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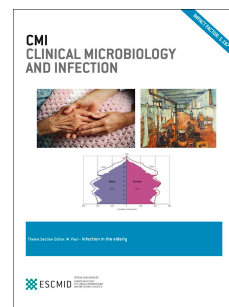
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1 **Original Article – E-only**

2

3 **Seroprevalence of seven pathogens transmitted by the *Ixodes ricinus* tick in forestry workers in France**

4

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37 *phagocytophilum* recombinant antigen.

38

39

40 Abstract

41

42 In order to assess the level of occupational exposure to the main pathogens transmitted by the *Ixodes ricinus* tick,
43 a seroprevalence study was performed on serum samples collected in 2003 from 2,975 forestry workers of
44 North-Eastern France. The global seroprevalence estimated for the seven pathogens studied was 14.1%
45 (419/2,975) for *B. burgdorferi* s.l, 5.7% (164/2,908) for *F. tularensis*, 2.3% (68/2,941) for TBEV, 1.7%
46 (50/2,908) for *A. phagocytophilum*, and 1.7% (48/2,908) for *B. henselae*. The seroprevalence of *B. divergens* and
47 *B. microti* studied in a subgroup of subjects seropositive for at least one of these latter pathogens was 0.1%
48 (1/810) and 2.5% (20/810) respectively. *B. burgdorferi* s.l seroprevalence was significantly higher in Alsace and
49 Lorraine and *F. tularensis* seroprevalence was significantly higher in Champagne-Ardenne and Franche-Comté.
50 The results of this survey also suggest low rates of transmission of *B. henselae* and *F. tularensis* by ticks and a
51 different West/East distribution of *Babesia* species in France. The frequency and potential severity of these
52 diseases justify continued promotion of methods of prevention of *I. ricinus* bites.

53

54 Key-Words: *Ixodes ricinus*, zoonotic agents, occupational exposure, seroprevalence, France

55

56

57 Introduction

58

59 Ticks are blood-feeding arthropods responsible for the transmission of numerous infectious agents that are
60 pathogenic for man and/or animals. *Ixodes ricinus* is the most widespread tick species in Europe and constitutes

61 the vector of numerous pathogens, especially *Borrelia burgdorferi* sl, *Anaplasma phagocytophilum*, tick-borne
62 encephalitis virus (TBEV), *Babesia spp.*, and some *Rickettsia* species [1]. It is also involved in the transmission of
63 *Francisella tularensis* and possibly *Bartonella henselae* [2, 3].

64
65 *I. ricinus* is present in almost all regions of France, in biotopes with persistent relative humidity (leafy forest
66 floor, tall grasses, broadleaf and conifer forests) [4-6]. The high level of infestation of *I. ricinus* by infectious
67 agents plays a leading role in the epidemiology of tick-borne diseases [7]. The estimated incidence of Lyme
68 borreliosis in France from 2009 to 2012 was 42 per 100,000 inhabitants (an estimated average of 26,500 cases
69 per year) [8]. Several human cases of tick-borne encephalitis are regularly reported, and cases of human
70 anaplasmosis, babesiosis and tularaemia after tick bites have been published in France [9-13].

71
72 In Europe, Lyme borreliosis is the most common tick-borne disease, with a mean annual number of cases,
73 estimated by a review in 2009, between 65,500 and 80,500 and an incidence rate that may be higher than 200
74 cases per 100,000 inhabitants in some countries such as Slovenia [14, 15]. The second most common disease is
75 tick-borne encephalitis with an average of 3,000 cases per year for all European endemic countries and an
76 incidence exceeding 10 cases per 100,000 inhabitants in Estonia and Slovenia [16]. Between 70 and 100
77 confirmed or probable cases of anaplasmosis have been reported since 1997, especially in Slovenia and
78 Scandinavia and almost 60 cases of babesiosis (including about 40 cases of *B. divergens*) have been reported [10,
79 12, 17, 18]. Ticks represent an important vector of tularaemia in some European countries (Switzerland,
80 Slovakia) [19]. Recent data have shown that ticks could be able to transmit *B. henselae* to man: detection of
81 *B. henselae* DNA in ticks removed from infected subjects, description of a few possible human cases of *B.*
82 *henselae* infection after tick bites, demonstration of the capacity of *I. ricinus* to transmit *B. henselae* by means of
83 a tick artificial nutrition method [3, 20-22].

84
85 Human seroprevalence studies conducted in workers exposed to tick bites have essentially concerned *B.*
86 *burgdorferi* sl, TBEV and *A. phagocytophilum*. Only three studies have been conducted in forestry workers in
87 Europe to simultaneously evaluate the seroprevalence of other tick-borne pathogens [23-25]. The objective of the
88 present study was to estimate the seroprevalence of seven pathogens transmitted by *I. ricinus* in workers exposed
89 to ticks (*B. burgdorferi* sl, TBEV, *A. phagocytophilum*, *F. tularensis*, *B. henselae*, *B. microti* and *B. divergens*) in

90 order to assess the frequency of human exposure to these different microorganisms in a region of high exposure
91 to tick-borne pathogens in France [7, 8].

92

93

94 **Method**

95

96 **Recruitment and inclusion of subjects**

97

98 This cross-sectional study was conducted among forestry workers in North-Eastern France. Subjects were
99 recruited by *Mutualité Sociale Agricole* occupational health physicians from December 2002 to December 2003
100 in the Alsace, Lorraine, Champagne-Ardenne, Franche-Comté and Bourgogne regions.

101 Forestry workers (woodcutters, silviculturists, forest rangers, fishing guards, game wardens, personnel with
102 multiple forestry activities at least including woodcutting or silviculture, forestry machinery operators, sawmill
103 personnel, wood sellers or gardeners) were invited to participate in the study at the time of occupational health
104 surveillance examinations performed during the study period. Subjects with an immunodeficiency were
105 excluded. Occupational health physicians interviewed forestry workers after obtaining their signed informed
106 consent by using a standardized, anonymous questionnaire to record demographic and occupational data,
107 including age, gender, place of residence and occupation over the previous twelve months, as well as previous
108 yellow fever, Japanese encephalitis and tick-borne encephalitis immunizations. A blood sample for serology was
109 drawn after the interview. This study was approved by our local ethical committee (CCPPRB, 29 avenue du
110 Maréchal de Lattre de Tassigny, Nancy).

111

112 **Laboratory samples**

113

114 Anonymous blood samples (7 to 10 ml of blood) stored at room temperature were centrifuged within a maximum
115 of 12 hours after collection, sera were then frozen at -20°C within 2 hours after centrifugation and stored at -
116 30°C within 12 hours until analysis. For each sample, a first tube was used in 2003 to perform *B. burgdorferi* sl
117 serologies. A second tube, also stored at -30°C, was thawed in 2007 and divided into five aliquots, three of
118 which were used to perform TBEV, *A. phagocytophilum* and *F. tularensis* serologies. Two aliquots stored at -
119 30°C were subsequently used for *B. henselae* (in 2010) and *Babesia* (in 2011) serologies.

120 **Serological tests**

121 - Screening for anti-*Borrelia burgdorferi* IgG was performed by ELISA (Enzygnost® Borreliosis, Siemens®).

122 Doubtful or positive sera were tested by TPHA and VDRL to eliminate cross-reactions related to *Treponema*
123 *pallidum* and by Western blot for confirmation according to European guidelines [26].

124 - Screening for anti-TBEV IgG was performed by ELISA (Immunozyzm FSME, PROGEN®) on serum from
125 subjects who declared that they had not been vaccinated against tick-borne encephalitis, Japanese encephalitis or
126 yellow fever.

127 - Screening for anti-*Anaplasma phagocytophilum* IgG antibodies was performed by ELISA using a recombinant
128 protein P44 antigen [27]. Doubtful or positive sera were retested by IFA (*Anaplasma phagocytophilum* IFA
129 IgG/IgM kit, Focus®) (positive cut-off = 1/64).

130 - Screening for anti-*Francisella tularensis* IgG was performed by tube agglutination of *F. tularensis* antigen
131 particles (BD®). Sera positive for *F. tularensis* were then tested for *Yersinia* (*Yersinia* ELISA IgA kit,
132 Verion/Serion®) and *Brucella* by agglutination (*Brucella* Rose Bengal, Biorad® and *Brucella* Wright, Biorad®
133 kits). Doubtful or positive sera in relation to *Yersinia* or *Brucella* were excluded from the analysis.

134 - Screening for anti-*Babesia microti* and anti-*Babesia divergens* IgG antibodies was performed by IFA (positive
135 cut-offs 1/64 and 1/128, respectively). Due to the presumed low seroprevalence as reported in the literature for
136 these 2 pathogens and the amount of human workload of IFA serology, these tests were only performed on sera
137 positive for *B. burgdorferi* s.l., TBEV, *A. phagocytophilum* or *F. tularensis*.

138 - Screening for anti-*Bartonella henselae* IgG was performed by ELISA. In order to increase the sensitivity of this
139 test, the antigen used was a mixture of four strains of *Bartonella henselae*: Bhl (Houston-1 G5436^T, ATCC
140 49882T), BhlII (Marseille, strain URLLY 8, CIP 104756), Berlin-1 (isolated from the cutaneous bacillary
141 angiomatosis lesions of an HIV-infected patient), Berlin-2 (isolated from the blood of a pet cat).

142

143 **Statistical analysis**

144

145 All data were entered with Ethnos® software and exported to Excel® 2007. For analysis of the results, doubtful
146 serological results in relation to the various pathogens tested were classified as negative.

147 A descriptive analysis of the subjects included and calculation of seroprevalence rates for each pathogen were
148 performed. Seroprevalence rates were compared by age-group, region and occupational group by Chi-square test

149 or Fisher's exact test. The variation of seroprevalence rates by age-group was studied by Chi-square test for
150 linear trends.

151 For pathogens with an sufficient number of seropositive cases, the odds ratios of prevalence, adjusted for age,
152 occupation and region of residence, were estimated by a logistic regression model. Confidence intervals and tests
153 of significance were calculated at the α limit of 5%. Calculations were performed with EpiInfo™ 7.1.1.1
154 software.

155

156

157 **Results**

158

159 **Description of the population**

160

161 Of the 5,461 subjects invited to participate in the study, 3,033 replied and 2,975 were finally included (2,916
162 men and 59 women). Subjects excluded from the study were personnel with little or no forestry exposure (39),
163 subjects refusing to sign the informed consent form (11), with an intercurrent disease or receiving
164 immunosuppressive therapy (4), or for whom the questionnaire or blood samples were not available (4). The
165 subjects included worked in the five regions of the study, distributed throughout the territory of the study (Figure
166 1). The participation rate and characteristics of the subjects differed slightly according to the region (Table 1).

167 *B. burgdorferi* sI and TBEV serology was available for all subjects included (2,975) and *A. phagocytophilum*, *F.*
168 *tularensis* and *B. henselae* serology was available for 2,908 subjects (the volume of serum was insufficient to
169 perform all three additional serologies for 67 subjects).

170

171 ***B. burgdorferi* sI seroprevalence**

172

173 Of the 2,975 subjects tested for *B. burgdorferi* sI, 419 were positive, corresponding to a seroprevalence rate of
174 14.1%. Seroprevalence increased significantly with age, reaching a maximum of 25.1% (85/338) for subjects 55
175 years and older ($p < 10^{-4}$) (Fig. 2a), and was significantly higher in woodcutters (17.5%, 200/1,145) compared to
176 other occupations and in Alsace (26.9%, 171/636) and Lorraine (16.5%, 146/885) compared to the other three
177 regions studied (Table 2).

178 After adjustment for age and region of residence, seroprevalence was significantly higher in woodcutters and/or
179 silviculturists. Alsace, Lorraine and Champagne-Ardenne presented a higher seroprevalence compared to
180 Franche-Comté (Table 3).

181

182 **TBEV seroprevalence**

183

184 After exclusion of subjects who reported having been vaccinated against TBE virus, Japanese encephalitis or
185 yellow fever (34), 68 of the 2,941 sera were positive for TBEV, corresponding to a seroprevalence rate of 2.3%.

186 Only age was significantly associated with the subject's serological status ($p = 0.001$): the proportion of
187 seropositive subjects was lower among young subjects (0.9%, 7/748 for subjects younger than 35 years) and
188 higher among older subjects (4.8%, 16/333 for subjects 55 years and older) (Fig. 2b and Table 2).

189

190 ***A. phagocytophilum* seroprevalence**

191

192 Of the 2,908 subjects tested for *A. phagocytophilum*, 50 were positive, corresponding to a seroprevalence rate of
193 1.7%. No significant association was demonstrated between the subject's serological status and age, occupation
194 or region of residence (Fig. 2c and Table 2).

195

196 ***F. tularensis* seroprevalence**

197

198 Of the 2,908 subjects tested for *F. tularensis*, 197 were positive and none of these subjects were simultaneously
199 positive for *Brucella*; 33 sera were also positive or doubtful for *Yersinia* and were excluded from the analysis.

200 The seroprevalence rate was therefore 5.7% (164/2,875) and was significantly associated ($p < 10^{-4}$) with
201 occupation, reaching 9.2% (63/684) among silviculturists. Significant regional variations were also observed
202 ($p < 10^{-4}$): from 3.6% in Alsace and Lorraine to 11.2% (53/474) in Champagne-Ardenne (Table 2). After
203 adjustment for other factors, seroprevalence was significantly higher among silviculturists and in the
204 Champagne-Ardenne and Franche-Comté regions (Table 4).

205

206 ***B. henselae* seroprevalence**

207

208 Of the 2,908 subjects tested for *B. henselae*, 48 presented positive serology, corresponding to a seroprevalence
209 rate of 1.7%. No significant association was demonstrated between the subject's serological status and age,
210 occupation or region of residence (Fig. 2e and Table 2).

211

212 ***B. microti* and *B. divergens* seroprevalence**

213

214 Among the 810 subjects who were seropositive for *B. burgdorferi* sI or TBEV or *A. phagocytophilum* or *F.*
215 *tularensis*, only 1 was positive for *B. divergens* and 20 were positive for *B. microti*, corresponding to a
216 seroprevalence rate of 0.1% (1/810) and 2.5% (20/810) respectively in this subgroup.

217 A higher proportion of seropositive subjects was observed among subjects 55 years and older, silviculturists, and
218 subjects living in Lorraine and Champagne-Ardenne (Fig. 2f and Table 2).

219

220 **Multiple seropositivities**

221

222 Among the subjects tested for both *B. burgdorferi* sI, TBEV, *A. phagocytophilum*, *B. henselae* and *F. tularensis*,
223 the serology was positive for a single pathogen in 21.5% (627/2,908) subjects and for 2 pathogens (other than
224 *Babesia*) in 2.0% (57/2,908), especially *B. burgdorferi* sI together with *F. tularensis* (22/57), TBEV (11/57),
225 *B. henselae* (9/57) or *A. phagocytophilum* (7/57) (Figure 3). Age was significantly associated with the multiple
226 serological status ($p=0,001$): the proportion of subjects with multiple seropositivities was lower among subjects
227 younger than 35 years (0.8%, 6/739) and higher among subjects older than 55 years (4.6%, 15/329). Significant
228 regional variations were also observed ($p<10^{-4}$): from 0.8% (4/512) in Franche-Comté to 4.0% (25/623) in
229 Alsace.

230

231

232 **Discussion**

233

234 In this study, *B. burgdorferi* sI seroprevalence among forestry workers was 14.1%. This seroprevalence rate was
235 considerably higher than that of the other pathogens studied: 5.7% for *F. tularensis*, 2.3% for TBEV, 1.7% for *A.*
236 *phagocytophilum* and 1.7% for *B. henselae*, respectively. The overall seroprevalence of *B. divergens* and

237 *B. microti* was 2.6% but was only calculated among subjects seropositive for at least one other pathogen, which
238 could overestimate the prevalence.

239 Since date of the sample collection, some factors could have possibly lead to an increase of prevalence of these
240 pathogens in ticks,: climate change, increase of the population size of wild animals hosting ticks: deers roe deers,
241 wild boars (data from 2002/2003 to 2014/2015 provided by the Fédération des Chasseurs and the Office National
242 de la Chasse et de la Faune Sauvage), modifications in agricultural and forest landscapes that could lead to a
243 higher density of tick populations [28-30].

244
245 Since only one human case of *Rickettsia helvetica* infection has been described in France up to now and that
246 *Rickettsia slovaca* infections have been reported mostly from Southern France and are transmitted by
247 *Dermacentor* ticks, seroprevalence of *Rickettsia* spp. among forestry workers was not investigated in our study
248 [31, 32].

249
250 Classification of seropositive subjects was optimized by the use of validated laboratory tests and by the
251 exclusion of cases with a suspected cross-reaction with other pathogens.

252
253 This cross-sectional seroprevalence study among forestry workers mainly reflects old or recent exposure to an
254 infectious agent, based on the generally prolonged persistence of antibodies detectable in blood, without taking
255 into account the clinical expression of the disease and its mode of transmission. Although a transmission of
256 *F. tularensis* and *B. henselae* by tick bites has been hypothesized in the literature, the results of this study did not
257 confirm or infirm a possible tick transmission of these pathogens for which human infection usually occurs by
258 direct skin contact with the animal or by inoculation (scratch or bite) respectively [13,33].

259
260 Other studies of *B. burgdorferi* sl seroprevalence in Europe have also been conducted among occupationally
261 exposed workers using various techniques and kits (ELISA with or without western blot confirmation, IFA, with
262 or without differential detection of IgG and IgM antibodies) and based on very variable sample sizes, thereby
263 limiting comparisons. In studies using western blot analysis, the seroprevalence of anti-*B. burgdorferi* IgG
264 antibodies was 9.4% in Romania and varied significantly according to regions from 0.7% to 23.2% in Italy [34-
265 36]. The seroprevalence, without distinguishing IgG and IgM, was 18.1% in The Netherlands, 28.0% in Poland

266 and 34.6% in Germany [37-39]. Studies based on the use of ELISA alone reported IgG seroprevalence rates of
267 23.8% in Slovenia, 33.1% in Germany and 35% in Switzerland [25, 40, 41].

268 The high *B. burgdorferi* s.l. seroprevalence observed in our study is similar to that reported by other previous
269 surveys among occupationally exposed workers in France [42, 43]. Our study shows a predominance of this
270 seroprevalence in the two most North-Eastern regions of France. In particular, the high prevalence in Alsace is
271 concordant with the tick density and infestation rates reported in this region, which are among the highest in
272 Europe, the densities of some animal hosts (we consider the number of roe deer and wild boar killed by hunters -
273 tableau de chasse 2002/2003 provided by The Fédération des Chasseurs and The Office National de la Chasse et
274 de la Faune Sauvage) and the incidence of human Lyme borreliosis (154 cases per 100,000 inhabitants), which is
275 one of the highest rates of all Western and Central European countries [7, 8, 30, 44].

276
277 TBEV seroprevalence among exposed forestry workers varies considerably according to country, region and
278 various studies: 19.8% to 81.3% in Eastern Poland [45, 46], 0% to 5.7% in Italy [35, 47], 7.3% in South-Western
279 Germany with variations according to district ranging from 0 to 43% [39]. The TBEV seroprevalence observed
280 in our study is similar to that reported by previous French studies conducted among subjects in contact with the
281 forest [48]. This seroprevalence is consistent with the low and stable number of cases of human clinical TBE
282 diagnosed in France (an average of about ten cases per year from 1968 to 2003), especially confined to Eastern
283 France (essentially Alsace, Lorraine, Franche-Comté) and the low prevalence in *Ixodes ricinus* which varies
284 from 0.1% to 5% in European areas where TBE is endemic [9, 49]. The incidence of TBE in France is lower
285 than that observed in neighbouring countries such as Germany (0.3 to 0.7 cases per 100,000) or Switzerland (1.5
286 to 3.3 cases per 100,000), while the greatest number of clinical cases are reported in Czech Republic, Baltic
287 States and Slovenia (incidence exceeding 10 cases per 100,000 inhabitants depending on the year) [50]. These
288 differences in incidence rates must be analysed as a function of respective vaccine coverage rates [51].

289
290 Few data are available in the literature concerning the seroprevalence of *B. microti* and/or *B. divergens* among
291 forestry workers: only three countries in Europe have published seroprevalence rates for these pathogens. The
292 seroprevalence estimated in our study among workers occupationally exposed to tick bites is comparable to that
293 reported for *B. microti* among forestry workers in Poland (4.4%) [52], but is lower than that reported for *B.*
294 *divergens* in Slovenia (8.4%) [53] and in a German study, in which 9.3% of asymptomatic seropositive subjects
295 or subjects with clinical Lyme borreliosis or who had reported a tick bite, presented anti-*B. microti* antibodies

296 and 4.9% presented anti-*B. divergens* antibodies [54]. The low seroprevalence rates for *B. microti* and *B.*
297 *divergens* observed in our study are consistent with the small number of clinical cases of human babesiosis
298 reported in the regions of our study (2 cases in Alsace to date), the identification of *B. microti* and *B. divergens*,
299 in *I. ricinus* from a forest area in Alsace and the very low prevalence rates of *B. divergens* in ticks found in the
300 French Ardennes [55-57]. It is noteworthy that the higher seroprevalence of *B. microti* compared to *B. divergens*
301 (20/1) suggests that *B. microti* infections may be more frequent in North-Eastern France. *B. divergens* infections
302 were more often identified in Western and Central France, where they are responsible for bovine babesiosis and
303 a dozen cases of human babesiosis [58]. Despite the *B. microti* seroprevalence reported in our study, no human
304 cases related to this species have been reported to date in France and only 3 cases have been reported in Europe,
305 suggesting that this species would be less pathogenic and more frequently responsible for asymptomatic or
306 paucisymptomatic infections [59-62].

307
308 *A. phagocytophilum* seroprevalence among subjects exposed to tick bites varies from 1% (UK) to 25%
309 (Slovakia) [63-64]. High seroprevalence rates (between 10 and 20%) have also been reported in Slovenia,
310 Poland, Norway and Sweden [65-68]. The low *A. phagocytophilum* seroprevalence rate observed in our study is
311 consistent with the existence of human cases in France, but suggests that such cases would be rare. This low
312 seroprevalence is also compatible with the low rate of tick infestation in France, which ranges from 0.3% in
313 Western France to 2.6% in Eastern France [57, 69] and the small number of clinical cases identified (9
314 confirmed cases between 2003 and 2009 in North-Eastern France) [10, 11]. Despite the predominance of these
315 cases in Alsace, no significant difference in seroprevalence rates was demonstrated between the various regions
316 of the study. Human anaplasmosis also appears to be rare in Europe (clinical cases reported essentially in
317 Slovenia (25), Scandinavia (25) and Poland (13)), but the high *I. ricinus* infestation rates (8 to 14% in Slovakia,
318 Serbia and Poland) and the high seroprevalence rates reported in some European countries suggest that human
319 anaplasmosis may be underestimated or asymptomatic [70-74].

320
321 In Europe, *F. tularensis* seroprevalence studies among forestry workers have reported seroprevalence rates of
322 1.7% and 4.0% in Germany, 2.1% in Poland, and 3.4% in Austria [25, 75-77]. No *F. tularensis* seroprevalence
323 study in occupationally exposed workers has been published in France to date. The seroprevalence of 5.8%
324 observed in our study is high, with rates as high as 11.2% in Champagne-Ardenne and 7.9% in Franche-Comté.
325 In Alsace, *F. tularensis* seroprevalence (3.7%) was comparable to that reported in a study conducted on 400

326 forestry workers in 1996 [4.0%; Jaulhac B., personal communication]. Epizootic diseases have been regularly
327 reported between 1993 and 2004 in Champagne-Ardenne and Franche-Comté, especially in hares, while only
328 sporadic animal cases have been reported in Lorraine and Bourgogne [78]. On the basis of human surveillance
329 data from 2002 to 2012, Champagne-Ardenne can also be classified as one of the French regions with the highest
330 incidence [13]. In our study, the highest seroprevalence was observed among silviculturists (9.2%).
331 Silviculturists, who attend to the plantation, organization and maintenance of forests, are probably also
332 frequently exposed to this agent by direct or indirect non-vectorial contacts with the animal reservoir or
333 contaminated soil earth. Furthermore, a history of tick bite was reported in only about 20% of cases of
334 tularaemia in France and in the regions of the present study, while the rate of tick infestation by *F. tularensis* is
335 low in these regions (1%) [13, 79]. Inversely, vectorial transmission of *F. tularensis* (by ticks and mosquitoes) is
336 the predominant mode of transmission in other European countries [19].

337
338 *B. henselae* is primarily transmitted to humans by cat scratch or bite. Cat fleas are well established vectors for *B.*
339 *henselae* which could be transmitted directly to humans by the bite of infected cat fleas, although this has not
340 been proven [33]. Transmission by ticks has also been suggested [3, 20-22]. Our study demonstrated a very low
341 *B. henselae* seroprevalence rate among forestry workers, which may reflect the low real risk of transmission of
342 this *Bartonella* species by *I. ricinus*, at least in this part of France, especially as high prevalence levels of DNA
343 in ticks has been found in some specific regions of Alsace (38,2%) and in Ardennes (17,6%) [21, 57].

344
345 Very few forestry workers were seropositive for at least two of the seven pathogens studied (including *B.*
346 *burgdorferi* s.l and TBEV), which may reflect the low seroprevalence of these pathogens observed in our study
347 except for *B. burgdorferi* s.l and the limited role of *I. ricinus* in the transmission of *F. tularensis* or *B. henselae*.
348 Simultaneous seropositivity for *B. burgdorferi* s.l and *A. phagocytophilum* or *Babesia* spp. was low in our study
349 (0.2% for *Anaplasma*) suggesting a very low risk of human co-infection by these pathogens.

350
351 In conclusion, our study confirms occupational exposure of forestry workers to these seven pathogens
352 transmissible by *Ixodes ricinus* and allows risk classification among forestry workers in North-Eastern France in
353 relation to these main tick-borne pathogens. Exposure to *B. burgdorferi* s.l appears to be by far the most frequent
354 type of exposure among these workers, while the levels of exposure to *B. microti*, *B. divergens*, *A.*
355 *phagocytophilum* or *B. henselae* remain low. The level of exposure to *F. tularensis* is probably related more to

356 the work environment than to the role of the vector. Incidence studies would allow a more accurate risk
357 assessment, but would be difficult to perform due to the small number of cases and the nonspecific symptoms.
358 The high density of tick populations in these regions and the potential severity of some clinical forms of these
359 infections justify continued promotion of primary and secondary prevention messages and especially personal
360 protection measures against this vector (systematic examination of the skin at the end of every working day and
361 early removal of ticks with surveillance of the bite overalls, use of clothes possibly impregnated with
362 insecticides, possible use of skin insect repellents).

363
364

365 **References**

366

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Table 1 Description of subjects included in the study according to region of residence, North-Eastern France, 2003

	TOTAL	Region of residence ^a				
		Alsace	Lorraine	Champagne -Ardenne	Bourgogne	Franche- Comté
Participation rate	54.5%	56.6%	52.6%	58.4%	46.0%	59.7%
Number included	2,975	636	885	485	400	554
Age (years)						
Mean	42.0	43.3	41.9	40.4	41.8	40.6
Median	43.0	44.0	43.0	41.0	42.5	42.0
Minimum	17.0	18.0	18.0	18.0	18.0	17.0
Maximum	81.0	68.0	77.0	73.0	68.0	81.0
Age-group (years)						
<35 years	761	118 (18.5%)	201 (22.7%)	157 (32.4%)	113 (28.2%)	164 (29.6%)
[35-44] years	915	202 (31.8%)	290 (32.8%)	142 (29.3%)	112 (28.0%)	167 (30.1%)
[45-54] years	961	243 (38.2%)	303 (34.2%)	137 (28.2%)	124 (31.0%)	151 (27.3%)
≥55 years	338	73 (11.5%)	91 (10.3%)	49 (10.1%)	51 (12.8%)	72 (13.0%)
Occupation						
Woodcutter	1145 (38.5%)	406 (63.8%)	330 (37.3%)	145 (29.9%)	122 (30.5%)	138 (24.9%)
Silviculturist	715 (24.0%)	100 (15.7%)	192 (21.7%)	138 (28.4%)	138 (34.5%)	145 (26.2%)
Rangers	347 (11.7%)	52 (8.2%)	73 (8.2%)	95 (19.6%)	77 (19.2%)	47 (8.5%)
Other (machinery operators...)	221 (7.4%)	38 (6.0%)	47 (5.3%)	49 (10.1%)	39 (9.8%)	43 (7.7%)
Multiple activities	547 (18.4%)	40 (6.3%)	243 (27.5%)	58 (12.0%)	24 (6.0%)	181 (32.7%)

^a15 subjects worked in these regions, but lived outside of this zone.

Comment citer ce document :

Rigaud, E. (Auteur de correspondance), Jaulhac, B., Garcia-Bonnet, N., Hunfeld, K. -P., Femenia, F., Huet, D., Goulvestre, C., Vaillant, V., Deffontaines, G., Abadia-Benoist, G. (2016). Seroprevalence of seven pathogens transmitted by the Ixodes ricinus tick in forestry workers in France. *Clinical Microbiology and Infection*, 22 (8), 1-27. DOI : 10.1016/j.cmi.2016.05.014

Table 2 Prevalence of anti-*B. burgdorferi*, anti-TBEV, anti-*A. phagocytophilum*, anti-*Babesia*, anti-*F. tularensis*, anti-*B. henselae* antibodies in occupationally exposed workers in North-Eastern France according to occupation and region of residence, 2003

	<i>B. burgdorferi</i> sI		TBEV		<i>A. phagocytophilum</i>		<i>B. microti</i> , <i>B. divergens</i>		<i>B. henselae</i>		<i>F. tularensis</i>	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Occupation												
Woodcutter	200	(17.5)	27	(2.4)	23	(2.1)	5	(1.5)	21	(1.9)	50	(4.5)
Silviculturist	106	(14.8)	20	(2.8)	11	(1.76)	9	(4.1)	7	(1.0)	63	(9.2)
Ranger	26	(7.5)	6	(1.7)	4	(1.2)	2	(3.2)	9	(2.6)	8	(2.3)
Other (machinery operators...)	18	(8.2)	2	(0.9)	1	(0.5)	1	(2.2)	3	(1.4)	10	(4.6)
Multiple activities	69	(12.6)	13	(2.4)	11	(2.1)	4	(2.7)	8	(1.5)	33	(6.3)
TOTAL	419	(14.1)	68	(2.3)	50	(1.7)	21	(2.6)	48	(1.7)	164	(5.7)
Region of residence												
Alsace	171	(26.9)	20	(3.2)	16	(2.6)	6	(2.5)	13	(2.1)	22	(3.6)
Lorraine	146	(16.5)	20	(2.3)	11	(1.3)	8	(3.2)	14	(1.6)	31	(3.6)
Champagne-Ardenne	40	(8.2)	8	(1.7)	7	(1.4)	4	(3.1)	15	(3.1)	53	(11.2)
Bourgogne	30	(7.5)	9	(2.3)	4	(1.0)	2	(2.7)	2	(0.5)	17	(4.3)
Franche-Comté	31	(5.6)	10	(1.8)	12	(2.3)	1	(0.9)	4	(0.8)	40	(7.9)
TOTAL	418	(14.1)	67	(2.3)	50	(1.7)	21	(2.6)	48	(1.6)	163	(5.7)

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Table 3 Odds ratios of anti-*B. burgdorferi* antibody prevalence in occupationally exposed workers in North-Eastern France, adjusted for age, occupation and region of residence, 2003

	Anti- <i>B. burgdorferi</i> sI IgG			
	TOTAL	Seropositive (%)	AOR ^a (95%CI)	p
Age-group				
< 35 years	761	31 (4.1)	1	
[35-44] years	915	114 (12.5)	2.97 [1.96-4.50]	< 10 ⁻⁴
[45-54] years	961	189 (19.7)	5.00 [3.35-7.45]	< 10 ⁻⁴
≥55 years	338	85 (25.1)	8.02 [5.13-12.54]	< 10 ⁻⁴
Occupation				
Other (machinery operators...)	242	18 (8.2)	1	
Woodcutter	1145	200 (17.5)	2.00 [1.19-3.39]	0.0093
Silviculturist	715	106 (14.8)	2.22 [1.29-3.82]	0.0038
Ranger	347	26 (7.5)	1.02 [0.53-1.94]	0.9620
Multiple activities	526	69 (12.6)	2.12 [1.20-3.76]	0.0098
Region of residence				
Franche-Comté	554	31 (5.6)	1	
Alsace	636	171 (26.9)	6.08 [3.98-9.28]	< 10 ⁻⁴
Lorraine	885	146 (16.5)	3.28 [2.17-4.95]	< 10 ⁻⁴
Champagne-Ardenne	485	40 (8.2)	1.76 [1.07-2.89]	0.0261
Bourgogne	400	30 (7.5)	1.46 [0.86-2.49]	0.1644

^a odds ratio adjusted for age-group, occupation and region of residence

Table 4 Odds ratios of anti-*F. tularensis* antibody prevalence in occupationally exposed workers in North-Eastern France, adjusted for age, occupation and region of residence, 2003

	Anti- <i>F. tularensis</i> IgG			
	TOTAL	Seropositive (%)	AOR ^a (95%CI)	p
Age-group				
< 35 years	733	34 (4.6)	1	
[35-44] years	893	56 (6.3)	1.42 [0.91-2.22]	0.1243
[45-54] years	925	57 (6.2)	1.51 [0.96-2.35]	0.0721
≥55 years	324	17 (5.2)	1.20 [0.65-2.21]	0.5532
Occupation				
Other (machinery operators...)	217	10 (4.6)	1	
Woodcutter	1109	50 (4.5)	1.37 [0.65-2.87]	0.4033
Silviculturist	684	63 (9.2)	2.47 [1.20-5.10]	0.0142
Ranger	343	8 (2.3)	0.54 [0.20-1.43]	0.2172
Multiple activities	522	33 (6.3)	1.79 [0.83-3.87]	0.1398
Region of residence				
Lorraine	873	31 (3.6)	1	
Alsace	629	22 (3.6)	1.09 [0.61-1.92]	0.7796
Champagne-Ardenne	474	53 (11.2)	3.82 [2.39-6.12]	< 10⁻⁴
Bourgogne	396	17 (4.3)	1.29 [0.70-2.40]	0.4141
Franche-Comté	547	40 (7.9)	2.29 [1.40-3.72]	0.0009

^a odds ratio adjusted for age-group, occupation and region of residence

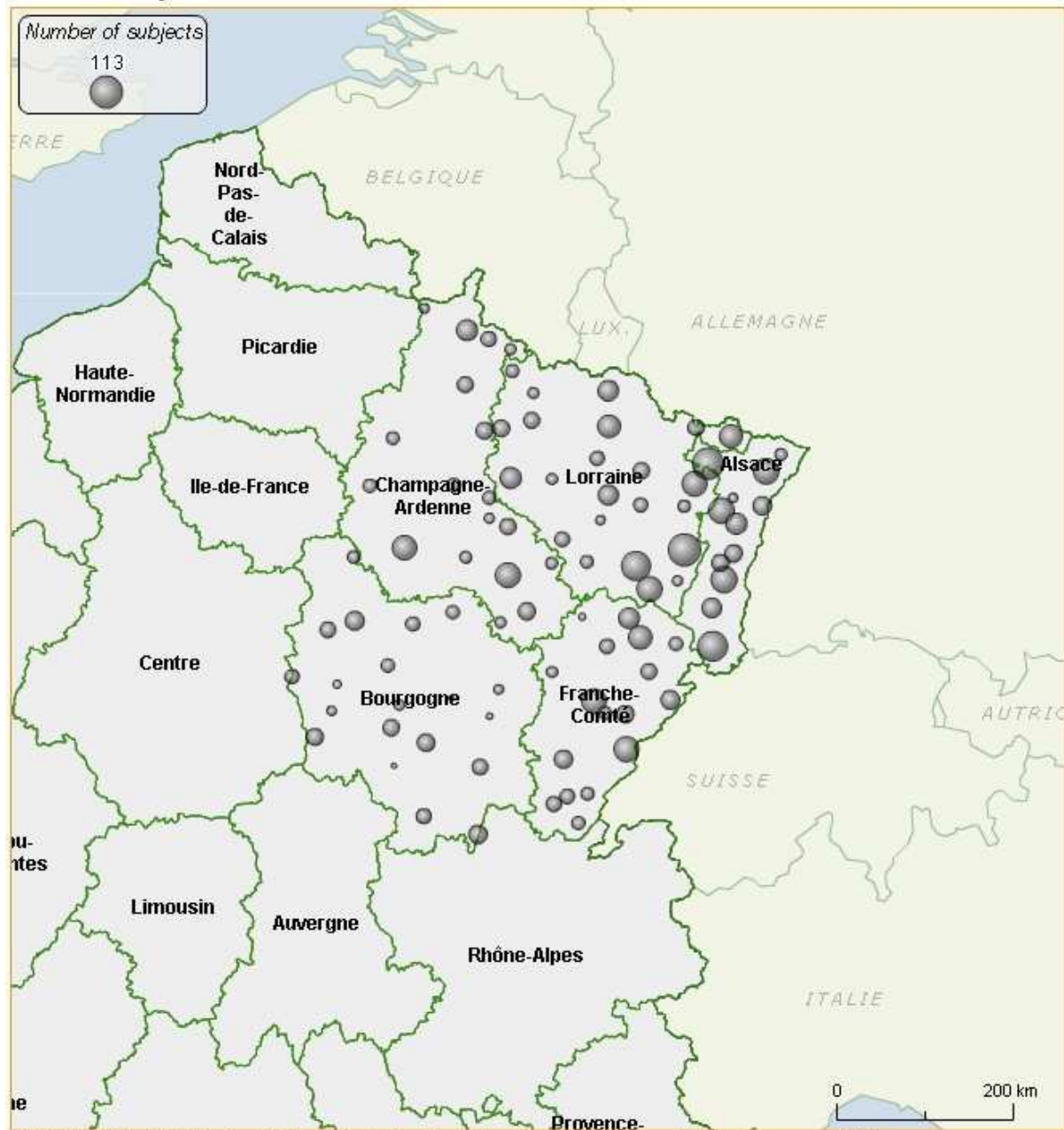
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L'Observatoire
des Territoires

Number of subjects

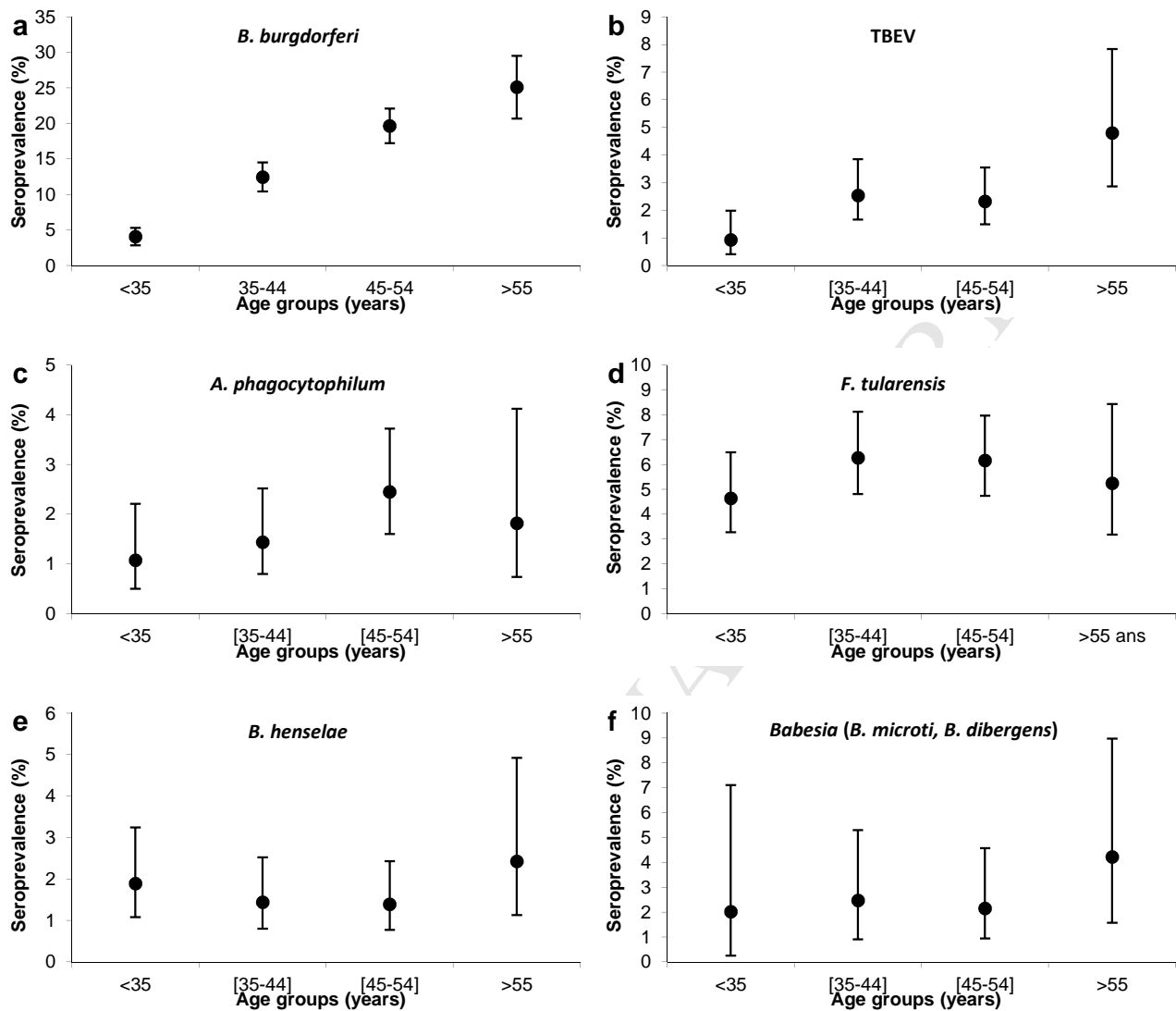


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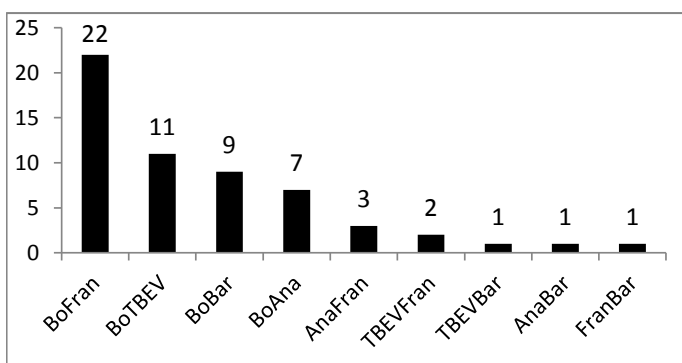
Fig. 2 Prevalence of tick-borne pathogens antibodies in occupationally exposed workers in North-Eastern France by age-group, with 95% confidence intervals, 2003 (**a** anti-*B. burgdorferi* antibodies, **b** anti-TBEV antibodies, **c** anti-*A. phagocytophilum* antibodies, **d** anti-*F. tularensis* antibodies, **e** anti-*B. henselae* antibodies, **f** anti-*Babesia* antibodies)



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Fig. 3 Seropositivities for different pathogens among 2,908 subjects analysed for *B. burgdorferi* sl, TBEV, *A. phagocytophilum*, *B. henselae* and *F. tularensis*



Bo : *Borrelia burgdorferi* sl, Ana : *Anaplasma phagocytophilum*,
Bar : *Bartonella henselae*, Fran : *Francisella tularensis*