liter

353 PCR: Polymerase chain reaction

354 rDNA: Recombinant Desoxyribonucleic Acid

355 SENLAT: Scalp Eschar and Neck LymphAdenopathy after Tick bite

356 TIBOLA: Tick BOrne LymphAdenopathy

357

358 **Declarations:**

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361 clinicians and technicians who helped collect the clinical, epidemiological and entomological
362 data.

363

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369

370 **Availability of data and materials**

371 The raw data supporting the conclusions of this article are protected under French law.
372 Requests to access the datasets should be directed to the corresponding author.

373

374 **Authors' contributions**

375 All the authors contributed to the study conception and design. Material preparation, data
376 collection and analysis were performed by Jeanne Kotzyba, Elisabeth Baux, Yves Hansmann,
377 Nathalie Boulanger and Benjamin Lefèvre. The first draft of the manuscript was written by
378 Jeanne Kotzyba, and all the authors commented on previous versions of the manuscript. All
379 the authors read and approved the final manuscript.

380

381 **Ethics approval and consent to participate**

382 This study complies with the principles outlined in the Declaration of Helsinki and its later
383 amendments. This study was approved by the Nancy Hospital Ethics Committee (April 22,
384 2022; decision no. 348). Patients received complete information about the study
385 (ClinicalTrials.gov ID NCT05458245). In accordance with French law, patient consent was
386 not needed. Nevertheless, patients could decline to participate.

387

388 **Consent for publication**

389 Not applicable.

390

391 **Competing interests**

392 The authors declare that they have no competing interests.

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514

515 Table 1. Characteristics of patients retrospectively identified with TIBOLA in
 516 several hospitals in northeastern France between 2016 and 2021

Sociodemographic data	
Female, No. (%)	29 (83)
Male, No. (%)	6 (17)
- Median age, years (IQR _a)	32.5 (10-55)
< 18 years old, No. (%)	12 (34)
- Median age, years (IQR)	9 (6-9)
Place of residence	
Rural, No. (%)	20 (57)
Urban, No. (%)	15 (43)
Living close to field, gardens, forests or watercourses, N = 20, No. (%)	18 (90)

517 _a: IQR: Interquartile range.

518 When N is not precise, the denominator is the total effective rate (N = 35).

519

520 Table 2. Clinical characteristics of patients retrospectively identified as having
 521 TIBOLA in several hospitals in northeastern France between 2016 and 2021

Median incubation period ^a , N = 23, days (IQR ^b)	4 (2-8)
Inoculation eschar, No (%)	35 (100)
- Scalp	30 (86)
- Trunk	2 (6)
- Lower limbs	2 (6)
- Brow bone	1 (3)
Lymphadenopathies, No (%)	35 (100)
- Only neck	26 (77)
- Neck and other localization	7 (20)
- Unique, N = 34	8 (23)
- Multiple, N = 34	26 (76)
- Supra-centimetric, N = 23	18 (76)
- Painful, N = 23	17 (74)
Other symptoms, No (%)	33 (94)
Fever	19 (54)
Headache	14 (40)
Asthenia	12 (34)

Rash	10 (29)
Arthromyalgia	6 (17)
Generalized rash	6 (17)
Neck pain	6 (17)
Alopecia	5 (14)
Facial edema	4 (11)
Chills	3 (9)
Median duration of symptoms _c , days (IQR)	17 (11-27)

522 ^a: Incubation period: time between the tick bite and the appearance of the first symptom.

523 ^b: IQR: Interquartile range.

524 ^c: Duration of symptoms: time between the appearance of the first symptom and the resolution
525 of the last symptom.

526 When N is not precise, the denominator is the total effective range (N = 35).

527 Table 3. Details of antibiotic therapy in patients retrospectively identified as
 528 TIBOLA in several hospitals in northeastern France between 2016 and 2021

Antibiotic treatment, N = 35	33
Doxycycline	26
Amoxicillin	13
Azithromycin	5
Amoxicillin- clavulanic acid	4
Topical fusidic acid	4
Pristinamycin	2
Ciprofloxacin	2
No treatment	2
Median duration, N = 30, days (IQR _a)	15 (7–19)
Median duration with effective molecule _b , N = 27 (IQR)	14 (6–15)
2 courses of antibiotics, %	34
>3 courses of antibiotics, %	14
Exposure to inappropriate antibiotics, %	51
Exposure to beta-lactam antibiotics, %	46

529 _a: IQR: Interquartile range.

530 _b: Effective molecules: doxycycline, azithromycin and ciprofloxacin (if *F. tularensis* was
 531 identified as the causal agent).

532 When N is not precise, the denominator is the total effective range ($N = 35$).

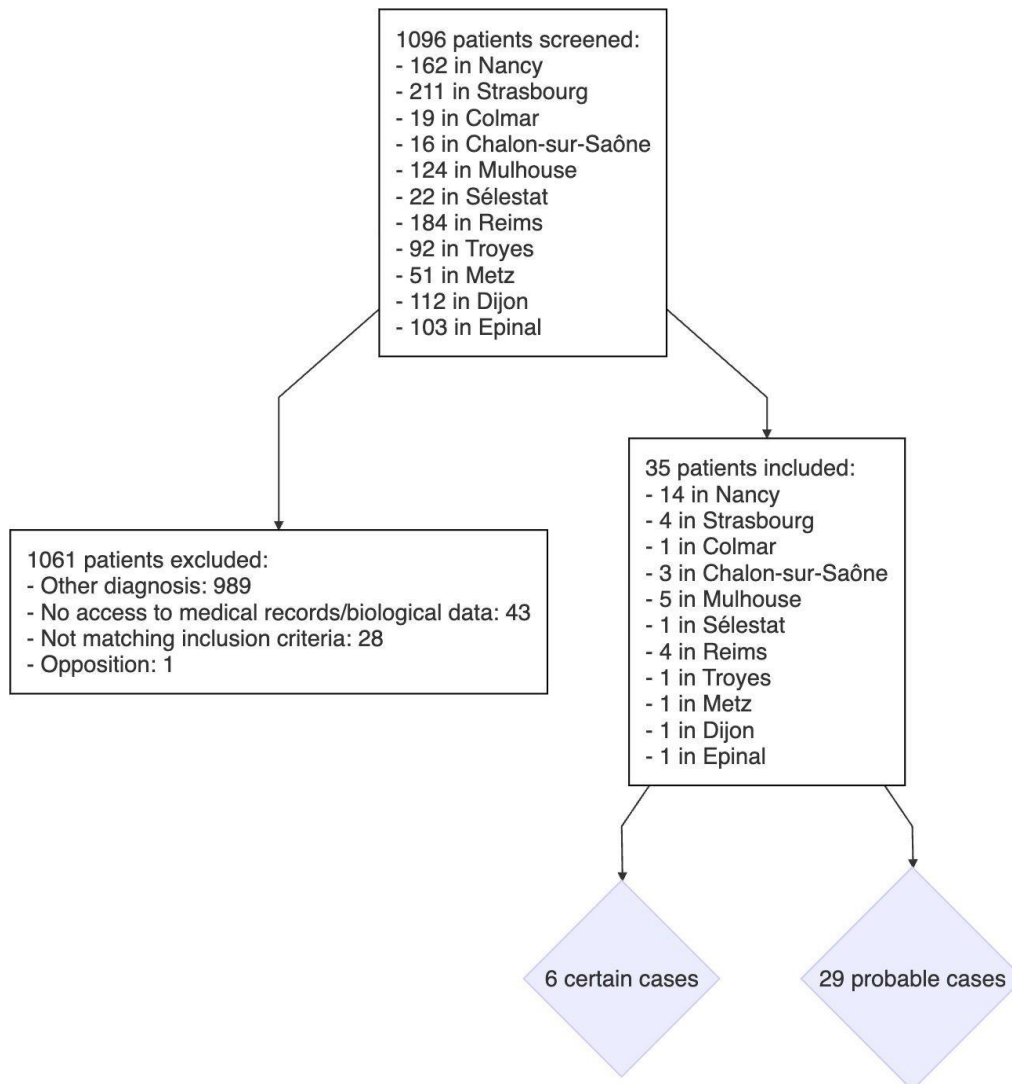
533 Table 4. Studies reporting cases of TIBOLA since 1997

Study	Location	Design	Inclusion criteria	No. of cases	Season	Median age (years old)	% females	Microbiological documentation (<i>Rickettsia</i> spp.)
Lakos et al. 1997 [1]	Hungary	Retrospective, multicentric, 1 year	Tick bite and clinical criteria	27	Not mentioned	>50% younger than 10		No microbiological confirmation
Lakos et al. 2002 [31]	Hungary	Prospective controlled, multicentric, 4 years	Tick bite or clinical criteria	86	March and April	13	72	Positive skin or lymph node PCR _a : 10/13 Positive serology: 19/73
Raoult et al. 2002 [26]	France and Hungary	Retrospective, multicentric, 4 years	Tick bite and clinical criteria Definite case: positive culture or PCR	67	France: February to May Hungary: March and April	Unknown	61	17 microbiological confirmations: Positive serology: 7/17 Positive skin biopsy (PCR): 4/7 Positive lymph node biopsy: 7/8 Positive serum (PCR): 11/17 Positive tick (PCR): 3/3
Oteo et al. 2004 [30]	Spain	Retrospective-prospective, multicentric, 11 years	Tick bite by a large tick from October to April and clinical criteria and negative serology for <i>Borrelia burgdorferi</i> and <i>F. tularensis</i>	22	January, spring, and autumn (pick in November)	38	55	Positive serology: 9/12 Positive skin biopsy (PCR): 0/3
Gouriet et al. 2006 [29]	France	Retrospective, multicentric, 1 year	Tick bite and clinical criteria	14	October to January and February to May	35	64	Positive serology: 10/14 Positive skin biopsy (PCR): 3 Positive serum (PCR): 1 Positive tick (PCR): 3
Ibarra et al. 2006 [27]	Spain	Retrospective-prospective,	Tick bite by a large tick from October to May and	54	April and November	37	59	Positive serology: 19/31 Positive serum (PCR): 9/21

		multicentric, 14 years	clinical criteria					Positive skin biopsy (PCR): 0 Positive tick (PCR): 10/10
Porta et al. 2008 [37]	Spain	Retrospective, monocentric, 6 years	Tick bite and clinical criteria	36	October April	to 16	44	Positive serology: 10 Positive PCR on skin, serum, and eschar swab: 0 Positive tick (PCR): 4/7
Selmi et al. 2008 [28]	Italy	Prospective, multicentric, 2 years	Tick bite and clinical criteria, consulting the emergency department to remove the tick	5	Spring		60	Positive tick (PCR): 3/5
Parola et al. 2009 [3]	France	Retrospective, multicentric, 6 years	Tick bite and serum/skin biopsy/tick received at the laboratory or clinical criteria Certain case: culture or PCR positive on patient sample Probable case: serology or positive PCR on tick	86	February May	to 32	71 (among certain cases)	56 microbiological confirmations: Positive serology: 66/78 Positive tick (PCR): 13/18 Positive skin biopsy (PCR): 4/19 Positive skin biopsy (culture): 3/19 Positive serum (PCR): 1
Lakos et al. 2012 [38]	Hungary	Retrospective (case control study) Multicentric, 3 years	Tick bite and clinical criteria	50	May November	to 9	82	Positive serology: 23/47
Beytout et al. 2013 [39]	France	Retrospective Monocentric, 15 years	Tick bite and/or clinical criteria	17				Positive serology: 6/14 Positive skin biopsy (PCR): 1
Rigal et al. 2014 [40]	France	Series of cases, monocentric,	Tick bite and clinical criteria	5	November and June		100	Positive serology: 1

		10 months							
Dubourg et al. 2014 [16]	France	Prospective, multicentric, 5 years	Tick bite and clinical criteria Definite case: positive culture or PCR or serology	56	Spring and Autumn	42	68	Positive serology: 2/45 Positive skin biopsy (PCR): 3/16 Positive eschar swab or crust (PCR): 6/34 Tick positive (PCR): 7/9 Positive culture (tick, skin biopsy or eschar swab): 4	
Silva-Pinto et al. 2014 [8]	International	Literature review, multicentric, 16 years	Not standardized	37 articles 537 patients	Spring, autumn and winter	Always younger than 40	64	Microbiological confirmation in 149 cases	
Santibañez et al. 2022 [4]	Spain	Retrospective, multicentric, 19 years	Clinical and epidemiological criteria	216	November, April and May	40	65	Positive serology: 91/109 Positive serum (PCR): 14/104 Positive skin biopsy (PCR): 7/7 Positive eschar swab (PCR): 69/142 Positive tick (PCR): 71/71	
Barbiero et al. 2023 [20]	Italy	Retrospective, monocentric, 7 years	Tick bite and clinical criteria	10	March to May	46	100	No microbiological confirmation Positive serology: 0/10 Positive skin biopsy (PCR): 0/2 Positive serum (PCR): 0/5 Positive eschar swab (PCR): 0/4	
Present study	France	Retrospective, Multicentric, 6 years	Tick bite and clinical criteria Certain case if positive PCR or serology, probable case if not	35	April and May	33	83	Positive serology: 1/19 Positive skin biopsy (PCR): 1/2 Positive eschar swab (PCR): 2/12 Positive tick (PCR): 1/2	

535 **Fig. 1** Flow chart of patients retrospectively identified as TIBOLA in northeastern France
536 between 2016 and 2021



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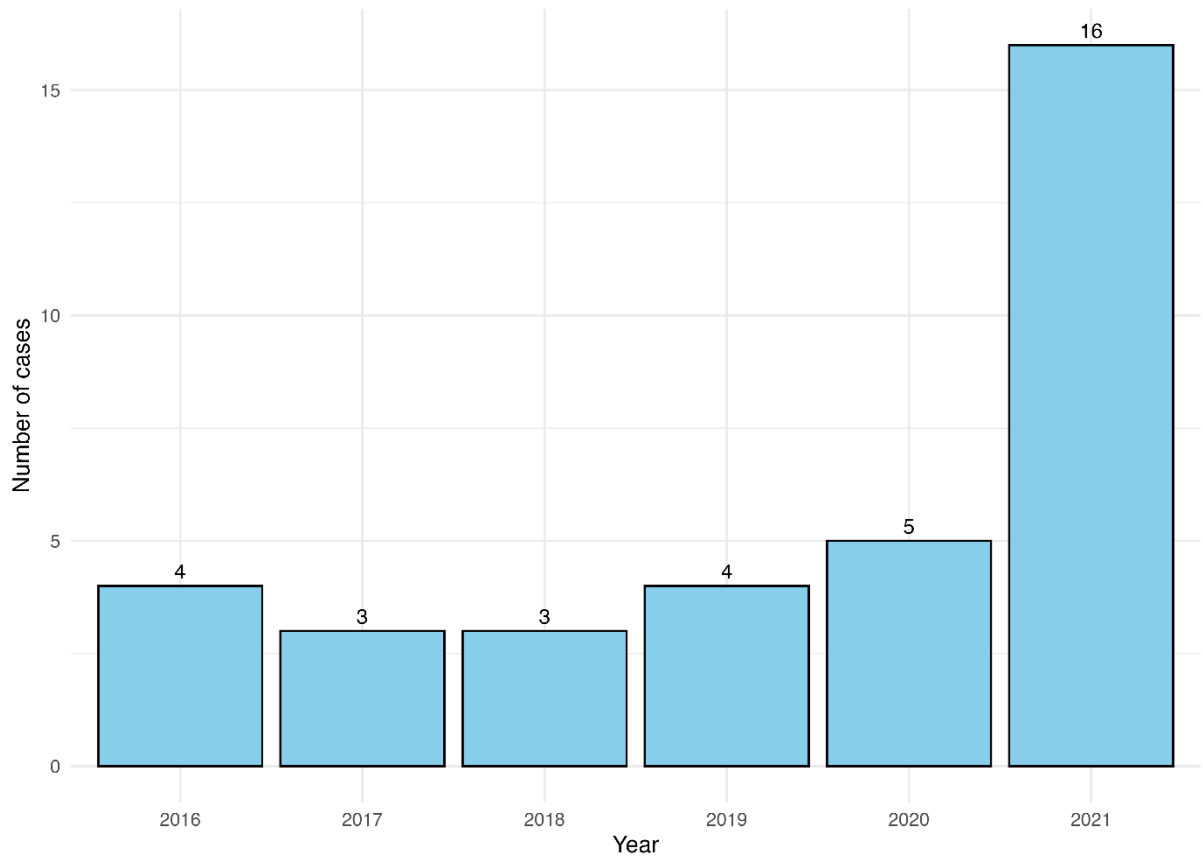
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544 **Fig. 2** Evolution of the number of TIBOLA cases between 2016 and 2021 in northeastern
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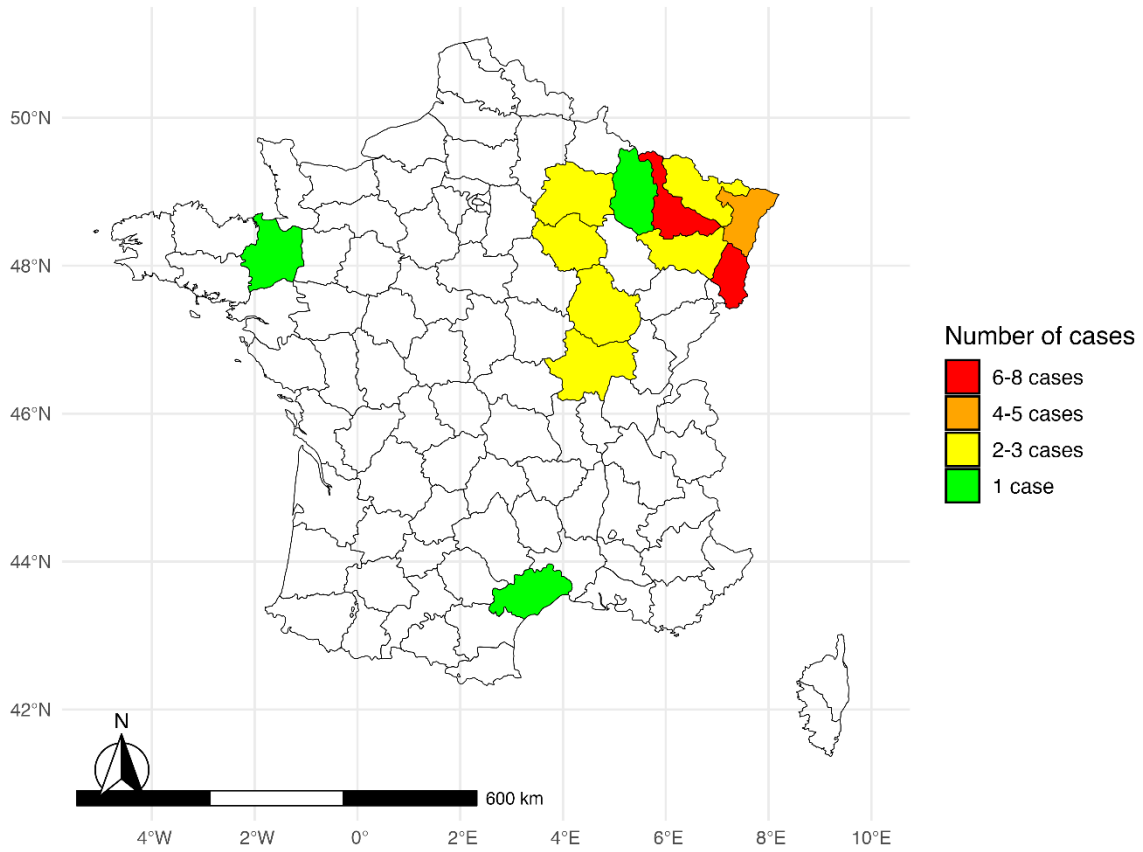
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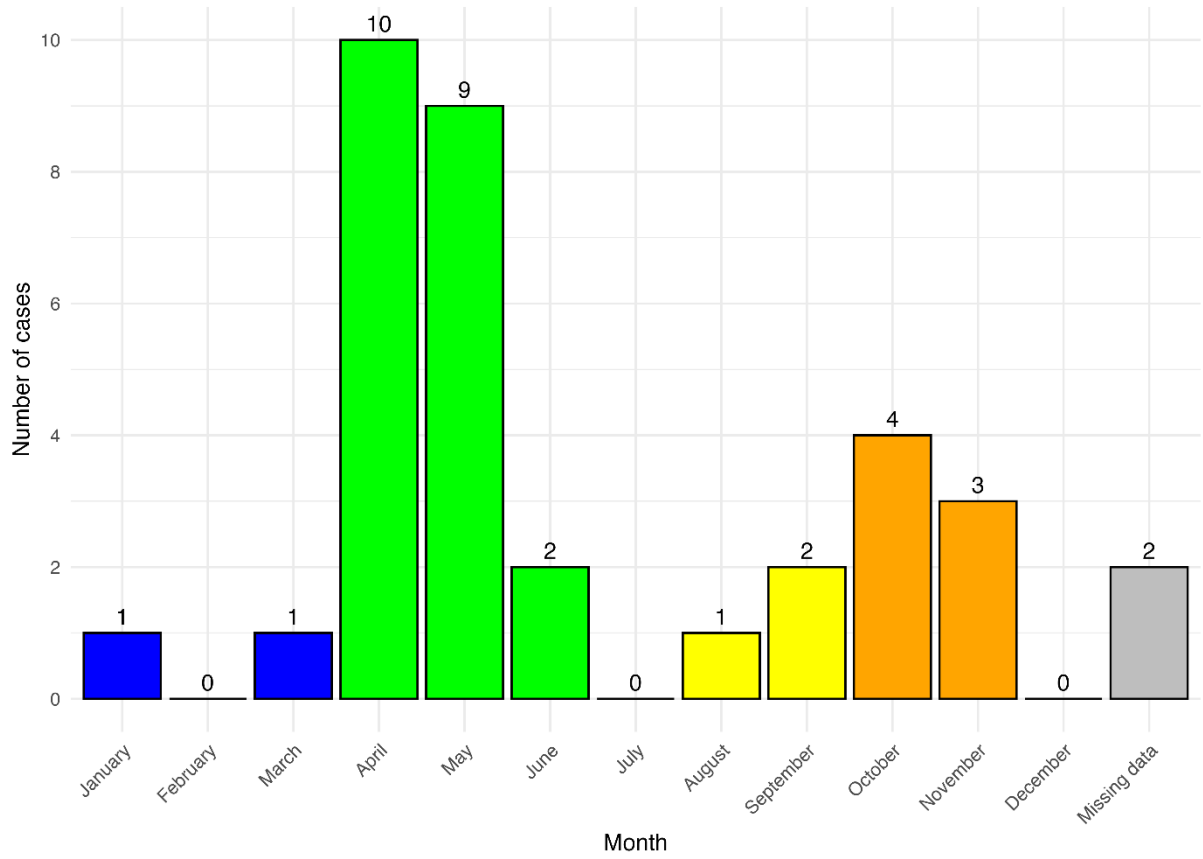
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556 **Fig. 3** Spatial distribution of the locations in which patients affected by TIBOLA were bitten
557 (or if unavailable, their place of residence)



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567 **Fig. 4** Monthly distribution of TIBOLA cases diagnosed between 2016 and 2021 in
568 northeastern France



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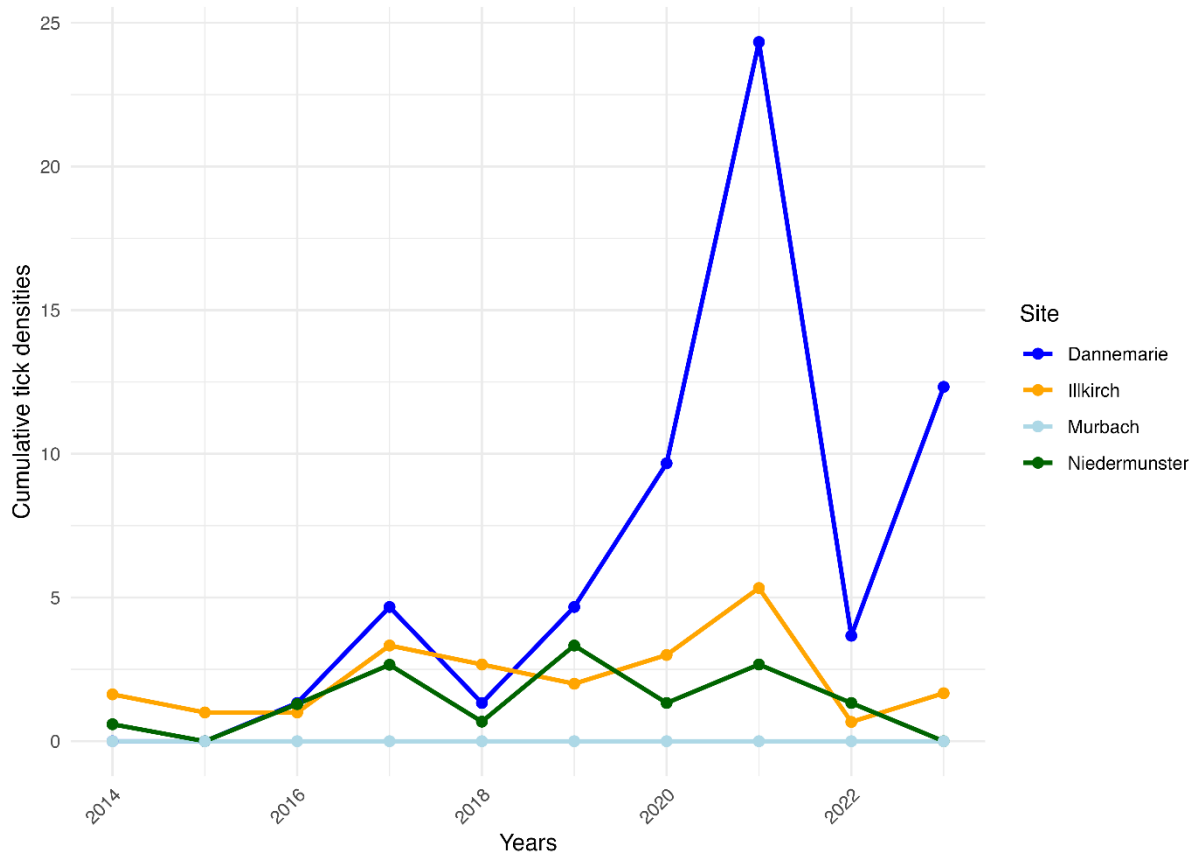
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577 **Fig. 5** Longitudinal study of the cumulative *Dermacentor* density at four sites in the Alsace
578 region from 2014 to 2023



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