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1 **Assessment of the cost-effectiveness of alternative bovine tuberculosis surveillance protocols in**
2 **French cattle farms using the mixed interferon gamma test**

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9

10 **ABSTRACT**

11 Periodic screening in farms, using intradermal cervical comparative tuberculin test (ICCT), is a
12 component of the French *ante mortem* surveillance of bovine tuberculosis (bTB). Previous studies have
13 estimated the cost-effectiveness of the French mandatory bTB screening protocols. In these protocols,
14 a second ICCT (ICCT2) is performed 42 days after the first one (ICCT1), either on the entire herd (strict
15 protocol) or in series on animals with non-negative results (reactors) to ICCT1 (compliant protocol).
16 The 42-days interval reduced protocols' cost-effectiveness. To minimize this interval, we suggested
17 two alternative protocols, in which a mixed interferon gamma test (IFNMIX), with better sensitivity
18 than ICCT2 and comparable specificity, replaces the ICCT2, and is carried out directly after the ICCT1.
19 In the strict alternative protocol, reactors to ICCT1 are culled to perform laboratory analyses (PCR,
20 bacteriology). Negative results to these analyses imply the IFNMIX testing of the entire herd. In the
21 compliant alternative protocol, only reactor(s) to ICCT1 are tested with IFNMIX, and animals with
22 positive results to IFNMIX are culled for laboratory analyses. We evaluated these protocols through
23 scenario tree modelling.

24 The estimated cost-effectiveness indexes showed that the compliant alternative protocol was the most
25 efficient. The strict protocols (mandatory and alternative) were never the most efficient, but were the
26 most effective. Therefore, using IFNMIX instead of ICCT2 may be useful in reducing the costs of the
27 compliant protocol used when the probability of infection is considered low. The strict alternative
28 protocol may become more attractive would IFNMIX's price decreased.

29 KEYWORDS: interferon, scenario tree, bovine tuberculosis, cost-effectiveness, surveillance, sensitivity.

30 INTRODUCTION

31 In France, widespread milk pasteurization and a significant reduction of the prevalence of bovine
32 tuberculosis (bTB) infection in cattle has reduced the risk of its transmission to human. bTB is therefore
33 no longer considered as a public health issue in France. Nevertheless, the bTB-free status facilitates
34 international exchanges of living cattle that are essential the economic health of the agricultural sector.
35 This justifies the bTB European control measures. Since 2004, an increasing number of outbreaks have
36 been detected in some areas of France, and bTB prevalence is currently close to official bTB-free status
37 threshold in Europe (Delavenne *et al.*, 2019). Indeed, more than 60 years of control measures have not
38 achieved bTB total eradication. In this context, the surveillance and control system's assessment is
39 crucial.

40 There is no consensus in animal health neither about the method to evaluate a surveillance system nor
41 about the attributes to evaluate (usefulness, simplicity, feasibility, sensitivity, specificity, costs, etc)
42 (Drewe *et al.*, 2012; RISKSUR, 2013; Calba *et al.*, 2015). BTB surveillance's semi-quantitative evaluation
43 was previously performed in France, allowing the identification of critical points of the surveillance
44 system (Gorecki, 2012). Our goal is to provide a more detailed evaluation for each protocol composing
45 the *ante mortem* surveillance system. The purpose was to assess quantitatively the efficiency of each
46 protocol to compare them, and to propose operational improvements. We chose to evaluate the herd
47 sensitivity for each protocol, as the main attribute of a protocol's effectiveness. Furthermore, the
48 durability of a surveillance system depends on a reasonable cost to ensure its financing. Therefore, we

49 also assessed each protocol's cost. Among methods to evaluate the sensitivity of a surveillance system,
50 scenario tree modelling (Martin *et al.*, 2007) has been frequently used (Hadorn *et al.*, 2009;
51 Christensen *et al.*, 2011; Foddai *et al.*, 2016). It is possible with this approach to use various and
52 complex data that can be easily updated. Besides, the variability and uncertainty about the surveillance
53 parameters can be accounted for with a stochastic approach (Martin *et al.*, 2007). Finally, this method
54 allows the concomitance estimation of the costs of the system (Hadorn *et al.*, 2009; Rivière *et al.*, 2015;
55 Hénaux and Calavas, 2017). We thus used this method to evaluate quantitatively the efficiency of bTB
56 *ante mortem* surveillance in France.

57 In a previous study, we estimated with scenario tree modelling the cost-effectiveness of periodic
58 screening in French farms (Poirier *et al.*, 2019), depending on the herd type considered (type of
59 production, herd size and herd turnover). We studied the three mandatory French protocols (strict
60 protocol, compliant quick-path protocol, and compliant slow-path protocol). The strict and compliant
61 quick-path protocols imply the direct slaughter of any intradermal cervical tuberculin test (ICT)-
62 reactive animals for laboratory analyses. In the strict protocol, a suspect farm can only recover its bTB-
63 free status after negative results to a second screening with the intradermal cervical comparative
64 tuberculin test (ICCT). In the compliant quick-path protocol, negative results for the laboratory tests of
65 culled reactors are sufficient for the herd to regain its bTB-free status. In the compliant slow-path
66 protocol, ICCT-reactive animals are tested for interferon gamma; the results of this test influence the
67 path of further investigation.

68 In France, the protocol is chosen according to the probability – qualitatively estimated by the health
69 authorities – for the suspected herd (herd with at least one non-negative result to the first ICT) to be
70 infected. If this probability is considered high (high prevalence area, positive result to ICCT, former
71 outbreak...), the strict protocol is used to maximise herd sensitivity. Otherwise, one of the compliant
72 protocol is chosen.

73 One of the main issues of the strict and the compliant slow-path protocols identified in our previous
74 study was the duration of the procedure (Poirier et al., 2019). Indeed, the second ICCT (ICCT2) involves
75 an irreducible six-week waiting period to avoid post-tuberculin anergy due to the first ICCT (ICCT1)
76 (Radunz and Lepper, 1985). This waiting period is difficult for the farmers, mainly because of the
77 economic burden (animal sales are ban during this period).

78 Furthermore, the ICCT is technically challenging. Indeed, the skin thickness must be measured before
79 and three days after the injection. Bovine and avian tuberculin must be injected into two distinct points
80 on the neck of the cattle. Proper execution of this test thus requires two visits, efficient animals'
81 restraint and a substantial amount of time (de la Rua-Domenech *et al.*, 2006; Humblet *et al.*, 2010;
82 Guillon *et al.*, 2018). Conversely, the interferon gamma test (IFN γ) requires only one blood sample (de
83 la Rua-Domenech *et al.*, 2006). Therefore, it is easier to perform in the field, and only one visit is
84 needed. Moreover, in France, the results are quickly obtained (within a few days) (personal
85 communication from the national laboratory of reference for bTB (NLR)). The only constraint of this
86 test is that blood samples must arrive at the laboratory within six hours after sampling to avoid a loss
87 of sensitivity (Gormley *et al.*, 2004). This requires good coordination between the sampling and the
88 collection of the samples by laboratories. An analysis of the data collected for the evaluation of IFN γ
89 testing in a French study (Praud *et al.*, 2015) estimated the characteristics of IFN γ based on stimulation
90 by specific antigen MIX (Peptide Cocktail Prionics, ThermoFisher), called IFNMIX). The sensitivity of the
91 IFNMIX was estimated to be significantly higher than the sensitivity of ICCT2 and had similar specificity,
92 suggesting the possibility of replacing ICCT2 by IFNMIX (Praud et al., 2019). Besides, a blood sample
93 for IFN γ testing can be taken immediately after an ICCT test with no effect on IFN γ sensitivity (Gormley
94 et al., 2004; Rangen et al., 2009). However, the European Union (EU) does not currently authorise this
95 use of IFNMIX. Indeed, the EU only allows the parallel use of the interferon gamma test, to improve
96 the sensitivity of the detection of infected animals in bTB infected herds (European directive
97 CE/64/432). Nevertheless, its experimental use in series was allowed in several national protocols,
98 including French surveillance protocols (EFSA, 2012). European Food Safety authority (EFSA) advocates

99 for its authorisation (EFSA, 2012). All additional proof of its efficiency will help to promote it. Therefore,
100 it appeared timely to perform a cost-effectiveness evaluation of alternative protocols in which IFNMIX
101 is used instead of ICCT2 to reduce the duration of the investigations, using the same method and based
102 on the same hypothesis we used to evaluate the three mandatory protocols. The purpose was to assess
103 the potential interest of these alternative methods in terms of cost-effectiveness for each herd type.

104

105 MATERIALS AND METHODS

106 1. Scenario tree modelling

107 The use of scenario tree modelling to evaluate the efficiency of surveillance systems is well described
108 by Martin and his collaborators (2007). This method requires the development of an event tree for
109 each protocol of the surveillance system. The tree describes all possible pathways, from the infection
110 of the studied population to its detection by the protocol. Tree's nodes divide the population into
111 groups with the same probability of infection and/or of detection of the infection. For each node
112 outcome, a specific probability of occurrence is associated. It can be a fixed value (probabilistic
113 approach) or a probability distribution (stochastic approach allowing the accountancy of variability
114 and/or uncertainty about this probability). The probability of occurrence of each pathway is the
115 product of the probabilities along the corresponding branch. Each protocol step's cost can also be
116 added in the corresponding parts of the tree (Hadorn *et al.*, 2009; Rivière *et al.*, 2015; Hénaux and
117 Calavas, 2017). The mean cost of the protocol is therefore the sum of each tree branch's cost weighted
118 by its probability of occurrence (Poirier *et al.*, 2019).

119 We used this method to assess the sensitivity and the costs of the protocols of bTB periodic screening.

120 2. Mandatory protocols

121 In a previous study, we developed scenario-tree models to estimate the cost and sensitivity of the
122 three mandatory French protocols of bTB surveillance on farms (Poirier *et al.*, 2019). These protocols

123 start with cattle screening using ICCT (ICCT1). If at least one result (from any animal within the herd:
124 called a reactive animal or reactor) is non-negative (positive or doubtful), the farm is suspected of bTB
125 outbreak. One of the three mandatory protocols can then be used to confirm or refute the suspicion.

126 In the strict protocol, reactors are culled to perform laboratory tests (PCR, histology, and bacteriology).
127 The detection of *Mycobacterium tuberculosis*, *M. bovis* or *M. caprae* confirms a bTB outbreak in the
128 herd. If the laboratory tests results are negative, the herd is tested again, 42 days later, with ICCT
129 (ICCT2). The herd recovers a bTB-free status if all results to ICCT2 are negative.

130 In the compliant quick-path protocol, the results of the laboratory tests of culled reactors determine
131 the herd's status. If bTB is detected, the outbreak is confirmed; otherwise, the herd regains its official
132 bTB-free status, without an ICCT2.

133 In the compliant slow-path protocol, IFN γ is performed on ICCT1 reactors. If at least one IFN γ is
134 positive, the corresponding animal is culled and laboratory tests are performed; otherwise, ICCT1
135 reactors are tested again with the ICCT (ICCT2) six weeks later.

136 A glossary summarises the main steps of these protocols. It is a reminder to refer to through the
137 reading of this article.

138 In the previous studies, we created scenario trees at the individual animal level to model these
139 protocols (Poirier *et al.*, 2019; Guétin-Poirier *et al.*, 2020). They accounted for herd type (production
140 type: beef/dairy/mixed, herd size: big/small, and herd turnover: less/more than 40%), cattle age
141 (younger/older than 24 months, which is the age limit for ICCT testing in France), herd's and considered
142 animal's bTB infectious status, and the results of ICCT, IFN γ , and laboratory (PCR, histology, and
143 bacteriology) tests. Data about the ICCT practices and notification habits of the veterinarians were also
144 secondly accounted for (Guétin-Poirier *et al.*, 2020). Their implementation is detailed in the
145 corresponding published articles (Poirier *et al.*, 2019; Guétin-Poirier *et al.*, 2020) and summarized in
146 **table 1. Appendices 1 to 3** illustrate the scenario trees used.

147 Here, we compared in terms of cost-effectiveness these three mandatory protocols to the two
148 alternative protocols that we modelled for the first time, in order to assess the relevance of each
149 protocol.

150 3. Alternative protocols

151 Using the same framework as developed for the strict and compliant slow-path protocols, we built two
152 scenario trees. They modelled hypothetical alternative protocols, substituting ICCT2 with IFNMIX, to
153 investigate their possible benefit in terms of sensitivity and/or cost relative to the mandatory
154 protocols. These two protocols (the “strict alternative protocol” and “compliant alternative protocol”)
155 are described in **figures 1 and 2**. First, all animals older than 24 months are tested by ICCT (ICCT1). If
156 at least one reactor is identified in a herd, authorities consider the farm to be suspect of bTB, and an
157 investigation protocol is applied. In the alternative strict protocol, all ICCT1 reactors are culled and
158 laboratory tests (PCR, histology, and bacteriology) are performed. If one of these tests detects
159 *Mycobacterium tuberculosis*, *M. bovis* or *M. caprae*, the herd is officially considered to be infected.
160 Otherwise, negative results for the IFNMIX of the remaining animals of the herd are needed to recover
161 the bTB-free status. In the alternative compliant protocol, ICCT1 reactors are tested by the IFNMIX. If
162 they are all negative, the herd regains its bTB free status. Otherwise, reactors to ICCT1 and IFNMIX are
163 culled and the results of laboratory tests determine the herd’s status.

164 We implemented these models using the same parameters as for the mandatory protocols (**table 1**).
165 The characteristics of the IFNMIX for an ICCT1 reactor were modelled according to the results
166 published by Praud *et al.* (2019). Thus, the sensitivity and specificity of the IFNMIX were represented
167 by normal distributions restrained between zero and one, $N(0.83, 0.06)$ and $N(0.861, 0.0081)$,
168 respectively.

169 4. Outcomes estimations

170 We used these scenario trees to estimate the mean herd sensitivity and cost of each protocol studied
171 and their 2.5th and 97.5th percentiles for one year (bTB is a chronic disease and screening of farms

172 occurs every year) from 10,000 simulated values for each herd type. We programmed the scenario
173 trees and ran simulations using RStudio (version 1.1.383.0). The mean estimations were compared
174 using Student's t tests corrected by the Bonferroni method for multiple comparisons. We accepted a
175 risk of error α of 1%.

176 4.1. Sensitivity

177 We computed the herd sensitivity for each herd type and for each protocol, setting the probability for
178 a herd to be infected to one, to estimate the probability of detection of at least one infected animal in
179 an infected herd (*i.e.* herd sensitivity).

180 In the models, the probability of the occurrence of each path was computed at each iteration as the
181 product of the probabilities of the occurrence of the path's branches (Martin *et al.*, 2007). Then, for
182 each herd type k , the model added up every path with a positive outcome, to estimate the individual
183 sensitivity of this herd type (Se_k). Given the model structure, individual specificity was equal to 100%
184 (**figure 1-2 and table 1**). Finally, the model estimated herd sensitivity for each herd type (CSe_k)
185 according to formula (1).

$$186 \quad (1) \quad CSe_k = 1 - (1 - Se_k)^{\text{herd size} * \text{within-herd prevalence}}$$

187 We provided the mean sensitivity of the protocols and their 2.5th and 97.5th percentiles, for each
188 protocol and each type of herd.

189 4.2. Costs

190 The costs of surveillance protocols can be direct (screening tests, organisation of the screening
191 campaigns, laboratory analyses, etc.) or indirect (losses due to the ban of selling animals or
192 unpasteurised milk). In France, the State and farmers share all costs. Farmers must pay for
193 programmed screening and cover indirect losses, whereas the State pays for all tests applied during
194 the investigation of suspected cases and compensates farmers for culled animals. We computed the
195 mean direct and indirect costs for infected (herd-level prevalence set at 100%) and uninfected herds
196 (herd-level prevalence fixed at 0%) for each surveillance protocol by herd type using the same method

197 as in our preliminary study (Poirier *et al.*, 2019). In this study, direct costs were collected for 40/95
198 administrative areas and were used in the model to parameter each cost with a Pert distribution. These
199 costs and distributions are detailed in the complementary materials (C4). For indirect costs, the
200 estimation of daily immobilisation cost of animals within the suspected herd, from each production
201 type and animal category (calves, female over or under 24 months, male over or under 6 months old)
202 (Buczinski and Reuillon, 2015) (C5) was used. These costs were weighted by the number of animals of
203 each category sold each month (by herd type, from the BDNI database) and by the duration between
204 each protocol's steps (estimated for the SIGAL database, C6). We adapted the model with the following
205 distribution for variables related to the use of IFNMIX. To model the costs for IFNMIX, we used the
206 same probability distribution as for the bTB IFN test (PERT(min = 3, mode = 53, max = 68)) (Poirier *et al.*,
207 2019), given that laboratories declared they would charge the same price for an IFNMIX as for the
208 usual IFNy.

209 The times to obtain the IFNMIX and IFNy results (in days) in the two alternative protocols were
210 modelled similarly (personal communication, NLR) (PERT(min = 2, mode = 2, max = 7)) (Poirier *et al.*,
211 2019).

212 In the compliant slow-path and alternative protocols, the times (in days) between a positive IFNMIX
213 result or a positive IFNy result, respectively, and the culling of the corresponding animal were modelled
214 using the same probability distribution (PERT(min = 3, mode = 24, max = 136)). The parameters of this
215 distribution were estimated from the time intervals reported in 2016 in the French national database
216 for disease regulation (SIGAL) (Poirier *et al.*, 2019; complementary materials C6).

217 In the alternative strict protocol, we modelled the delay between ICCT1 and the culling of reactors as
218 for the strict protocol (PERT(min = 1, mode = 21, max = 150)) (Poirier *et al.*, 2019 ; complementary
219 materials C6). The times between a positive IFNMIX result or a positive ICCT2 result (in the strict
220 protocol) and culling of the corresponding animal was modelled similarly (PERT(min = 3, mode = 22,
221 max = 69)) (Poirier *et al.*, 2019 ; complementary materials C6). No current field situation was

222 sufficiently close to the time between the culling of ICCT1 reactors and IFNMIX testing of the remaining
223 animals in the strict alternative protocol. We therefore modelled this time interval using a uniform
224 distribution $U(\text{min} = 2, \text{max} = 8)$. Indeed, we assumed that veterinarians would come back to the farm
225 to re-test the herd from two to eight days after the negative result for the first laboratory analyses.
226 This interval relies on the matched timing of the blood sample collection by laboratories and the six-
227 hour interval between blood sampling and sample stimulation for IFN γ testing.

228 The total cost calculated for each protocol by herd type corresponds to the sum of the direct and
229 indirect costs associated with the corresponding branches of the tree, weighted by the probability of
230 occurrence. All calculated costs are tax-free.

231

232 5. Cost effectiveness analysis (CEA)

233 For each protocol and each herd type, a cost-sensitivity index was computed at each model iteration
234 by dividing the total cost for this herd type by the corresponding estimated sensitivity. We ran 10,000
235 iterations. We provided the mean cost-sensitivity index and its 2.5th and 97.5th percentiles, for each
236 protocol and each type of herd. We selected the most efficient protocol using the rule “The higher the
237 cost-sensitivity index, the lower the efficiency”.

238 6. Sensitivity analysis

239 We performed several sensitivity analyses to assess which model input had the most influence on the
240 two possible outputs (herd sensitivity and total cost). Some model inputs were interdependent. Thus
241 we could not use the One-At-a-Time method and instead used the McKay method (McKay, 1995),
242 which can be used if the inputs are interdependent (Jacques *et al.*, 2006), with 20 replications of Latin
243 hypercube samples. We ran the sensitivity analyses using the R package “sensitivity dependent”
244 developed by Jacques, an INRA researcher (complementary materials C7).

245

246 RESULTS

247 1. Herd sensitivity

248 The results are presented in **table 2**.

249 The mean sensitivity for the mandatory protocols ranged from 11.93% for the compliant slow-path
250 protocol (in big beef farms with high turnover (Bbsup)) to 42.61% for the strict protocol (in big mixed
251 farms with a low turnover (Mbinf)). The mean herd sensitivity of the compliant alternative protocol
252 ranged from 10.31% to 35.55%, depending on herd type. For the strict alternative protocol, the
253 estimated mean herd sensitivity ranged from 17.63% to 48.21%.

254 Among the mandatory and alternative protocols, the strict alternative protocol had the highest mean
255 herd sensitivity for all herd types and the compliant alternative protocol had the lowest, regardless of
256 herd type.

257 For all protocols, the mean herd sensitivity was lower for high turnover herds, regardless of production
258 type and herd size. This is due to the smaller number of animals older than 24 months (and thus
259 submitted to surveillance protocols) than in other herd types. The differences in mean herd sensitivity
260 between herd types for the same protocol were all significant, except, for the compliant slow-path
261 protocol and the strict alternative protocol, between small mixed herds with a high turnover (Mssup)
262 and small beef herds with a low turnover (Bsinf).

263 Mandatory protocols were compared to their alternative equivalent. Therefore, we compared mean
264 herd sensitivities of the strict protocol with those of the strict alternative protocol and the mean herd
265 sensitivity of the compliant slow-path protocol with those of the compliant alternative protocol. The
266 results of these comparisons are summarised in **table 3**. The substitution of ICCT2 by IFNMIX in the
267 strict protocol increased the mean herd sensitivity of between 4.18 and 6.96%, depending on herd
268 type. For the compliant slow-path protocol, such substitution resulted in a decrease of mean herd
269 sensitivity between 1.62 and 4.03%, depending on herd type.

270 2. Cost

271 The mean, 2.5th and 97.5th percentiles of the output distribution of total costs by protocol and herd
272 type are presented in **table 4**. All protocols were found to be much more expensive in big mixed herds
273 than in other herd types, because of the larger herd size (> 124 animals).

274 For mandatory protocols, the mean cost of each protocol was between 773 and 22,126 euros for the
275 compliant slow-path protocol, 1,106 and 13,979 euros for the compliant quick-path protocol, and
276 1,982 and 26,092 euros for the strict protocol (Guétin-Poirier *et al.*, 2020). The strict protocol was the
277 most expensive, regardless of herd type. The compliant quick-path protocol was the least expensive
278 for all big herds and small mixed herds. For other herd types, the compliant quick-path protocol was
279 the least expensive, except for small mixed herds, for which the mean cost difference of the compliant
280 slow-path and compliant quick-path protocols were not significant.

281 For the alternative protocols (using IFNMIX instead of ICCT2), the mean cost was between 4,001 and
282 52,461 euros for the strict alternative protocol and 292 and 5,226 euros for the compliant alternative
283 protocol. The strict alternative protocol was the most expensive of all protocols, regardless of herd
284 type. The compliant alternative protocol was the least expensive, from eight to thirty-eight times less
285 expensive than the least expensive mandatory protocol, depending on herd type.

286 3. Cost-effectiveness index

287 The mean cost-sensitivity index estimated for each protocol, by herd type, is shown in **figure 3**. A high
288 cost-sensitivity index is associated with poor efficiency of the protocol. Among mandatory protocols,
289 the strict protocols (mandatory and alternative) were never the most cost-effective, regardless of herd
290 type. The compliant quick-path protocol was the most efficient, among mandatory protocols, for big
291 beef herds with a low turnover (Bbinf), big dairy, and big mixed herds. The compliant slow-path
292 protocol was the most efficient mandatory protocol for the other herd types. All differences were
293 significant, but the difference of the cost-effectiveness index between the slow path and quick path
294 compliant protocols was very small for dairy and beef herds with a low turnover. The compliant

295 alternative protocol was the most efficient of all protocols, regardless of herd type, whereas the strict
296 alternative protocol was the least efficient, regardless of herd type, despite its better herd sensitivity.

297 4. Sensitivity analyses

298 4.1. Impact of inputs on herd sensitivity

299 We performed sensitivity analysis of the herd sensitivity output for each protocol by herd type. The
300 **figure 4** represents, by herd type and for each protocol, the Mc Klay indices of the inputs > 10%. This
301 index estimates the proportion of the output's variation caused by the input's variability and
302 uncertainty. ICCT sensitivity had the greatest influence on variations in herd sensitivity for small herds
303 and big dairy herds for all mandatory protocols and the compliant alternative protocol. In other big
304 herds, ICCT sensitivity, within-herd prevalence, and herd size shared responsibility for this variation.
305 For the strict alternative protocol, inputs with the greatest influence on variations in herd sensitivity
306 were herd size for Bbinf herds, ICCT specificity for Bsinf, Bssup, Dsinf, and Mssup herds. In other herd
307 types, it was the within-herd prevalence.

308 4.2. Impact of inputs on total cost

309 We performed the same sensitivity analysis for total cost outputs (**figure 5**). The most influential input
310 on total costs for the compliant slow-path protocol was ICCT specificity. Size was also an influential
311 input for small beef and dairy herds (for any turnover) and for Bbinf herds. For the compliant quick-
312 path protocol, the most influential input on total cost variation was the interval between ICCT1 and
313 the culling of ICCT non-negative animals, except for dairy and mixed herds with a low turnover for
314 which ICCT specificity was the most influential variable. In the strict mandatory protocol, the interval
315 between the first and second ICCT was the most influential variable except for dairy herds with a low
316 turnover for which the most influential variable was ICCT specificity.

317 For the strict alternative protocol, the interval between ICCT1 results and the culling of reactors was
318 the most influential input on the total cost in beef herds, dairy herds with a high turnover, and Mbinf
319 herds. In other herds, depending on the herd type, this input shared responsibility in the variation of

320 total costs with ICCT specificity, compensation costs, herd size, and the time between a non-negative
321 result to the first IDC test and culling of the reactors.

322 ICCT specificity and herd size were the main inputs responsible for the total cost variations for the
323 compliant alternative protocol. The time between a positive result to IFNMIX and culling of the reactors
324 had a non-negligible influence in some herd types.

325

326 DISCUSSION

327 1. Assessments

328 The methodology used to model the surveillance protocols and implement the scenario trees and the
329 estimations if the IFNMIX has been discussed extensively in our previous studies (Poirier *et al.*, 2019;
330 Guétin-Poirier *et al.*, 2020). We chose to assess alternative protocols using IFNMIX as an alternative to
331 ICCT2 to reduce the time needed for suspicion's investigation and therefore reduce indirect costs of
332 these investigations, which are difficult to support for farmers and which probably lead to a reduction
333 of the acceptability of the protocols (Gully *et al.*, 2018). According to EFSA, no other test can yet be
334 considered as an alternative to ICCT (EFSA, 2012). For example, serologic test could allow this time gain
335 in suspicion's investigation, but its sensitivity and specificity are too low to be a possible alternative to
336 ICCT (Waters *et al.*, 2006; van der Heijden *et al.*, 2016).

337 The IFN γ was used in the program leading to the successful eradication of bTB in New-Zealand, in
338 particular for serial testing skin test positive cattle when non-specific reactions are suspected (Buddle
339 *et al.*, 2001; Wood and Jones, 2001). The serial testing of ICT positive cattle with IFN γ is also allowed
340 in the United Kingdom, the Republic of Ireland (de la Rua-Domenech *et al.*, 2006), and in the United
341 States (Anonymous, 2004). It is similar to the compliant alternative protocol we proposed. The serial
342 use of IFN γ efficiency in other countries is difficult to compare with our evaluation as the cattle
343 populations, antigens used by the laboratories (Bovigam, ESAT) and cut-off values for the interpretation

344 were different. In addition, to our knowledge, no study assessed the efficiency of the global screening
345 protocol as we did. In these countries, they rather assessed the sensitivity and the specificity of the
346 IFN γ .

347 Hereunder we focus on the simulation results and the potential interest of the alternative protocols
348 for bTB control in France.

349 The substitution of ICCT2 by the IFNMIX increased the mean herd sensitivity for the strict protocol,
350 which was expected, given the higher sensitivity of the IFNMIX. However, such a substitution in the
351 compliant protocol resulted in a decrease in mean herd sensitivity, which is counterintuitive. This may
352 be explained by the fact that the alternative protocol proposed to replace the compliant slow-path
353 protocol not only substituted ICCT2 by the IFNMIX but also excluded the IFN γ performed before ICCT2
354 in the mandatory slow-path protocol. Thus, the sensitivity gain resulting from the substitution of ICCT2
355 by the IFNMIX appears to be insufficient to compensate the loss in herd sensitivity caused by the
356 removal of the IFN γ . However, we did not account for the hypothetical beneficial effect that the
357 decreased time interval could have on the notification of non-negative ICCT1 results by the
358 veterinarians. Indeed, some veterinarians hesitate to notify non-negative results: they fear that this
359 will have an unjustified (in case of false-positive results) detrimental impact on their customer (the
360 farmer), as it will prevent him from selling any animal during the entire investigation protocol (Gully,
361 2018; Crozet *et al.*, 2019). Therefore, a reduction in the duration of the protocol could reduce
362 veterinarians' reluctance to notify the authorities of non-negative results. If the decrease of the time
363 interval actually improve veterinarians' notification frequency and was considered for the herd
364 sensitivity estimation, the estimated mean herd sensitivity of the alternative protocols would have
365 been higher and perhaps the compliant alternative protocol would have had an equivalent or higher
366 mean herd sensitivity than the compliant slow-path protocol.

367 Substitution of the ICCT by the IFNMIX in the protocols could help to ensure repeatability and
368 standardisation of the screening methods. This is very difficult with ICCT due to the constraints

369 inherent to this test. However, IFNMIX increased cost (approximately 10 fold that of ICCT), the
370 necessity to stimulate the sample within six hours, and the limited number of laboratories certified to
371 perform IFN γ testing prevent the substitution of the ICCT by IFNMIX as a first test for the annual
372 screening of cattle. Nevertheless, it would be conceivable to substitute ICCT2 in suspected herds by
373 the IFNMIX to reduce the investigation period. Such a substitution for the strict protocol resulted in an
374 improvement of herd sensitivity in parallel with a tremendous increase in the cost (which is two times
375 that of the strict protocol), making the alternative strict protocol the most effective but the least
376 efficient, regardless of herd type. Therefore, such a substitution cannot be recommended for all cases.
377 For the compliant protocol, using the IFNMIX instead of ICCT2 resulted in a decrease in herd sensitivity
378 between 1 and 4 % while dividing the cost by three- to seven, depending on the herd type. This
379 suggests that this compliant alternative protocol is the most efficient of all. Thus, this protocol could
380 potentially replace the compliant slow-path protocol, regardless of herd type. The use of the compliant
381 alternative protocol would substantially reduce costs without significantly decreasing herd sensitivity.

382 According to the higher herd sensitivity of the strict alternative protocol, this protocol could be used
383 in specific contexts, assuming deciders agreed to invest more money into investigating suspect bTB
384 cases to improve herd sensitivity. We addressed this possibility by assessing the mean cost-
385 effectiveness indices of the strict alternative protocol and the strict mandatory protocol for each herd
386 type (**figure 6**). Each point represents a herd type. The lines allow comparing the cost-effectiveness
387 index (CE) of the strict alternative protocol (ordinate) and the strict mandatory protocol (abscissa).
388 Points below a considered line indicate that, for the matching herd type, the CE is higher for the strict
389 alternative protocol than for the strict mandatory protocol (for the line $x = y$). It thus indicates that for
390 this herd type, the strict alternative protocol is less cost-efficient than the mandatory one. This figure
391 confirms that the strict alternative protocol would never be the most efficient (its mean index was
392 always higher than that of the mandatory strict protocol), regardless of herd type. Assuming that
393 authorities would agree to invest twice as much to obtain better herd sensitivity ($2x = y$), the strict
394 alternative protocol could be an option for all herd types, except Mbinf. If they are not willing to invest

395 more than 1.5 times more (line $1.5x = y$), the strict alternative protocol could be considered only for
396 Dssup and Mssup herds. For the other herd types, the cost of this alternative protocol is still too high
397 relative to the sensitivity gain.

398 Sensitivity analyses of the outcome “herd sensitivity” globally led to the same results for the alternative
399 and mandatory protocols: ICCT sensitivity within-herd prevalence, and herd size were the most
400 influential inputs for herd sensitivity uncertainty and variability. However, ICCT sensitivity had a
401 somewhat smaller influence on the alternative protocols, because ICCT2 is not performed in these
402 protocols.

403 In the sensitivity analyses of the outcome “cost” for the strict mandatory protocol, the most influential
404 factor was the time between ICCT1 and ICCT2, whereas this lag period does not exist in the strict
405 alternative protocol. The most influential variables on cost variability and uncertainty in the compliant
406 alternative protocol were the time between non-negative test results (ICCT1 or IFNMIX) and the culling
407 of the corresponding animal.

408 2. Field recommendations

409 The veterinarians’ perception of bTB testing has been found to influence both their ICCT practices and
410 willingness to notify the authorities of non-negative results (Guétin-Poirier *et al.*, 2020). An
411 improvement of the protocol that leads to better cost-effectiveness, a decrease in the number of ICCTs
412 to perform (no more ICCT2), and a decrease in waiting time could positively influence the perception
413 of veterinarians of bTB control, as the protocols would less penalize the farmers. The proposed
414 alternative protocols improve the effectiveness of the surveillance system by inciting veterinarians
415 to follow prescribed practices (Pfeiffer, 2006). The results of the cost-effectiveness evaluation of these
416 alternative protocols and their comparison with the mandatory protocols showed that the interest in
417 their use may be more moderate.

418 If enough authorised laboratories to perform sample stimulation (for the IFNMIX) would be available;
419 the mandatory compliant slow-path protocol could be substituted by the alternative protocol. This

420 would drastically reduce investigation's costs and duration, which would certainly have a positive
421 impact on both the farmers' opinion and the veterinarians' perception of bTB control. This would
422 possibly ensure a better acceptability of the protocol. It would therefore increase the notification of
423 non-negative results by veterinarians, as they would be less concerned about penalizing their
424 customers with a long-lasting selling ban. Indeed, Crozet *et al.* (Crozet et al., 2019) estimated that
425 approximately 25 % of veterinarians think it is necessary to stop blocking herds for six weeks in case of
426 non-negative screening test results. In addition, the main concern of 25 % of the answering
427 veterinarians when they found a non-negative result was false positive results that would
428 unnecessarily block the farm for several weeks.

429 However, the substitution of ICCT2 by the IFNMIX is not a good option for the strict protocol. Indeed,
430 using the IFNMIX on an entire herd would be too expensive, unless authorities would be willing to
431 invest more to gain herd sensitivity in specific cases. If and when the cost of IFN γ testing decreases and
432 enough laboratories are authorised to perform these tests, the strict alternative protocol could
433 potentially replace the current strict protocol, with an important gain of herd sensitivity.

434 Finally, the results of our cost-effectiveness analyses suggest that replacing the ICCT2 by the IFNMIX
435 would only be interesting for the compliant protocols. Currently, such substitution is not authorised by
436 the European Union (European directive CE/64/432) but an evolution of the regulation is possible.
437 Indeed, several countries have been already allowed by the EU to use the IFN γ in series. This
438 authorisation allowed to collect data about the IFN γ characteristics on the field (for example in France:
439 Praud *et al.*, 2015 and 2019) and EFSA scientific opinion was favorable towards IFN γ authorisation in
440 Europe (EFSA, 2012). Our results add quantitative data advocating for the authorisation of the use of
441 IFN in bTB surveillance in Europe.

442 CONCLUSION

443 We highlight the potential interest of alternative bTB surveillance methods incorporating IFNMIX,
444 which would decrease the number of ICCTs to perform and the duration of the investigation of

445 suspected bTB outbreaks. Such substitution of ICCT2 by the IFNMIX would be cost-effective for the
 446 compliant slow-path protocol. Authorities could thus consider replacing the mandatory compliant
 447 slow-path protocol by the compliant alternative one. Nevertheless, given the currently high cost of
 448 IFN γ testing, this alternative method is not cost-effective for the strict alternative protocol, in which
 449 an entire herd must be screened.

450 **Glossary**

Periodic screening protocols	Main steps	Comments
Strict	ICCT1, diagnostic culling of reactive animals, second ICCT on all herd	
Compliant quick path	ICCT1, diagnostic culling of reactive animals	Mandatory protocols evaluated in Poirier et al., 2019 and Guétin-Poirier et al., 2020
Compliant slow path	ICCT1, IFN on reactive animals, diagnostic culling of animals positive to IFN, second ICCT on animals reactive to ICCT1	
Strict alternative	ICCT1, diagnostic culling of reactive animals, IFNMIX on all herd	
Compliant alternative	ICCT1, IFNMIX on animals reactive to ICCT1, diagnostic culling of animals positive to IFNMIX	Alternative protocols

451

Tests	Definition
ICCT	Intradermal tuberculin cervical comparative test
IFNγ	Interferon gamma tuberculin test
IFNMIX	Interferon gamma tuberculin test interpreted with the MIX antigen
Diagnostic culling	Animals culled for diagnostic : laboratory analyses are performed on samples : histology, PCR and bacteriology to detect <i>Mycobacterium bovis</i> , <i>M. tuberculosis</i> or <i>M. caprae</i>

452

Herd types	
Bbinf	big beef farm with a turnover < 40%
Bbsup	big beef farm with a turnover \geq 40%
Bsinf	small beef farm with a turnover < 40%
Bssup	small beef farm with a turnover \geq 40%
Dbinf	big dairy farm with a turnover < 40%
Dbsup	big dairy farm with a turnover \geq 40%
Dsinf	small dairy farm with a turnover < 40%
Dssup	small dairy farm with a turnover \geq 40%
Mbinf	big mixed farm with a turnover < 40%
Mbsup	big mixed farm with a turnover \geq 40%
Msinf	small mixed farm with a turnover < 40%
Mssup	small mixed farm with a turnover \geq 40%

453

454

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462

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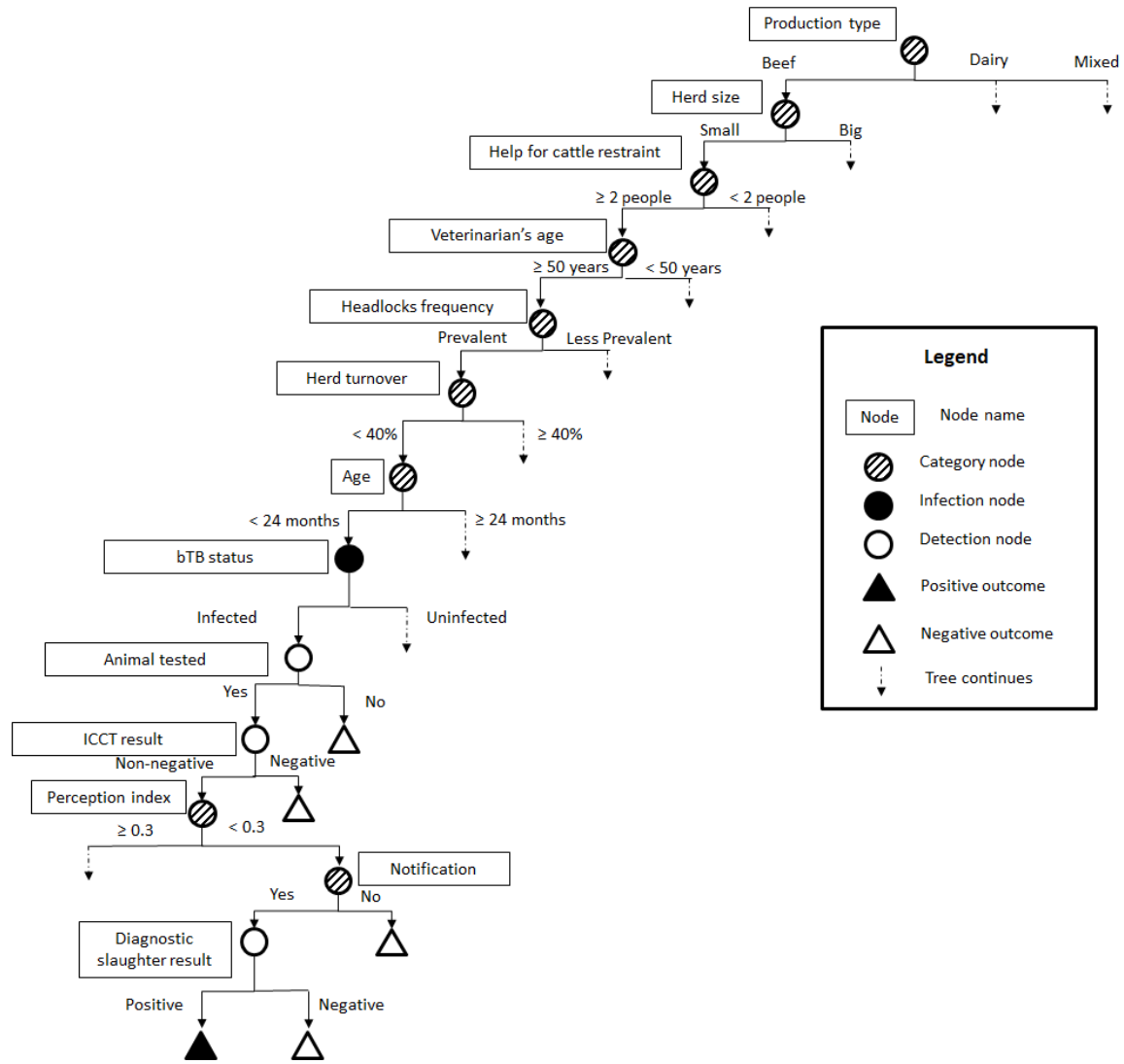
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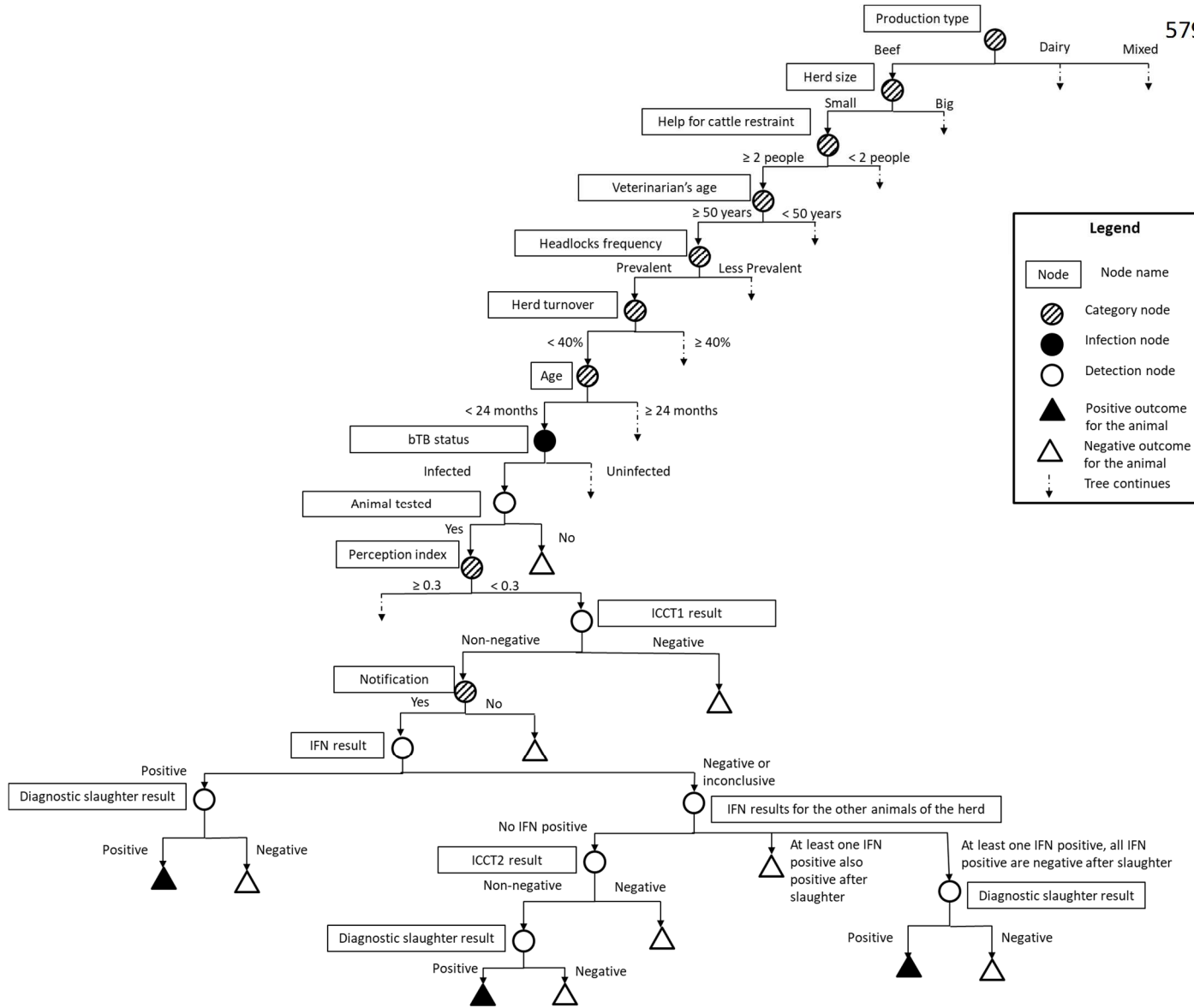
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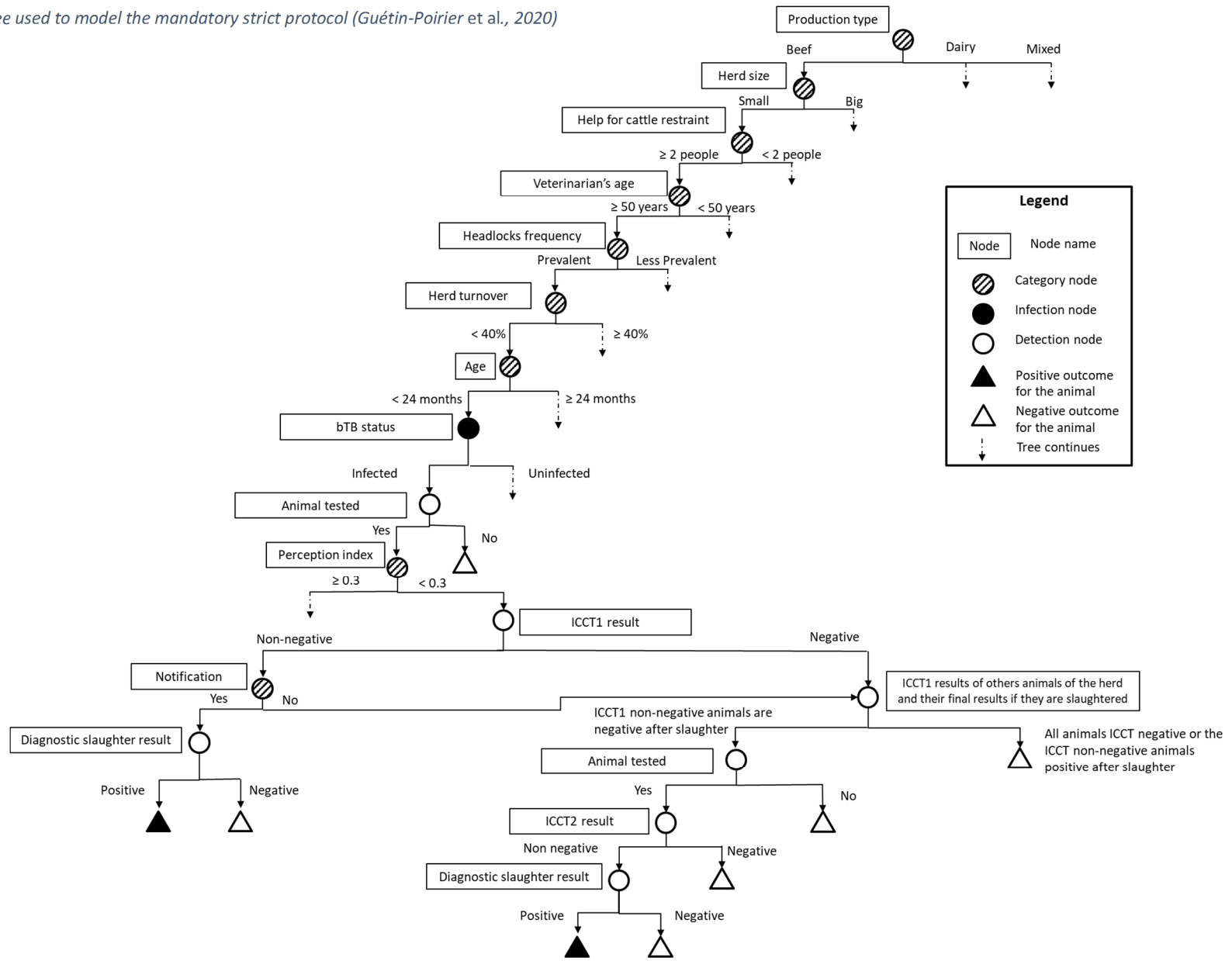


Figure 1. Scenario tree used to model the alternative strict protocol

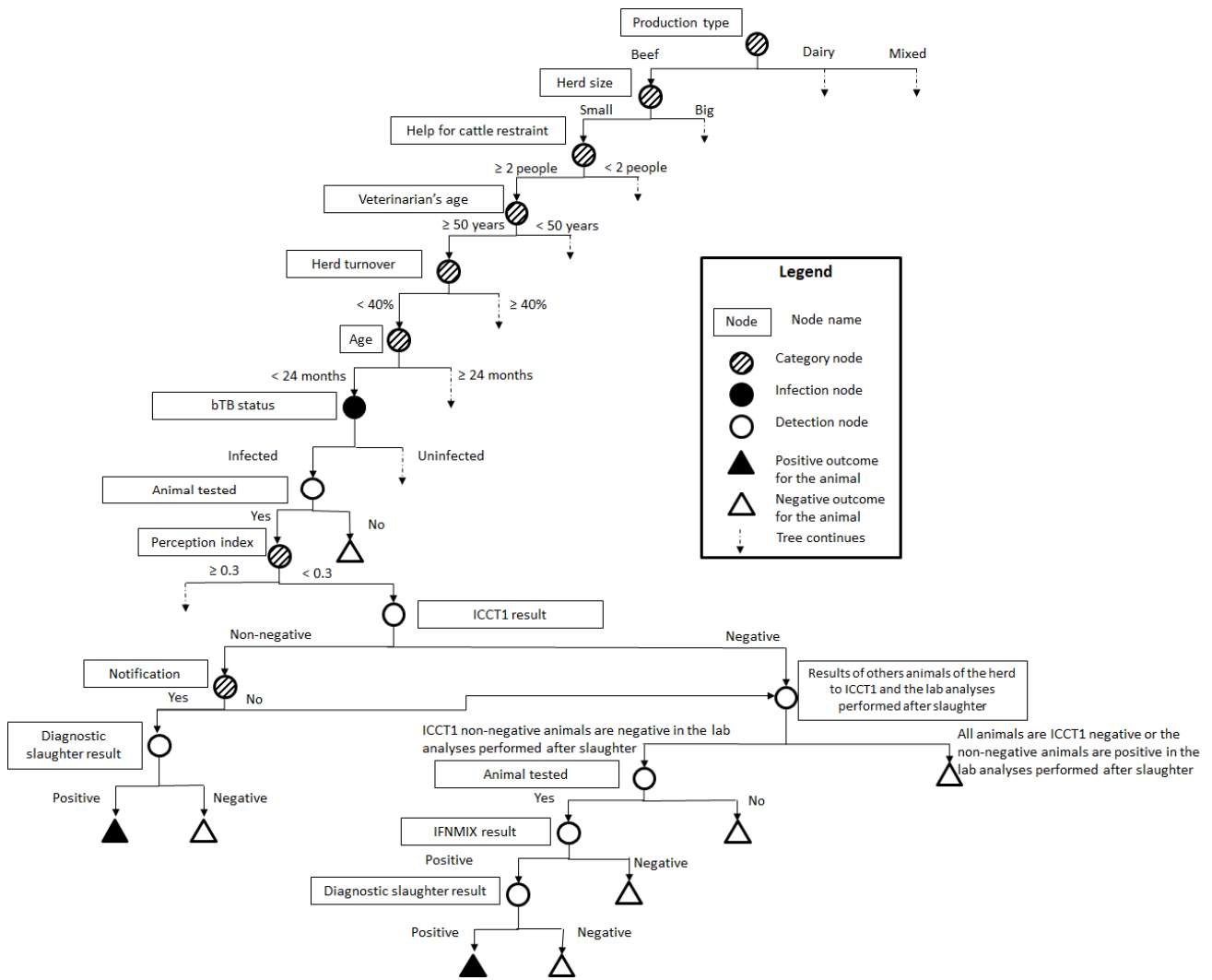


Figure 2. Scenario tree used to model the alternative compliant protocol

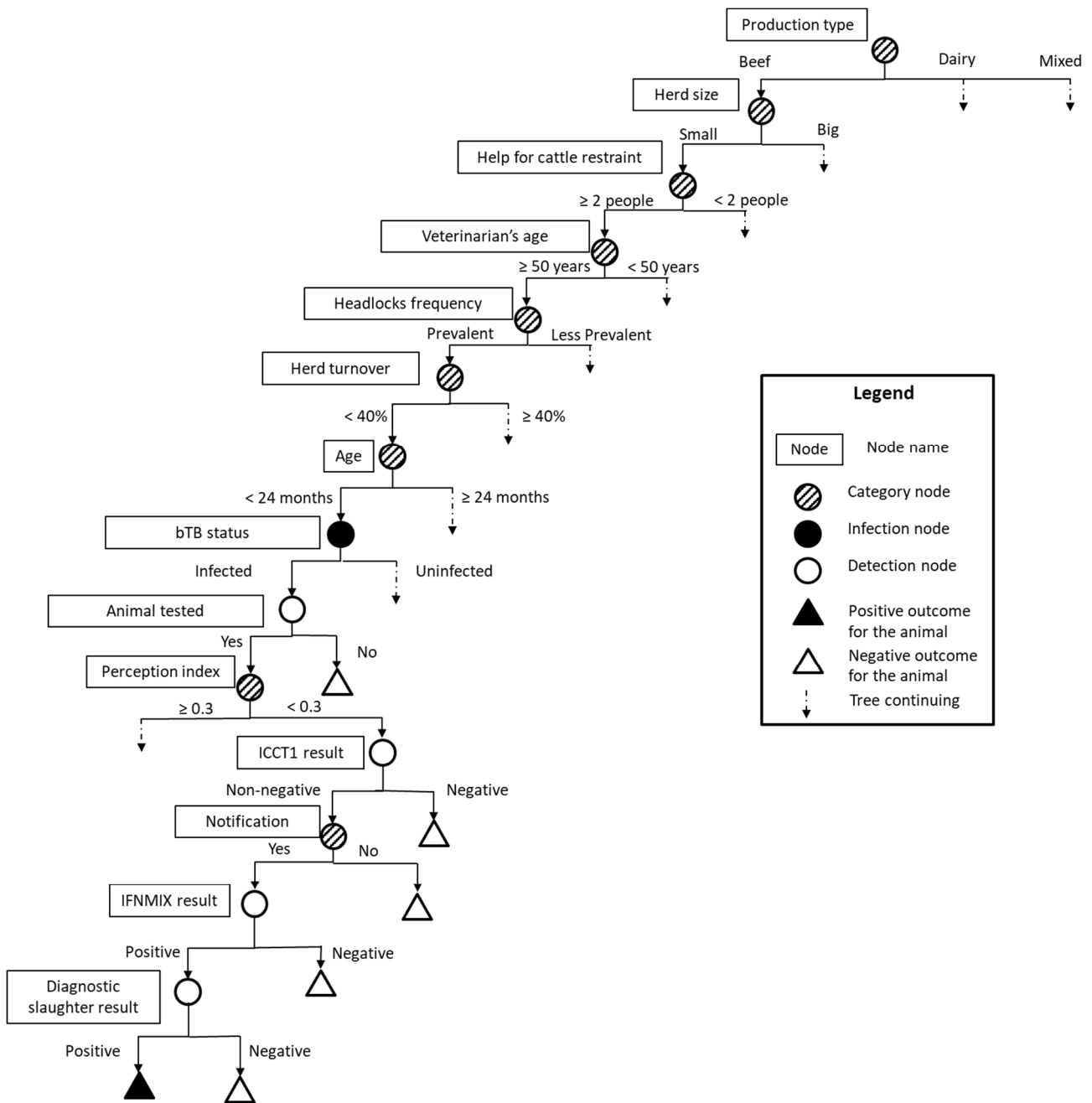
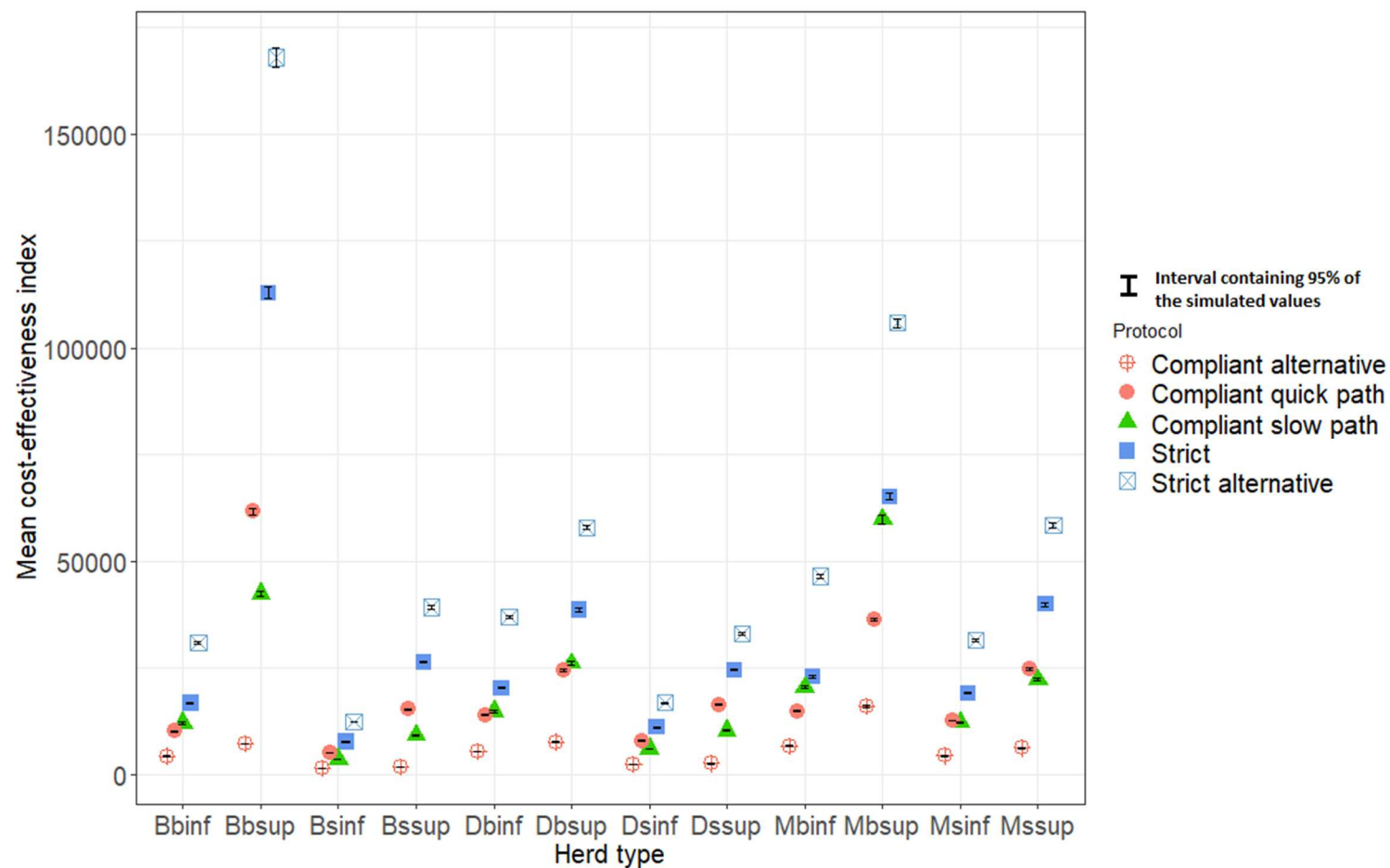


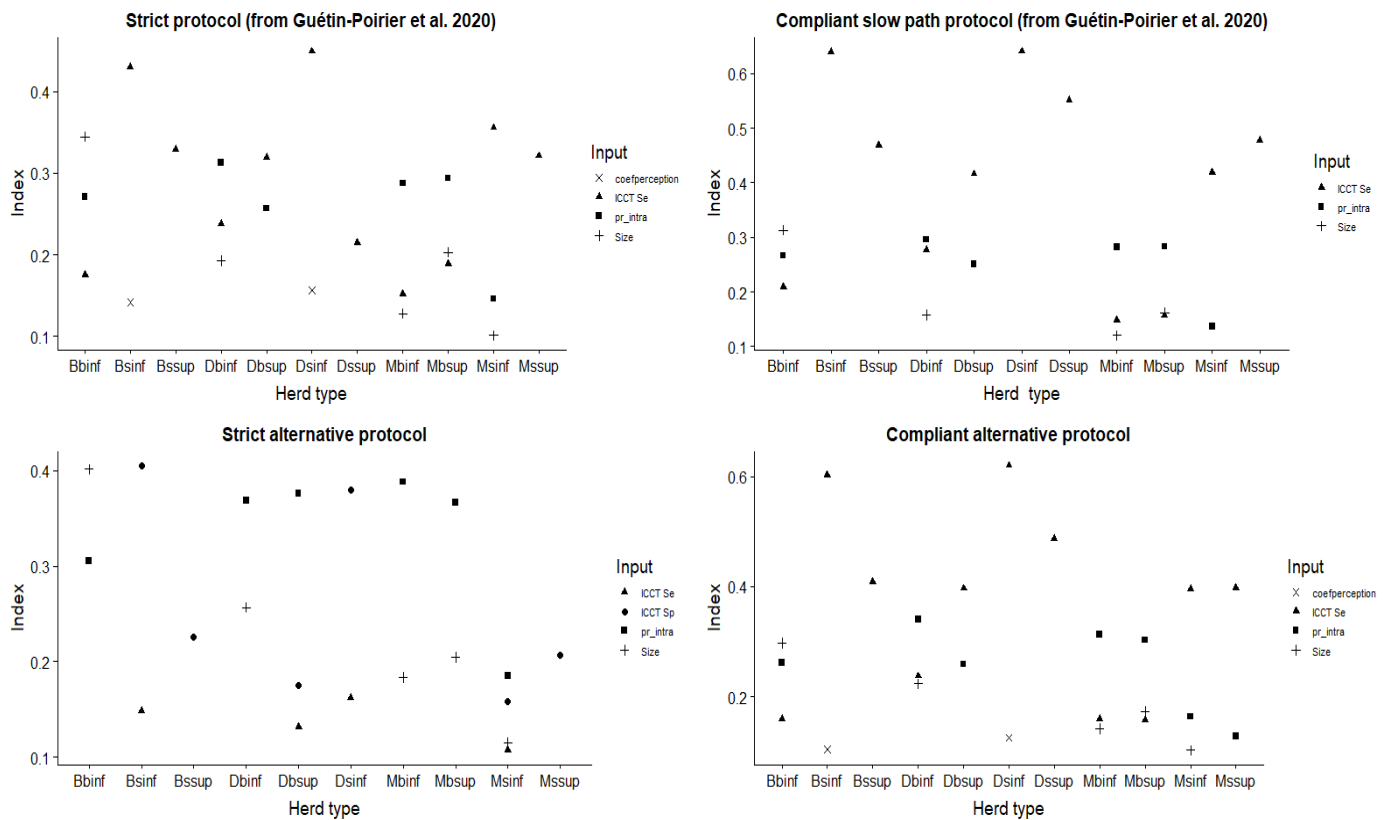
Figure 3. Cost-sensitivity index for the three mandatory protocols and the two alternative protocols of bTB surveillance in France by herd type (10,000 iterations)



Legend: Bbinf: big beef farm with a turnover of < 40%, Bbsup: big beef farm with a turnover of > 40%, Bsinf: small beef farm with a turnover of < 40%, Bssup: small Beef farm with a turnover > 40%, Dbinf: big dairy farm with a turnover of < 40%, Dbsup: big dairy farm with a turnover > 40%, Dsinf: small dairy farm with a turnover of < 40%, Dssup: small dairy farm with a turnover > 40%, Mbinf: big mixed farm with a turnover of < 40%, Mbsup: big mixed farm with a turnover > 40%, Msinf: small mixed farm with a turnover of < 40%, Mssup: small mixed farm with a turnover of > 40%.

A high cost-sensitivity index indicates poor efficiency of the protocol.

Figure 4: Sensitivity analysis indexes above 10% (Mc Kay method) for the output "herd sensitivity" by herd type for each protocol



Legend:

The higher the index, the more influent the parameter on the variations of the "herd sensitivity" output of the model.

Herd types are defined in the glossary at the end of the manuscript. (D-: dairy ; B-:beef ; M- : mixed ; -s- : small ; -b- : big ; -inf : low turnover (<40%) ; -sup : high turnover (≥40%))

Coefperception : index representing the veterinarian perception (good or bad) of bTB surveillance and control in France

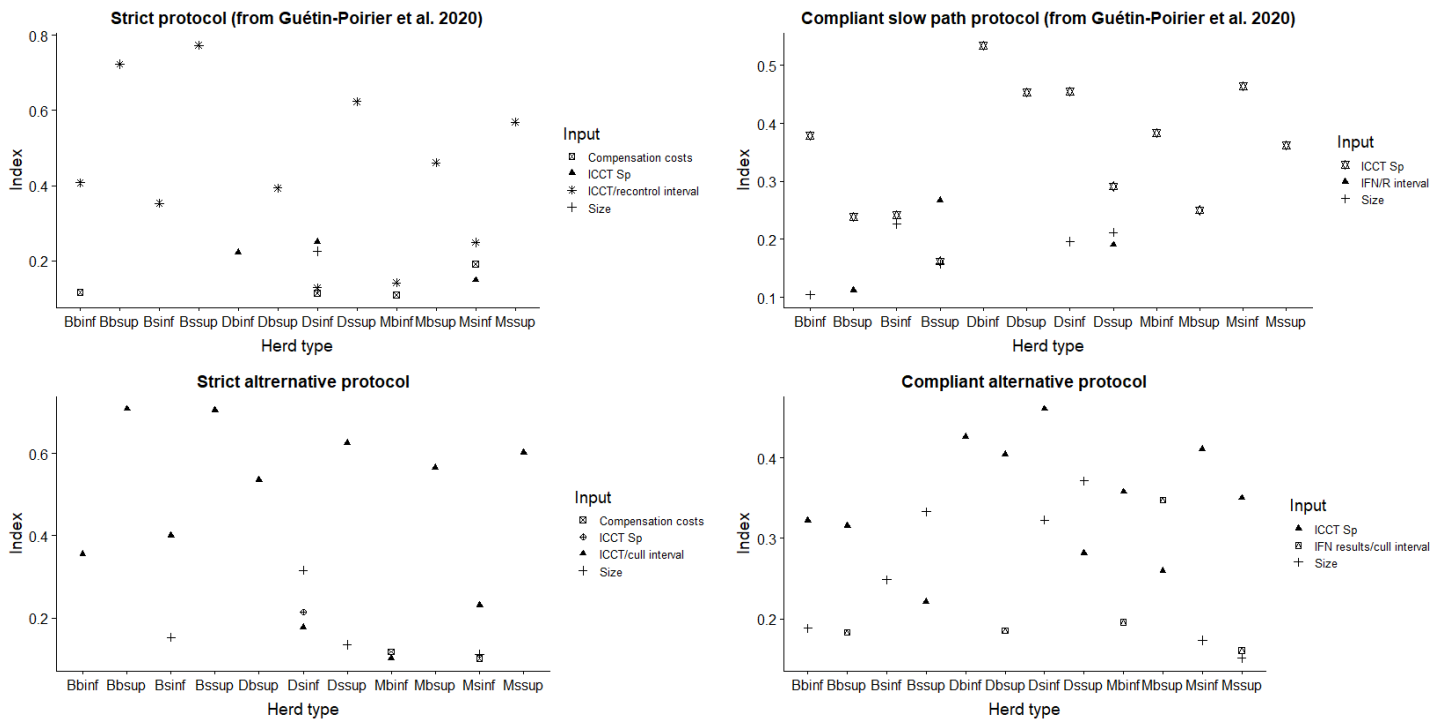
ICCT Se: sensitivity of the intradermal cervical comparative tuberculin test.

ICCT Sp: specificity of the intradermal cervical comparative tuberculin test.

pr_intra: within-herd prevalence of bovine tuberculosis

Size: herd size

Figure 5. Sensitivity analysis indexes above 10% (Mc Kay method) for the output "total cost" by herd type for each protocol



Legend:

The higher the index, the more influent the parameter on the variations of the "total cost" output of the model.

Herd types are defined in the glossary at the end of the manuscript. (D-: dairy ; B-:beef ; M- : mixed ; -s- : small ; -b- : big ; -inf : low turnover (<40%) ; -sup : high turnover (≥40%))

Compensation costs : cost, for the State, of the indemnisation paid to the farmer when one of his bovine is culled for diagnosis. This indemnisation is fixed by the State but the meat value is deducted from this fixed price (Poirier *et al.*, 2019), the compensation cost is therefore variable.

ICCT/recontrol interval : interval between the first ICCT (ICCT1) and the second screening of the herd with ICCT in the strict protocol

IFN/R interval : interval between the results of IFN test on animals with non-negative results to ICCT1 and their recontrol by a second ICCT (compliant slow path protocol)

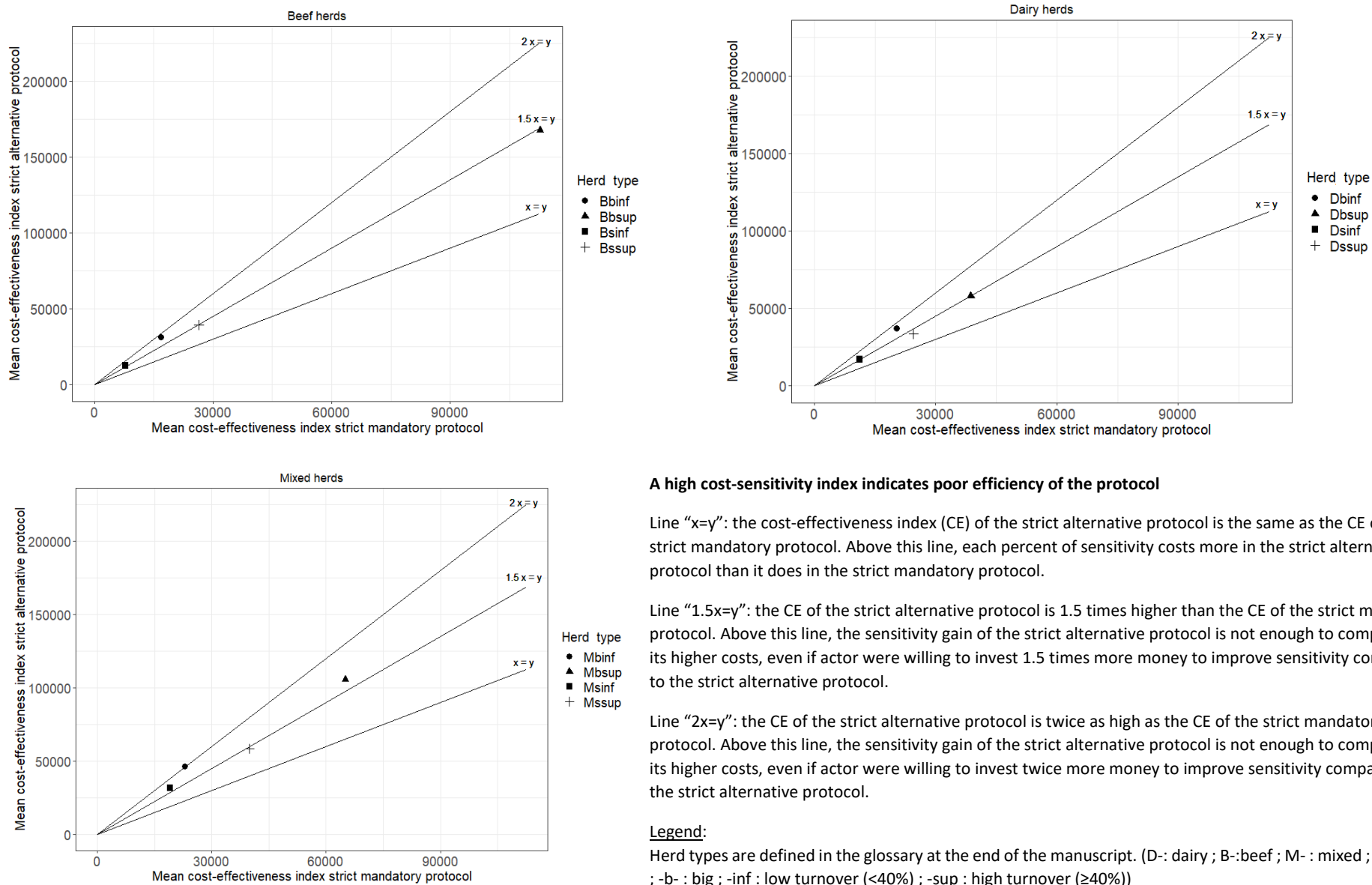
ICCT/cull interval : interval between a non-negative result to ICCT1 and the diagnostic culling of the corresponding animal

IFN results/cull interval : interval between a positive result to the IFN test and the culling of the corresponding animal

ICCT Sp: specificity of the intradermal cervical comparative tuberculin test

Size : herd size

Figure 6. Mean cost-effectiveness index of strict alternative protocol and of strict mandatory protocol for each herd type



A high cost-sensitivity index indicates poor efficiency of the protocol

Line “x=y”: the cost-effectiveness index (CE) of the strict alternative protocol is the same as the CE of the strict mandatory protocol. Above this line, each percent of sensitivity costs more in the strict alternative protocol than it does in the strict mandatory protocol.

Line “1.5x=y”: the CE of the strict alternative protocol is 1.5 times higher than the CE of the strict mandatory protocol. Above this line, the sensitivity gain of the strict alternative protocol is not enough to compensate its higher costs, even if actor were willing to invest 1.5 times more money to improve sensitivity compared to the strict alternative protocol.

Line “2x=y”: the CE of the strict alternative protocol is twice as high as the CE of the strict mandatory protocol. Above this line, the sensitivity gain of the strict alternative protocol is not enough to compensate its higher costs, even if actor were willing to invest twice more money to improve sensitivity compared to the strict alternative protocol.

Legend:

Herd types are defined in the glossary at the end of the manuscript. (D-: dairy ; B-:beef ; M- : mixed ; -s- : small ; -b- : big ; -inf : low turnover (<40%) ; -sup : high turnover (≥40%))

Table 1. Distributions used to model epidemiologic parameters of the scenario trees modelling mandatory and alternative protocols for periodic screening

Node	Parameter	Distribution	Comments	Reference
Production type Herd size Herd turnover	Herd type	$N^{(1)}$	Fitted to the real repartition of herd types (data from the BDNl*) in 2016, in Cantal, a French administrative area which has the proportion of each herd type closest to the national mean	(Poirier <i>et al.</i> , 2019)
Help for cattle restraint	At least two people to help the veterinarian	$\beta(49 ; 64.9)$	These parameters were identified as influent on either ICCT practices or perception of bTB surveillance (positive or negative) by the veterinarian thanks to a quantitative survey on 210 French veterinarians	(Guétin-Poirier <i>et al.</i> , 2020)
Veterinarian's age	Proportion of veterinarians over 50 years old	Constant = 0.33		
Headlock frequency	Headlocks are prevalent in the farms of the veterinarian's clients	$\beta(39.9 ; 74.1)$		
Perception index	Value of the perception index	$\beta^{(1)}$	Parameters fitted for each veterinarian's age, help for cattle restraint and headlock frequency, to the results of the quantitative survey about veterinarians' practices of ICCT and perception about bTB surveillance. The perception index was found to influence ICCT practices and notification of non-negative results habits of the veterinarian	(Complementary materials C1; Guétin-Poirier <i>et al.</i> , 2020)
Age	Proportion of bovine older than 24 months old	$N^{(1)}$	12 distributions (one for each herd type) fitted on real French data (from BDNl*), by herd type	(C2; Poirier <i>et al.</i> , 2019)
Herd infection	prevalence	1 or 0	We assumed successively that the herd was - infected to estimate herd sensitivity and cost of the protocols in an infected herd - uninfected to estimate the cost in an uninfected herd	
bTB status	Within-herd prevalence	PERT(0.008 ; 0.0094 ; 0.031)	An unpublished French study tested by PCR and bacteriology all animals of an infected herd and found 0.94 % of within-herd prevalence. In most breakdowns 1 to 3 animals are found infected with bTB in each breakdown	(Bouveret, 2017; Poirier, 2017)
Animal tested (ICCT1)	Proportion of tested animals (ICCT1)	Uniform(0.95 , 0.99)	Minimum and maximum in French data base, data quality did not allow to use a more informative distribution	(Poirier <i>et al.</i> , 2019)
ICCT1 result	ICCT1 Se	$N_{\text{asym}}(0.74 ; 0.43 ; 0.95)$		(de la Rua-Domenech <i>et al.</i> 2006; Clegg <i>et al.</i> 2011 ; Praud and Dufour, 2016 ; Pucken <i>et al.</i> 2017 ; Nuñez-García <i>et al.</i> 2018)
	ICCT1 Sp	$N_{\text{asym}}(0.99 ; 0.80 ; 1)$		
Notification	Notification of a non-negative ICCT1 result by the vet to health authorities	$\beta(60 ; 1)$ for a low perception index (<0.30)	Perception index was found to influence the probability for a veterinarian to notify to authorities a non-negative result to ICCT1, the	(Guétin-Poirier <i>et al.</i> , 2020)

		$\beta(49 ; 6)$ for a high perception index	distributions was fitted to the results of a quantitative survey (210 veterinarians)		
Animal tested (ICCT2)	Proportion of tested animals (ICCT2 of strict protocol)	PERT (1/herd size** ; 1 ; 1) for small herds PERT (1/herd size** ; 53/herd size** ; 1) for big herds	Analyses of SIGAL*** database showed a minimum of one adult and a maximum of 100% of the adults tested with ICCT2. In most of small herds all adults were tested with ICCT2, whereas a mean of 53 adults tested with ICCT2 was found for big herds. Limited data about the number of tested animals did not allow to fit normal distributions for this parameter	(C3; Poirier et al., 2019)	
ICCT2 result	ICCT2 Se and Sp conditional to a negative result to the first ICCT1	Same distribution than for ICCT1	We assumed that the result for the second ICCT has the same characteristics as the first ICCT, because animals screened by ICCT at year n are mainly animals already negative to the screening with an ICCT at year $n-1$.	(Poirier et al., 2019)	
	ICCT2 Se conditional to a first non-negative result to ICCT1	$N_{\text{asym}}(0.73 ; 0.43 ; 0.83)$		(de la Rua-Domenech et al., 2006; Praud et al., 2015; Praud and Dufour, 2016 ; Pucken et al., 2017)	
	ICCT2 Sp conditional to a first non-negative result to ICCT1	$N_{\text{asym}}(0.89 ; 0.87 ; 0.90)$		(Praud and Dufour, 2016)	
IFN results	IFN Se	$N(0.93 ; 0.0255)$	Estimated from French data, conditional to a first non-negative ICCT result	(Praud and Dufour, 2016)	
	IFN Sp	$N(0.458 ; 0.00969)$			
IFNMIX results	IFNMIX Se	$N(0.83 ; 0.06)$	Estimated under French conditions, conditionally to a first ICCT non-negative result	(Praud et al., 2019)	
	IFNMIX Sp	$N(0.861 ; 0.0081)$			
Diagnostic culling result	PCR Se	With lesions	Diagnostic culling sensitivity and specificity were calculated at each iteration of the model, using sensitivity and specificity of histology, PCR and bacteriology and the probability for an animal to present macroscopic bTB-like lesions (modelled from French data)	(Courcoul and Boschioli, 2013)	
		Without lesions			$N_{\text{asym}}(0.887 ; 0.825, 0.923)$
	PCR Sp	With lesions			$N_{\text{asym}}(0.909 ; 0.873 ; 0.943)$
		Without lesions			$N_{\text{asym}}(0.970 ; 0.943 ; 0.990)$
	Histology Se	$N_{\text{asym}}(0.998 ; 0.994 ; 1)$			
Histology Sp	$N_{\text{asym}}(0.936 ; 0.899 ; 0.969)$				
	Bacteriology Se and Sp	1	Se and Sp of the tests performed by the NRL (bacteriology, spoligotyping and PCR) were assumed to be perfect	M-L. Boschioli, director of the French NRL	

Legend: $\beta(a ; b)$ = beta distribution ; $N_{\text{asym}}(\text{mean} ; \text{min} ; \text{max})$ = Normal asymmetric distribution (Sicard, 2013) ; $N(\text{mean} ; \text{sd})$ = normal distribution ; PERT(min ; mode ; max) = Pert distribution ; Se = sensitivity, Sp=specificity; ICCT = intradermal cervical comparative tuberculin test; IFN = interferon test; NRL = national laboratory of reference for bTB.

*BDNI =National database of bovine identification = French data base in which all bovine are register associated with their age, race and all commercial exchanges of live animals.

**herd size was modelled by normal distributions fitted to French data of herd size in Cantal's herds, by herd type (see complementary materials or (Poirier et al., 2019) for details

*** SIGAL is the French database that centralised data about all bTB-related interventions (surveillance or control) in French farms

Line of the table Parameters taking into account the ICCT practice in our evaluation of the periodic screening protocols (method's details in Guétin-Poirier et al., 2020)

⁽¹⁾For more details on these distributions, see (Poirier et al., 2019) or complementary materials (C1—C3)

Table 2. Herd sensitivity estimation (in %) for each protocol by herd type

Production type	Herd size category	Herd turnover	Compliant slow-path protocol ⁽¹⁾		Compliant quick-path protocol ⁽¹⁾		Compliant alternative protocol ⁽²⁾		Strict protocol ⁽¹⁾		Strict alternative protocol ⁽²⁾	
			Mean	Percentile ⁽³⁾	Mean	Percentile ⁽³⁾	Mean	Percentile ⁽³⁾	Mean	Percentile ⁽³⁾	Mean	Percentile ⁽³⁾
Dairy farm	small (< 74 adults)	< 40%	24.67	24.56-24.78	25.60	25.49-25.72	21.24	21.14-21.34	30.01	29.89-30.13	36.96	36.85-37.07
		≥ 40%	17.66	17.58-17.74	18.29	18.21-18.38	15.16	15.09-15.23	21.10	21.02-21.19	25.28	25.19-25.38
	big (≥ 74 adults)	< 40%	29.86	29.68-30.04	31.30	31.11-31.49	26.30	26.13-26.47	33.28	33.1-33.46	40.03	39.9-40.17
		≥ 40%	23.81	23.69-23.94	24.89	24.76-25.02	20.72	20.61-20.84	27.38	27.25-27.51	34.31	34.21-34.41
Beef farm	small (< 66 adults)	< 40%	21.56	21.46-21.65	22.34	22.25-22.44	18.54	18.46-18.63	26.25	26.14-26.35	32.14	32.03-32.24
		≥ 40%	18.33	18.25-18.41	18.98	18.89-19.06	15.74	15.67-15.81	22.06	21.97-22.15	26.67	26.58-26.77
	big (≥ 66 adults)	< 40%	28.06	27.87-28.25	29.41	29.21-29.61	24.71	24.54-24.89	31.21	31.03-31.4	37.78	37.62-37.93
		≥ 40%	11.93	11.83-12.02	12.38	12.28-12.48	10.31	10.23-10.4	13.50	13.4-13.6	17.63	17.52-17.74
Mixed farm	small (< 124 adults)	< 40%	25.48	25.34-25.62	26.58	26.43-26.72	22.17	22.04-22.3	29.42	29.29-29.56	36.38	36.27-36.49
		≥ 40%	22.01	21.9-22.13	22.90	22.78-23.02	19.05	18.94-19.15	25.51	25.39-25.62	32.31	32.21-32.42
	big (≥ 124 adults)	< 40%	39.58	39.35-39.81	41.58	41.34-41.82	35.55	35.33-35.77	42.61	42.39-42.84	48.21	48.04-48.38
		≥ 40%	36.42	36.2-36.63	38.20	37.97-38.42	32.54	32.33-32.75	39.34	39.12-39.56	45.28	45.12-45.45

⁽¹⁾French mandatory protocol (Guétin-Poirier *et al.*, 2020)

⁽²⁾Theoretical alternative protocols modelled in which the second ICCT was replaced by an IFNMIX test

⁽³⁾ 2.5th – 97.5th percentile: interval containing 95% of the 10 000 herd sensitivity estimations

Table 3. Differences between the mean herd sensitivity between the alternative protocols (strict alternative protocol and compliant alternative protocol), in which the second ICCT was replaced by the IFNMIX test, and the corresponding mandatory protocols (strict protocol and compliant slow-path protocol), by herd type.

Differences in mean herd sensitivity between the regulatory protocol and its alternative				
Production type	Herd size category	Herd turnover	strict protocols ⁽¹⁾	compliant protocols ⁽²⁾
Dairy farm	small	< 40%	6.95	-3.43
	(< 74 adults)	≥ 40%	4.18	-2.50
	big	< 40%	6.75	-3.56
	(≥ 74 adults)	≥ 40%	6.93	-3.09
Beef farm	small	< 40%	5.89	-3.01
	(< 66 adults)	≥ 40%	4.62	-2.59
	big	< 40%	6.56	-3.35
	(≥ 66 adults)	≥ 40%	4.13	-1.62
Mixed farm	small	< 40%	6.96	-3.31
	(< 124 adults)	≥ 40%	6.81	-2.97
	big	< 40%	5.59	-4.03
	(≥ 124 adults)	≥ 40%	5.94	-3.88

⁽¹⁾ mean herd sensitivity of the alternative strict protocol - mean herd sensitivity of the mandatory strict protocol

⁽²⁾ mean herd sensitivity of the alternative compliant protocol - mean herd sensitivity of the mandatory compliant slow-path protocol

Table 4. Mean total cost of each protocol, by herd type, for a suspect herd until confirmation or invalidation of the suspicion (in euros per herd)

Production type	Herd size category	Herd turnover	Compliant slow path protocol ⁽¹⁾		Compliant quick path protocol ⁽¹⁾		Compliant alternative protocol ⁽²⁾		Strict protocol ⁽¹⁾		Strict alternative protocol ⁽²⁾	
			Mean	Percentile ⁽³⁾	Mean	Percentile ⁽³⁾	Mean	Percentile ⁽³⁾	Mean	Percentile ⁽³⁾	Mean	Percentile ⁽³⁾
Dairy farm	small (< 74 adults)	< 40%	1,451	1,430-1,472	1,963	1,943-1,983	516	510-522	3,286	3,250-3,322	6,319	6,261-6,377
		≥ 40%	1,740	1,719-1,761	2,844	2,823-2,865	388	383-394	4,995	4,954-5,036	8,279	8,195-8,363
	big (≥ 74 adults)	< 40%	4,299	4,236-4,362	4,207	4,165-4,250	1,377	1,362-1,392	6,646	6,581-6,712	15,565	15,452-15,677
		≥ 40%	5,906	5,820-5,992	5,731	5,690-5,772	1,515	1,495-1,536	10,231	10,154-10,309	19,975	19,824-20,127
Beef farm	small (< 66 adults)	< 40%	773	763-784	1,106	1,096-1,116	292	289-296	1,982	1,963-2,001	4,001	3,962-4,040
		≥ 40%	1,615	1,592-1,638	2,761	2,737-2,785	295	290-300	5,588	5,537-5,638	10,267	10,149-10,385
	big (≥ 66 adults)	< 40%	3,324	3,266-3,382	2,854	2,828-2,880	1,055	1,042-1,069	5,078	5,034-5,122	12,247	12,149-12,345
		≥ 40%	4,672	4,592-4,751	6,689	6,628-6,750	714	699-728	13,691	13,564-13,819	27,677	27,363-27,991
Mixed farm	small (< 124 adults)	< 40%	3,013	2,964-3,062	3,229	3,196-3,262	954	942-966	5,491	5,436-5,545	11,795	11,695-11,895
		≥ 40%	4,733	4,654-4,812	5,342	5,301-5,383	1,153	1,134-1,171	9,793	9,716-9,870	18,836	18,668-19,003
	big (≥ 124 adults)	< 40%	8,447	8,312-8,582	6,414	6,348-6,480	2,464	2,433-2,496	10,291	10,195-10,387	25,282	25,096-25,468
		≥ 40%	22,126	21,732-22,519	13,979	13,872-14,086	5,226	5,134-5,319	26,092	25,891-26,294	52,461	52,020-52,903

⁽¹⁾French mandatory protocol (Guétin-Poirier *et al.*, 2020)

⁽²⁾Theoretical alternative protocols modelled, in which the second ICCT was replaced by an IFNMIX test

⁽³⁾ 2.5th – 97.5th percentile: interval containing 95% of the 10 000 herd sensitivity estimations