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1 **Sensitivity of bovine tuberculosis surveillance through intradermal tests in cattle in France:**
2 **an evaluation of different scenarios**

3

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23

24 **Abstract**

25 The current situation regarding bovine tuberculosis (TB) in Europe is spatially heterogeneous,
26 with stagnating or increasing trends in TB prevalence in many European regions, underlying
27 the challenge in controlling this disease. In France, in spite of the implementation of two
28 control programs in 2010-2012 to eradicate the disease and maintain the TB-free status, TB
29 prevalence has continued to increase, underlying the need to reinforce and adapt surveillance
30 measures. The goal of this study was to evaluate the effectiveness of TB surveillance in high-
31 risk areas in metropolitan France, with an emphasis on the criteria to select herds and
32 animals within herds in the context of programmed surveillance and movement testing.

33 The fraction of TB-infected herds detected by the surveillance was quantified using a
34 stochastic scenario tree modelling approach, with input parameter values based on
35 surveillance and cattle traceability data and literature. The detection fraction was assessed for
36 the current surveillance system and for alternative scenarios.

37 The model predicted that the median detection fraction of infected herds by the current
38 programmed surveillance in high-risk areas, which consists in annual testing of herds with a
39 minimum age of testing of 24 months, was 71.5% (interquartile interval: 47.4-89.4). The
40 results showed a significant gain of the detection fraction with a decrease from 24 to 12
41 months old (83.5% [60.6-95.9]) or to six weeks old (91.3% [71.6-99.0]). Regarding pre-
42 movement surveillance, tests are currently mandatory for bovines that originate from a
43 previously infected herd or from a herd epidemiologically linked to a TB-infected herd. The
44 median detection fraction predicted by the model for this surveillance scenario was 1.2% [0.7-
45 1.8]. For the alternative scenario, where surveillance would be extended to all herds in high-
46 risk areas, the model predicted a significant increase of the detection fraction to 26.5% [18.1-
47 37.9]. The results were sensitive to the following input values: the number of infected
48 bovines within herds, and to a lower extent, the comparative intradermal tuberculin test
49 sensitivity, for both models, and surveillance coverage for the model on pre-movement
50 surveillance.

51 Our study underlines several complementary ways to improve the detection of infected herds,
52 which is critical for implementing control measures and epidemiological investigations as early
53 as possible. These necessary changes in surveillance must be accompanied by a global
54 reflexion on surveillance financing.

55

56 **Keywords**

57 Bovine tuberculosis, scenario tree, detection fraction, effectiveness, programmed surveillance,
58 movement testing, sensitivity assessment

59

60 Introduction

61 Bovine tuberculosis (TB) is a chronic disease that generally, but not exclusively, results from
62 infection of cattle by *Mycobacterium bovis*. Cattle are also sensitive to infection by other
63 related bacteria belonging to the *Mycobacterium tuberculosis* complex (esp. *M. caprae*, *M.*
64 *microti* or *M. tuberculosis*) (Prodinger et al., 2005; Michelet et al., 2017). *M. bovis* is recognised
65 as a potentially important cause of human tuberculosis worldwide (Olea-Popelka et al., 2017).
66 Infected animals potentially excrete *M. bovis* in different tissues or materials, depending on
67 the clinical manifestations. As lungs are the preferred site of infection in cattle, respiratory
68 expectorations and excretions represent the main infectious materials, but other materials,
69 such as urine, faeces and milk can also lead to contamination of other animals or humans
70 (Grange and Yates, 1994; Menzies and Neill, 2000; Villarreal-Ramos et al., 2018). Finally, as
71 Mycobacteria are resistant in the environment (Maddock, 1933; Barbier et al., 2017), indirect
72 exposure can also take place (Menzies and Neill, 2000; Phillips et al., 2003). The disease leads to
73 important economic burden due to clinical manifestations and losses in infected animals,
74 condemnation of animals with lesions at slaughterhouse, and the transmission to humans
75 through direct/indirect contacts or ingestion of foodstuff (Caminiti et al., 2016). For all these
76 reasons, several countries have implemented surveillance and control programmes in order to
77 detect and eradicate the disease in ruminants, and especially cattle (Rivière et al., 2014). Yet,
78 stagnating or increasing trends in prevalence of TB-positive cattle herds demonstrate that
79 control and eradication of this disease is a challenge (European Food Safety Authority (EFSA)
80 and European Centre for Disease Prevention and Control (ECDC), 2018).

81 In metropolitan France, TB control strategies implemented in cattle herds at the end of the
82 20th century allowed the country to obtain the official free status in 2001 and to alleviate
83 surveillance. Yet, TB prevalence started to increase again from 2005, triggering the
84 implementation of two control programs in 2010 and 2012 to eradicate the disease and
85 maintain the TB-free status. Since 2010, the number of cases has stabilised, with
86 approximately 100 outbreaks detected annually in a few localized areas, especially in south-
87 western France (Nouvelle Aquitaine region) which gathers 80% of cases since several years
88 (Delavenne et al., 2019). Control strategies in infected herds include the slaughter of the entire
89 herd or part of the herd, coupled with risk assessment and regular testing during several
90 years until full eradication of infected bovines in the herd. Facing a slight increased
91 prevalence at country-scale, there is a need to reinforce and adapt surveillance measures to
92 differing regional contexts (French General Directorate for Food, 2018a).

93 TB surveillance in cattle in metropolitan France is based on several components: (i) the
94 inspection of all bovines slaughtered for human consumption; (ii) programmed surveillance in
95 herds, using an intradermal tuberculin (IDT) test or a gamma-interferon (IFNg) test on all
96 bovines aged over 12 or 24 months depending on the local epidemiological situation; (iii) pre-
97 or post-movement testing by IDT test under specific conditions, (iv) clinical surveillance and
98 (v) epidemiological investigations implemented when TB cases are identified. A specific
99 surveillance program, Sylvatub, also targets tuberculosis in wildlife (cervids, wild boars,
100 badgers) since 2011 (Réveillaud et al., 2018).

101

102 In areas where prevalence has been lower than 0.1% for six years or more, programmed
103 surveillance, *i.e.* regular testing of bovines by IDT or IFNg, is not applied anymore (French
104 Ministry of Agriculture, 2003). In the rest of the country, the rhythm of programmed

105 surveillance in herds varies in frequency, from annual to every four years, depending on the
106 local epidemiological situation and the risk level (French Ministry of Agriculture, 2003). In high-
107 risk areas, referred as reinforced prophylaxis zones (RPZ), the surveillance is strengthened with
108 annual testing of herds. There are two definitions of RPZ: (i) “historic” RPZ which include the
109 communes located in a 10-km radius around pastures used by herds found to be TB-infected
110 within the last five years and the communes located in a 10-km radius from capture sites of
111 TB-infected badgers within the last five years, and (ii) “prospecting” RPZ which include
112 communes located in a 2-km radius around pastures of recently identified and isolated cases
113 (French General Directorate for Food, 2018b).

114

115 For programmed surveillance and movement testing, IDT screening is performed using either a
116 single intradermal test (SIT) or a single intradermal comparative cervical tuberculin test (SICCT)
117 depending on knowledge of the risk of atypical reactions. The IDT and IFNg tests are
118 performed and interpreted as recommended by Council Directive 64/432/EEC. Testing in RPZ
119 is conducted by SICCT only.

120

121 Following a request of the Directorate for food of the French Agriculture ministry, an
122 evaluation of the effectiveness of surveillance was conducted, with an emphasis on the
123 criteria to select herds and animals within herds in the context of programmed surveillance
124 and movement testing. The present study aims to answer to the following questions
125 regarding:

- 126 1) programmed surveillance in RPZ: what is the gain in surveillance sensitivity expected
127 by a decrease of the minimum testing age from 24 months old to 18 months old, to
128 12 months old or to 6 weeks old?
- 129 2) movement surveillance: what is the gain in surveillance sensitivity expected by the
130 extension of pre-movement testing to all herds in RPZ (in contrast to testing only
131 bovines moving from previously infected herds and herds with an epidemiological link
132 with an infected or previously-infected herds)?

133

134 **Methods**

135 Detection fraction and scenario tree

136 The sensitivity of the surveillance corresponds in the case of an exotic pathogen to the
137 probability to detect the disease if it is present at or above a defined threshold in the
138 population. In the case of an endemic disease, as TB in France, surveillance effectiveness may
139 be evaluated using the detection fraction. This measure has been used previously to evaluate
140 the effectiveness of surveillance in poultry slaughter establishments (Huneau-Salaun et al.,
141 2015).

142 The detection fraction depends on the sensitivity and coverage of surveillance; the last
143 corresponding to the proportion of the population included in the surveillance. When the risk
144 level varies between epidemiological units, detection fraction is obtained using the following
145 equation:

146

$$DF = \sum_{g=1}^n \frac{x_g \times p_g \times SeU_g \times c_g}{P}$$

147 where n is the number of groups dividing the population under surveillance (the groups
148 corresponding to categories of the population showing different levels of TB risks), x_g is the
149 proportion of the population included in group g , p_g is the prevalence of the disease in
150 group g , SeU_g is the sensitivity of the surveillance in group g , c_g is the surveillance coverage
151 in group g and P is the prevalence in the population.

152 Surveillance sensitivity in a herd of group g (SeU) may be calculated using the scenario tree
153 method (Martin et al., 2007), which has been designed to take into account different levels of
154 risk in the population. This approach relies on a tree structure that describes the study
155 population and the surveillance component and allows to explicitly estimate the probability
156 that an infected animal in the herd is detected (FAO 2014). The scenario tree defines all
157 possible paths leading to the detection of an infected animal as a series of events, each
158 associated to a probability of occurrence (Martin et al., 2007; Food and Agriculture Organization
159 (FAO), 2014). This approach includes several steps: the stratification of the population in
160 several risk groups (within which each epidemiological unit has the same probability to be
161 detected), the description of the surveillance component as a tree taking into account the
162 different surveillance steps until the detection of an infected unit and, finally, the
163 quantification of the surveillance sensitivity. The epidemiological unit in our study is the herd;
164 and an infected herd corresponds to a herd with at least one infected bovine.

165 Programmed surveillance

166 As the first question deals with the evaluation of the detection fraction by the surveillance of
167 TB in RPZ, the analysis was restricted to herds located in those areas. The list of herds in
168 RPZ was extracted from the French National Cattle Register using the list of communes
169 included in RPZ in 2017-2018. These data concerned the departments of Côte d'Or and
170 Calvados and those included in the regions Nouvelle-Aquitaine and Occitanie and represented
171 95% of the RPZ areas in France. A department is a French administrative and territorial
172 division covering a mean surface area of 5,800 km².

173 Within RPZ, the cattle population was divided into three groups regarding TB risk, which
174 varies between types of production: beef/mixed herds, dairy herds and small herds. The
175 stratification in risk groups allows to characterize the higher risk of TB occurrence in
176 beef/mixed herds in comparison with dairy herds (Bekara et al., 2014) and to take into
177 account the difference in herd size. The type of production of each herd was determined
178 from a typology based on the mean number and breed of females aged two years or over,
179 the number of births and the presence of a fattening activity (Sala et al., 2019), using data
180 from the French National Cattle Register. A small herd corresponded to a herd with less than
181 ten births per year, a mean number of females aged two years or over under ten and a
182 number of males slaughtered for meat under ten. The proportions of herds within each risk
183 group was calculated for each department including a RPZ.

184 The calculation of surveillance sensitivity at the herd level in each risk group was based on the
185 scenario tree described in Figure 1:

186

$$SeU = 1 - (1 - P_{bov_test} \times Se)^{N_{bov_inf}}$$

187 with P_{bov_test} being the probability for a bovine to be tested (which depends on the minimum
188 age of testing and the herd size), Se the sensitivity of the test and N_{bov_inf} the number of
189 infected bovines in a herd.

190 Parameter values and data sources are provided in Table 1. For each herd in RPZ, the total
191 number of bovines (N_{bov}) and the number of bovines in each age class (six weeks and over,
192 12 months and over, 18 months and over and 24 months and over) were calculated at the
193 beginning of the 2017/2018 surveillance campaign (November 1st, 2017) to determine the
194 proportion of bovines tested (P_{bov_test}) in each surveillance scenario. We stress that the
195 proportions of bovines in each age class were the same at the end of the surveillance
196 campaign (March 31st, 2018). Regarding the implementation of the SICCT, two reagents are
197 used in France: Bovituber® purified protein derivatives and Avituber® antigen (Zoetis,
198 Malakoff, France). The sensitivity of the test (Se) assumes that the test is interpreted as
199 follows: the result is considered to be negative if the increase in skin thickness at the bovine
200 site (dB) of infection is below 2 mm or, when above, if the increase of skin thickness at the
201 bovine site is approximately equal to the increase at the avian site (dA) of injection (i.e. dB-
202 dA < 1 mm). The result is considered to be positive if dB > 2 mm and dB-dA > 4 mm. A test
203 is considered to be inconclusive when dB > 2 mm, but 1 mm < dB-dA < 4 mm.

204
205 The number of infected bovines (N_{bov_inf}) was determined from test results conducted as part
206 of the total stamping out of the outbreaks in 2014 (Cavalerie et al., 2015). Among the 61
207 culled herds, 32 presented only one positive case (detected by SICCT test). In the 29 other
208 herds, on average six bovines had clinical lesions, with a high variability among departments.
209 A negative binomial regression model was adjusted to these data and used (as a zero-
210 truncated distribution) to simulate a number of infected bovines per herd (using package
211 countreg in R (R Core Team, 2018)). For the risk group corresponding to small herds, the
212 number of infected bovine was fixed to one.

213 In absence of data on the methods of dealing with each outbreak (partial vs. total cull),
214 herd-level prevalence values for each type of production were calculated, for each department
215 with RPZ, using only the number of cases detected in 2017 and therefore did not take into
216 account infected herds detected before 2017 and still under control. Herd-level prevalence in
217 “small herds” group was assumed to be equal to the prevalence in “beef/mixed herds”
218 group. Population prevalence was calculated as the mean prevalence within each risk group,
219 weighted by the proportion of herds within each group. These latter proportions were
220 calculated from the French National Cattle Register data for the period extending from July
221 1st, 2017 to June 30th, 2018.

222 In RPZ, all herds are subject to annual programmed surveillance and consequently herd
223 coverage was assumed to be 100% for each scenario. The detection fraction was calculated
224 for four alternative scenarios depending on the minimum age of testing. For each analysis, all
225 herds in RPZ were covered by surveillance and all bovines that reached the age of testing
226 were supposed to be tested.

227 Pre-movement surveillance

228 Inter-herd movement surveillance depends on both the sanitary state and level of risk
229 regarding TB in the herd of origin, the duration of the movement between the origin and
230 destination herds and the production type of the destination herd (French General Directorate
231 for Food, 2017). These rules concern bovines aged six weeks and over. Pre-movement tests

232 are mandatory for animals that originate from a previously infected herd that recovered its
233 TB-free status after an outbreak (French Ministry of Agriculture, 2003; French General Directorate
234 for Food, 2017) or from the herds with a neighbourhood link with a TB-infected herd, i.e. with
235 proximity of pastures (referred as herds with an epidemiological link, hereafter).

236 The current pre-movement surveillance is conducted only in previously infected herds and in
237 herds with an epidemiological link. In the alternative scenario, surveillance would be extended
238 to all herds in RPZ and therefore surveillance coverage (c) was fixed to 100%. For the
239 scenario describing current surveillance, coverage was calculated by the following equation:

$$240 \quad c$$
$$241 \quad = \frac{\text{number of previously infected herds} + \text{number of herds with an epidemiological link}}{\text{number of herds within RPZ} + (1-z) \times \text{number of herds with an epidemiological link}}$$

242 with z being the proportion of herds with an epidemiological link that are located within a
243 RPZ. In the department Côte d'Or, 80.6% of herds with an epidemiological link were located
244 in a RPZ; therefore, z was fixed to 80% for all departments with a RPZ. Preliminary analyses
245 with z values ranging from 50 to 100% provided the same results (data not shown). Because
246 RPZ are defined around previously infected herds, these latter were all included in a RPZ. The
247 number of previously infected herds and the number of herds with an epidemiological link
248 were provided by the Directorate for food of the French Agriculture ministry for the
249 departments Côte d'Or and Calvados and for the departments within the regions Occitanie
250 and Nouvelle-Aquitaine.

251 The scenario tree depicting the different steps in the calculation of probability to detect an
252 infected animal (SeU) is described in Figure 2. Six risk groups were defined, considering two
253 levels of TB risk (i.e. herds in RPZ or/and herds with an epidemiological link versus previously
254 infected herds) and the type of production (beef/mixed, dairy, small herds). It was assumed
255 that herds in RPZ and herds with an epidemiological link presented the same risk of TB
256 infection. The probability to detect an infected animal (SeU) in a herd by a pre-movement
257 test corresponds to:

$$258 \quad SeU = 1 - (1 - P_U \times Se)^{s_g}$$

259 with Se corresponding to the sensitivity of the test, P_U the intra-herd prevalence and s_g the
260 number of bovine sales from the herd.

261 The proportion of bovines sold was determined from data on movement traceability recorded
262 in the French National Cattle Register for 2017-2018, as the ratio between the number of
263 sales of bovines (aged six weeks and over at the date of departure) and the total number of
264 bovines.

265 TB prevalence in previously infected herds was calculated as the proportion of TB-infected
266 herds identified in 2017 among herds that had already been infected during 2013-2016. TB
267 prevalence in other herds was calculated as the number of TB-infected herds identified in
268 2017 among herds that had not been infected during 2013-2016. Intra-herd prevalence was
269 obtained as the number of infected cattle per herd (predicted by the zero-truncated negative
270 binomial distribution for beef/mixed and dairy cattle herds and fixed to one for small herds)
271 divided by the total number of bovines per herd (N_{bov}).

272 Model simulations

273 The analyses were conducted in R (R Core Team, 2018) and the model was simulated 10,000
274 times for each scenario to take into account the variability in input parameter values. For
275 each analysis, a Wilcoxon-Mann-Whitney test was used to compare the detection fractions
276 between the scenario describing current surveillance and each alternative scenario. For each
277 comparison of two scenarios, the test was applied on a subset of 25 values of fraction
278 detection randomly drawn from the 10,000 simulations. The alpha statistical error risk
279 considered was 0.05.

280 Sensitivity analysis

281 A sensitivity analysis, based on a Latin hypercube sampling (LHS) (McKay et al., 1979), was
282 conducted to assess the influence of input parameter values on the detection fraction
283 predicted by the model. LHS consists in dividing the distribution of input parameters in K
284 equiprobable sections, then in sampling one value in each section. In consequence, K unique
285 subsets of parameter values are created by combining at random one sampled value for each
286 parameter. K was fixed to 50.

287 For each parameter, a linear correlation coefficient between initial parameter values and
288 detection fractions predicted by the model was calculated; a t-test was used to evaluate
289 whether the correlation coefficient was significantly different from zero. The sensitivity
290 analysis was conducted 100 times to obtain mean correlation coefficients and t-test
291 probabilities. A Bonferroni correction was applied to adjust for multiple comparisons: each
292 correlation was thus evaluated to the significance threshold of α/S , with α the initial
293 significance threshold ($\alpha = 0,05$) and S the number of parameters included in the sensitivity
294 analysis.

295

296 **Results**

297 Programmed surveillance

298 The median detection fraction predicted by the model for the current programmed
299 surveillance in RPZ herds (based on a minimum age of testing of 24 months) was estimated
300 to be 71.5% [interquartile interval: 47.4-89.4]. The model predicted that a decrease of the
301 minimum age of testing to 18 months would lead to an increase of the detection fraction to
302 76.7% [52.7-93.1]. With a minimum age of 12 months, the detection fraction was estimated
303 to be 83.5% [60.6-95.9]. At last, detection fraction was estimated to be 91.3% [71.6-99.0]
304 with a testing of all bovines aged six weeks and over (Table 2). Intervals are wide as a result
305 of limitations in our knowledge on how the tests perform and the expected prevalence in
306 infected herds.

307 The decrease of the minimum age of testing from 24 to 18 months old did not significantly
308 increase the detection fraction ($W = 395$, $p = 0.112$). However, the gain of detection fraction
309 became significant with a decrease from 24 to 12 months old ($W = 423$, $p = 0.032$) or to six
310 weeks old ($W = 145$, $p < 0.001$).

311 Pre-movement surveillance

312 The mean detection fraction predicted by the model for the current pre-movement
313 surveillance is 1.2% [0.7-1.8]. The scenario encompassing all herds within the RPZ, and not
314 only those that recovered the free status after an infection, or those with an epidemiological

315 link, will increase the detection fraction to 26.5% [18.1-37.9] (Table 3). This difference was
316 significant (Mann-Whitney-Wilcoxon test: $W = 0$, $p < 0.001$).

317 Sensitivity analysis

318 For the model dealing with the current programmed surveillance as well as the model on
319 pre-movement surveillance, the sensitivity analysis underlined a significant increase of the
320 detection fraction with an increasing number of infected bovines within herds and for SICCT
321 test sensitivity (Table 4). It also showed a significant effect for surveillance coverage for the
322 model on pre-movement surveillance.

323

324 **Discussion**

325 In France, the current TB surveillance system in cattle encompasses systematic post-mortem
326 examination in slaughterhouses, periodic testing of cattle herds (programmed surveillance) and
327 in some circumstances intradermal testing of cattle during movement between herds (French
328 Ministry of Agriculture, 2003). Our study provides an assessment of the effectiveness of
329 programmed and movement testing, using a stochastic approach to take into account the
330 known variability in model parameter values, especially test sensitivity, expected prevalence in
331 infected herds and heterogeneities in the populations tested; this variability explains the
332 relatively wide interquartile intervals around median detection fractions. Our results underlines
333 several, complementary, ways to improve the detection of infected herds. This assessment
334 follows a previous evaluation of Sylvatub, the surveillance system of TB in wildlife (Rivière et
335 al., 2015) and is part of a comprehensive plan to eradicate the disease (French General
336 Directorate for Food, 2018a).

337 Our results showed that the current programmed surveillance in RPZ allows to detect 71.5%
338 of infected herds (median detection fraction). This may be partly explained by the limited
339 cover of our current TB surveillance system. First, IDT testing frequency depends on the
340 sanitary situation, thus ranging from an annual testing in zones with an unfavourable
341 epidemiological situation to a testing every two, three or four years as the situation
342 improves; finally, in zones with the most favourable situation, herds are not subject to
343 programmed testing anymore. In RPZ, because of the high risk of TB exposure, herds are
344 tested annually. Second, until 2010, only animals aged 24 months and over were subject to
345 surveillance but local changes in surveillance modalities have been applied recently with a
346 minimum age of testing ranging from 12 to 24 months depending on the department. In
347 spite of these local differences in surveillance application, the analysis considered a same
348 minimum age of testing for all herds in each surveillance scenario, which means that the
349 predicted detection fraction for the current surveillance system is slightly underestimated.

350 In 2017/2018, among the departments included in the analysis, 8,853 herds were located in
351 RPZ communes and were subject to surveillance. These departments gathered about 95% of
352 herds in RPZ, which makes a total of 9,320 herds in RPZ in metropolitan France. This number
353 is still under-estimated as the herds located outside the RPZ but with bovines pasturing in
354 those RPZ would also be covered by the surveillance. By considering the mean proportion of
355 herds in each risk group (56% of dairy/mixed herds, 16% of dairy herds and 28% of small
356 herds) and the prevalence for each risk group (Table 1), 51 herds in RPZ were estimated to
357 be infected. This value is likely underestimated as the estimation of prevalence considered
358 only outbreaks detected in 2017, i.e. apparent prevalence. Accordingly, based on the model-

359 predicted detection fraction, the current programmed surveillance was predicted to detect 35
360 infected herds, while results of programmed surveillance for 2015-2017 reported the detection
361 of 58 herds annually (Delavenne et al., 2019). The sensitivity analysis showed that the
362 detection fraction depended primarily on the number of infected bovines within the herd,
363 and therefore the ability of surveillance to detect infected herds depends on the extent of
364 the diffusion of the pathogen within the herd.

365 Our study indicated that a decrease of the minimum age of testing to 12 months old or six
366 weeks old would increase the median detection fraction by 12 and 20% in comparison to
367 current surveillance, which would correspond to six and ten additional herds detected,
368 respectively. Even if the number of additional outbreaks detected seems rather limited, it is
369 worth to identify each of them as early as possible to implement control measures limiting
370 the spread to other herds and the environment, and consequently the occurrence of
371 secondary outbreaks. Furthermore, epidemiological investigations to find the source of
372 infection, identify epidemiological links with other herds, etc. will allow the detection of
373 related outbreaks, which will themselves be subject to epidemiological investigations and
374 control measures.

375 In favourable epidemiological situation, when bovine TB prevalence is below 0.2%, the age of
376 testing can be raised to 24 months, instead of six weeks (European Commission (EC), 1964;
377 French Ministry of Agriculture, 2003). However, the situation can hardly be considered as
378 favourable in RPZ and animals should be subject to testing when they are more than six
379 weeks old. Implementing such a minimum age of testing would be in accordance with the
380 current French and European regulations. However, this would require to overcome the
381 difficulties linked with the testing of young animals, as the tuberculin injection technique has
382 to be precise (World Organisation for Animal Health (OIE) 2009), which requires good restraining
383 conditions. Moreover, if tests are to be performed from six weeks of age, more animals will
384 be subject to a test, which will lead to more positive or inconclusive results. Part of
385 concerned animals will be truly infected, and it is obviously interesting to detect them but
386 others will be false positive. In France and other countries, a lack of acceptability has been
387 described (in relation with these false “non-negative” results) (Ciaravino et al., 2017; Crozet et
388 al., 2019) and must be addressed if more stringent measures, such as testing younger animals,
389 are to be implemented.

390 The effectiveness of pre-movement surveillance was predicted by the model to be limited,
391 with a median detection fraction of about 1%. In 2017-2018, in the departments Côte d’Or
392 and Calvados and in the departments of the regions Occitanie and Nouvelle-Aquitaine, there
393 were 327 previously-infected herds and 659 herds with an epidemiological neighbourhood link,
394 that is 986 herds subject to pre-movement surveillance. In some departments of the region
395 Nouvelle-Aquitaine, no information was available on the nature of the risk regarding TB,
396 which could be an epidemiological link by neighbourhood, by movement from a TB-infected
397 herd, a re-emergence from a previous TB infection or a link with a wildlife outbreak,
398 suggesting that some herds are likely excluded from this surveillance despite a potential risk.
399 Assuming that the herds covered by surveillance have the same sale pattern than the entire
400 population (regarding the annual number of sales), 85% carried out at least one sale of a
401 bovine aged six-weeks or more. Based on prevalence values in each risk group and the

402 detection fraction predicted by the model, seven of these herds were infected, among which
403 less than one herd per year was detected by the current surveillance system. This prediction
404 aligns with the results of surveillance in recent years: in 2014, 1% of the 105 incident herds
405 were identified through movement surveillance (including pre- and post-movement
406 surveillance) (Cavalerie et al. 2015), and for the 2015-2018 period, only two outbreaks were
407 found by a test during a movement (Delavenne et al., 2019).

408 If pre-movement tests had been applied to all herds in RPZ and not only to previously
409 infected herds and herds with an epidemiological link, 7,788 herds would have been
410 concerned, among which 45 herds would be infected. Our model showed that pre-movement
411 surveillance in such conditions would have allowed detecting 12 of those herds. The
412 sensitivity analysis showed that surveillance coverage could alter detection fraction, suggesting
413 that the detection fraction may vary between departments depending on the number of
414 herds in RPZ. Overall, given that cattle movements between herds play an important role in
415 TB spread, which was also demonstrated in France (Palisson et al., 2016), it is relevant to test
416 bovines from at-risk areas (like RPZ), before departure from the herd, in order to limit
417 disease spread.

418 Currently, pre-movement surveillance is not mandatory for bovines (in previously infected
419 herds and herds with an epidemiological link) that have been tested within the four months
420 preceding the movement (French General Directorate for Food, 2017). This derogation was not
421 considered in the model, which therefore overestimated the predicted detection fraction for
422 the two scenarios. Extending this derogation to all RPZ herds would further alter the
423 detection fraction; indeed, this rule implies a test exemption during four months each year,
424 since RPZ herds are subject to annual programmed surveillance. Therefore, the number of
425 herds covered by the alternative surveillance scenario would be decreased by about one third
426 each year. An IDT leads to a desensitisation, which is a decrease or an inability of the test
427 to detect the infection, during the six weeks following the test, which explains that it is
428 needed to respect such a delay between two IDT (Monaghan et al., 1994). Exempting bovines
429 from a pre-movement test during a six-week (rather than a four-month) delay after a
430 previous IDT would therefore be recommended to improve the surveillance effectiveness.

431 In addition to pre-movement surveillance, post-movement testing is required when the delay
432 of movement exceeds six days or when the bovine moves to a herd with a high-turnover
433 rate from a department where the cumulative five-year prevalence exceeds the current
434 national-scale mean prevalence. Using the same modelling approach, we found a very limited
435 sensitivity (less than 0.1%) of this surveillance (analysis and results not shown). This result
436 suggests that such a surveillance could become facultative.

437 In France, animals may be traded between departments with different testing schemes.
438 Indeed, while in some departments, testing occurs on an annual basis, there is an extended
439 delay (up to four years) between programmed surveillance campaigns or even an absence of
440 surveillance in live animals in departments with favourable epidemiological situation.
441 Therefore, movement tests aim to protect cattle buyers (as a biosecurity measure) and
442 contribute *de facto* to detect potentially infected bovines.

443 Additional levers could be applied to improve the herd protection, as conducting several tests
444 following the bovine introduction or considering the epidemiological risk. As test sensitivity
445 was found to have an influence on the ability of the surveillance to detect TB-infected herds,
446 using a test with a higher sensitivity would also provide a real gain regarding this objective.
447 For that purpose, SIT, known to be more sensitive than the SICCT test (Nuñez-Garcia et al.,
448 2018) should be considered. However, in France, SIT was not implemented as rigorously as
449 the SICCT test and thus its use led to a decrease in sensitivity (French General Directorate for
450 Food, 2018). This can be explained by the fact that SIT was described to be performed by
451 veterinarians with less compliance than SICCT , and non-negative results obtained by SIT were
452 less reported to veterinary authorities (Crozet et al., 2019). Nonetheless, the authors of that
453 previous study concluded that, providing a good implementation of the test, SIT would
454 increase the probability of detection of the infected cattle in bTB-infected areas. Likewise,
455 IFNg could also be considered to compensate for the reading issues of IDT in field conditions,
456 by lifting the constraints related to the animal contention and acceptability of tests by
457 stakeholders and by providing standardised results. Moreover, the development of high-quality
458 antigens and kits should contribute to improve test performances and could be used in
459 paratuberculosis-infected and/or -vaccinated herds (Srinivasan et al., 2019). Finally, all measures
460 aiming to improve the test sensitivity as well as the compliance and applicability of field
461 actions are recommended to improve the detection of infected herds and limit the spread of the
462 disease; this would include reinforcing the awareness and education of farmers, vets and
463 other stakeholders and the supervision of vets applying the intradermal assay. Since 2001, the
464 official disease-free status has conditioned the trade in livestock and animal products to
465 Europe and internationally, which is essential for the competitiveness of French cattle farming
466 (French General Directorate for Food, 2018a). TB surveillance and management has a strong
467 economic impact on the cattle farming industry, with a cost about 22.3 million € every year,
468 including 18.6 million € assumed by central government and 3.7 million € by farmers (Hénaux
469 et al., 2017). Our study showed that increasing the number of bovines tested each year during
470 the programmed surveillance campaign by decreasing the minimum age at testing and
471 extending pre-movement testing to all herds in RPZ would make surveillance more effective.
472 While the reinforcement of surveillance would facilitate the early detection of infected herds
473 and limit possible secondary infections, reducing therefore the consequences of outbreak
474 management, it will cause an increase of surveillance expenses for farmers, who takes in
475 charge the costs of programmed and pre-movement surveillance, in RPZ. Moreover, testing
476 more animals and/or using a more sensitive test will lead to more false positive results. In
477 the French context, where acceptance seems to be moderate (Crozet et al., 2019), that might
478 not be the most appropriate option. These necessary changes in surveillance must be
479 accompanied by a global reflexion on surveillance financing, as anticipated by the French
480 Platform for Animal Health Surveillance (Calavas et al., 2012), and cost-effectiveness assessment
481 of surveillance (Poirier et al., 2019).

482 **Conclusions**

483 Our study quantified the expected annual performance gains of the TB surveillance system in
484 France under different scenarios of evolution of the surveillance, including a decrease in the
485 minimum age of testing and an extension of pre-movement tests to all herds in RPZ.
486 Tailoring this system to be more effective in detecting infected herds should be accompanied

487 by a standardisation of surveillance regulations across the country and by the implementation
488 of any additional measures to improve TB test sensitivity and its implementation by field
489 actors.

490

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615 Figure 1: Scenario tree for programmed surveillance for bovine tuberculosis in cattle in
616 reinforced prophylaxis zones (RPZ) in France, depicting the different risk groups (top) and
617 the probability (SeU) that an animal is infected, tested and detected (bottom). Only the
618 pathway for one of the three risk groups is completed; assume other identical in
619 structure.

620 Figure 2: Scenario tree for pre-movement surveillance for bovine tuberculosis in cattle in
621 France, depicting the different risk groups (top) and the probability (SeU) that an animal is
622 infected, tested and detected (bottom). Only the pathway for one of the three risk groups
623 is completed; assume other identical in structure.

624

Table 1. Parameters values and information

Parameter	Symbol	Values	Distribution used for simulations	Data source	Model concerned by the parameter
Median proportion of herds of each type of production among herds in RPZ (interquartile interval)	x_g	Beef/mixed: 53% [23-70] Dairy: 14% [2-18] Small herds: 25% [13-34]	Pert	French National Cattle Register	Programmed surveillance, pre-movement surveillance
Median prevalence in RPZ by type of production (interquartile interval)	p_g	Beef/mixed: 0.57% [0.00-2.27] Dairy: 0.44% [0.00-4.03] Small herds: same values as for beef/mixed herds	Pert	French National Cattle Register, Directorate for food of the French Agriculture ministry	Programmed surveillance, pre-movement surveillance
Median prevalence by type of production among previously-infected herds (interquartile interval)	p_g	Beef/mixed: 1.62% [0.53-3.75] Dairy: 0.00% [0.00-8.60]	Pert	French National Cattle Register, Directorate for food of the French Agriculture ministry	Pre-movement surveillance
Median number of bovines per herd (interquartile interval)	N_{bov}	Beef/mixed: 118 [65-199] Dairy: 128 [84-190] Small herds: 5 [3-10]	Pert	French National Cattle Register	Programmed surveillance, pre-movement surveillance
Median proportions of bovines of each age class per herd (interquartile interval)	P_{bov_test}	Beef/mixed: ≥ 24 months old: 56% [51-62] ≥ 18 months old: 64% [59-70] ≥ 12 months old: 70% [66-75] ≥ 6 weeks old: 98% [94-100] Dairy: ≥ 24 months old: 60% [54-67] ≥ 18 months old: 69% [64-74] ≥ 12 months old: 79% [75-83] ≥ 6 weeks old: 96% [94-97] Small herds:	Pert	French National Cattle Register	Programmed surveillance

		<p>≥ 24 months old: 67% [50-100]</p> <p>≥ 18 months old: 78% [60-100]</p> <p>≥ 12 months old: 100% [67-100]</p> <p>≥ 6 weeks old: 100% [100-100]</p>			
Number of infected bovines per herd	N_{bov_inf}	Zero-truncated NegBin (3.39 ; 1.77)	Zero-truncated negative binomial	(Cavalerie et al., 2015)	Programmed surveillance, pre-movement surveillance
Median number of bovines sales (interquartile interval)	s_g	Beef/mixed: 26 [12-48] Dairy: 6 [2-14] Small herds: 3 [2-7]	Pert	French National Cattle Register	Pre-movement surveillance
SICCT test sensitivity	Se	Minimum : 26%, maximum : 86%	Uniform	(Nuñez-Garcia et al., 2018)	Programmed surveillance, pre- and post-movement surveillance
Proportion per department of herds with an epidemiological link with a TB-infected herd located in a RPZ	z	80%	Fixed value	French National Cattle Register, Directorate for food of the French Agriculture ministry (for department Côte d'Or)	Pre-movement surveillance
Median proportion of herds covered by the current pre-movement surveillance system per department (interquartile interval)	c	5,0% [1,4-9,2]	Pert	French National Cattle Register, Directorate for food of the French Agriculture ministry	Pre-movement surveillance

Table 2: Fraction (%) of TB-infected herds in RPZ detected by programmed surveillance depending on the minimum age of testing

Testing age	Mean \pm Standard error	Median [interquartile interval]
≥ 24 months old	67.6 \pm 24.2	71.5 [47.4-89.4]
≥ 18 months old	71.5 \pm 23.6	76.7 [52.7-93.1]
≥ 12 months old	76.4 \pm 22.0	83.5 [60.6-95.9] *
≥ 6 weeks old	82.9 \pm 19.5	91.3 [71.6-99.0] *

* Significant gain in comparison to a minimum age of testing of 24 months old

Table 3: Fraction (%) of TB-infected herds in RPZ detected by pre-movement surveillance depending on surveillance coverage

Surveillance coverage	Mean \pm Standard error	Median [interquartile interval]
Previously TB-infected herds + herds with an epidemiological link	1.4 \pm 0.8	1.2 [0.7-1.8]
Previously TB-infected herds + herds with an epidemiological link + all herds located in RPZ	29.1 \pm 14.1	26.5 [18.1-37.9] *

* Significant gain in comparison to current pre-movement surveillance

Table 4: Sensitivity analysis (influence of input parameter values on the detection fraction) of the models evaluating the effectiveness of TB detection by the current surveillance components (programmed surveillance with a minimum age of testing of 24 months old, pre-movement surveillance in previously TB-infected herds and herds with an epidemiological link)

Paramètre	Programmed surveillance		Pre-movement surveillance	
	Correlation	p-value	Correlation	p-value
Number of bovines in beef/mixed herds	-0.01	0.447	-0.17	0.325
Number of bovines in dairy herds	-0.01	0.527	-0.01	0.496
Number of bovines in small herds	-0.01	0.509	-0.12	0.390

Median proportion of beef/mixed herds	-0.03	0.516	0.07	0.488
Median proportion of dairy herds	-0.01	0.525	-0.02	0.523
Number of infected bovines within a herd	0.72	0.000	0.58	0.001
TB prevalence in beef/mixed herds	0.00	0.532	-	-
TB prevalence in dairy herds	0.01	0.529	-	-
Proportion of bovines tested in beef/mixed herds	0.01	0.548	-	-
Proportion of bovines tested in dairy herds	0.00	0.482	-	-
Proportion of bovines tested in small herds	0.05	0.491	-	-
Test sensitivity (SICCT)	0.51	0.004	0.38	0.035
Median surveillance coverage	-	-	0.50	0.004
TB prevalence in beef/mixed herds not previously infected	-	-	0.18	0.320
TB prevalence in dairy herds not previously infected	-	-	-0.04	0.465
TB prevalence in previously infected beef/mixed herds	-	-	-0.06	0.417
TB prevalence in previously infected dairy herds	-	-	-0.05	0.476
Number of bovine* sales in beef/mixed herds	-	-	0.19	0.301
Number of bovine* sales in dairy herds	-	-	0.04	0.483
Number of bovine* sales in small herds	-	-	0.11	0.406

* bovines aged six weeks and older



