Sensitivity of bovine tuberculosis surveillance through intradermal tests in cattle in France: An evaluation of different scenarios

Viviane Hénaux, Claire Ponsart, Justine Corre, Florence Etore, Henri-Jean Boulouis, Hervé Morvan, Lionel Grisot, Carole Peroz

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

Viviane Hénaux[a*], Claire Ponsart[b], Justine Corre[c], Florence Etore[c], Henri-Jean Boulouis[d], Hervé Morvan[e], Lionel Grisot[f], Carole Peroz[g]

[a] Université de Lyon – ANSES, Laboratoire de Lyon, Unité Epidémiologie et Appui à la Surveillance, 31 Avenue Tony Garnier, 69007 Lyon, France. viviane.henaux@anses.fr

[b] Université de Paris-Est, ANSES, Laboratoire de santé animale, Unité Zoonoses bactériennes, 14 rue Pierre et Marie Curie, 94706 Maisons-Alfort, France. claire.ponsart@anses.fr

[c] ANSES, Direction de l'évaluation des risques, Unité d'Evaluation des Risques liés à la Santé, à l'Alimentation et au Bien-Etre des animaux, 14 rue Pierre et Marie Curie, 94706 Maisons-Alfort, France. justine.corre@anses.fr – florence.etore@anses.fr

[d] UMR BIPAR, Laboratoire de Santé Animale, ANSES, INRAE, Ecole Nationale Vétérinaire d'Alfort, Paris-Est Sup, 7 avenue du Général de Gaulle, 94700 Maisons-Alfort, France. henri-jean.boulouis@vet-alfort.fr

[e] LABOCEA , 7 rue du Sabot, CS30054, 22440 Ploufragan, France. herve-morvan@orange.fr

[f] Groupement Technique Vétérinaire de Bourgogne – Franche-Comté & Groupe de travail Sécurité Sanitaire des Aliments de la Société Nationale des GTV, Clinique Vétérinaire des Tourbières, 1 rue de Beaucaire, 25560 Frasne, France. lionel.grisot@orange.fr

[g] INRAE, Oniris, BIOEPAR, 44300 Nantes, France. carole.peroz@oniris-nantes.fr

*corresponding author : viviane.henaux@anses.fr

Abstract

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

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

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

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

Keywords

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

Introduction

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

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

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

In areas where prevalence has been lower than 0.1% for six years or more, programmed surveillance, *i.e.* regular testing of bovines by IDT or IFNg, is not applied anymore (French Ministry of Agriculture, 2003). In the rest of the country, the rhythm of programmed surveillance in herds varies in frequency, from annual to every four years, depending on the local epidemiological situation and the risk level (French Ministry of Agriculture, 2003). In high-risk areas, referred as reinforced prophylaxis zones (RPZ), the surveillance is strengthened with annual testing of herds. There are two definitions of RPZ: (i) "historic" RPZ which include the communes located in a 10-km radius around pastures used by herds found to be TB-infected within the last five years and the communes located in a 10-km radius from capture sites of TB-infected badgers within the last five years, and (ii) "prospecting" RPZ which include communes located in a 2-km radius around pastures of recently identified and isolated cases (French General Directorate for Food, 2018b).

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

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

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

Methods

Detection fraction and scenario tree

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

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

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

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

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

Programmed surveillance

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

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

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

$$SeU = 1 - (1 - P_{bov\_test} \times Se)^{N_{bov\_inf}}$$

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

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

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

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

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

<u>Pre-movement surveillance</u>

Inter-herd movement surveillance depends on both the sanitary state and level of risk regarding TB in the herd of origin, the duration of the movement between the origin and destination herds and the production type of the destination herd (French General Directorate for Food, 2017). These rules concern bovines aged six weeks and over. Pre-movement tests are mandatory for animals that originate from a previously infected herd that recovered its TB-free status after an outbreak (French Ministry of Agriculture, 2003; French General Directorate for Food, 2017) or from the herds with a neighbourhood link with a TB-infected herd, i.e. with proximity of pastures (referred as herds with an epidemiological link, hereafter).

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

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

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

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

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

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

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

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

Model simulations

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

Sensitivity analysis

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

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

Results

Programmed surveillance

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

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

Pre-movement surveillance

The mean detection fraction predicted by the model for the current pre-movement surveillance is 1.2% [0.7-1.8]. The scenario encompassing all herds within the RPZ, and not only those that recovered the free status after an infection, or those with an epidemiological link, will increase the detection fraction to 26.5% [18.1-37.9] (Table 3). This difference was significant (Mann-Whitney-Wilcoxon test: W = 0, p < 0.001).

Sensitivity analysis

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

Discussion

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

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

In 2017/2018, among the departments included in the analysis, 8,853 herds were located in RPZ communes and were subject to surveillance. These departments gathered about 95% of herds in RPZ, which makes a total of 9,320 herds in RPZ in metropolitan France. This number is still under-estimated as the herds located outside the RPZ but with bovines pasturing in those RPZ would also be covered by the surveillance. By considering the mean proportion of herds in each risk group (56% of dairy/mixed herds, 16% of dairy herds and 28% of small herds) and the prevalence for each risk group (Table 1), 51 herds in RPZ were estimated to be infected. This value is likely underestimated as the estimation of prevalence considered only outbreaks detected in 2017, i.e. apparent prevalence. Accordingly, based on the model-predicted detection fraction, the current programmed surveillance was predicted to detect 35 infected herds, while results of programmed surveillance for 2015-2017 reported the detection of 58 herds annually (Delavenne et al., 2019). The sensitivity analysis showed that the detection fraction depended primarily on the number of infected bovines within the herd, and therefore the ability of surveillance to detect infected herds depends on the extent of the diffusion of the pathogen within the herd.

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

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

The effectiveness of pre-movement surveillance was predicted by the model to be limited, with a median detection fraction of about 1%. In 2017-2018, in the departments Côte d’Or and Calvados and in the departments of the regions Occitanie and Nouvelle-Aquitaine, there were 327 previously-infected herds and 659 herds with an epidemiological neighbourhood link, that is 986 herds subject to pre-movement surveillance. In some departments of the region Nouvelle-Aquitaine, no information was available on the nature of the risk regarding TB, which could be an epidemiological link by neighbourhood, by movement from a TB-infected herd, a re-emergence from a previous TB infection or a link with a wildlife outbreak, suggesting that some herds are likely excluded from this surveillance despite a potential risk. Assuming that the herds covered by surveillance have the same sale pattern than the entire population (regarding the annual number of sales), 85% carried out at least one sale of a bovine aged six-weeks or more. Based on prevalence values in each risk group and the detection fraction predicted by the model, seven of these herds were infected, among which less than one herd per year was detected by the current surveillance system. This prediction aligns with the results of surveillance in recent years: in 2014, 1% of the 105 incident herds were identified through movement surveillance (including pre- and post-movement surveillance) (Cavalerie et al. 2015), and for the 2015-2018 period, only two outbreaks were found by a test during a movement (Delavenne et al., 2019).

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

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

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

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

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

Conclusions

Our study quantified the expected annual performance gains of the TB surveillance system in France under different scenarios of evolution of the surveillance, including a decrease in the minimum age of testing and an extension of pre-movement tests to all herds in RPZ. Tailoring this system to be more effective in detecting infected herds should be accompanied by a standardisation of surveillance regulations across the country and by the implementation of any additional measures to improve TB test sensitivity and its implementation by field actors.

Acknowledgements

The authors thank the French Ministry of Agriculture, in particular F. Chevalier, for access to the French National Cattle Register and TB surveillance data, the ANSES Expert Committee on "Animal Health and Welfare" and M-L. Boschiroli for fruitful discussion and providing advices and recommendations on this study. This work was supported by ANSES.

References

Barbier, E., Rochelet, M., Gal, L., Boschiroli, M.L., Hartmann, A., 2017. Impact of temperature and soil type on Mycobacterium bovis survival in the environment. PLoS One 12, e0176315.

Bekara, M.E.A., Courcoul, A., Bénet, J.-J., Durand, B., 2014. Modeling Tuberculosis Dynamics, Detection and Control in Cattle Herds. PLoS One 9, e108584.

Calavas, D., Fediaevsky, A., Collin, E., Touratier, A., Amar, P., Moquay, V., Marcé, C., Bronner, A., Hendrikx, P., 2012. Plateforme nationale de surveillance épidémiologique en santé animale : missions prioritaires et organisation. Bull Epid Santé Anim Alim 48, 2-5.

Caminiti, A., Pelone, F., LaTorre, G., De Giusti, M., Saulle, R., Mannocci, A., Sala, M., Della Marta, U., Scaramozzino, P., 2016. Control and eradication of tuberculosis in cattle: a systematic review of economic evidence. Veterinary Record 179, 70.

Cavalerie, L., Courcoul, A., Boschiroli, M.L., Réveillaud, E., Gay, P., 2015. Tuberculose bovine en France en 2014: une situation stable. Bull Epid Santé Anim Alim 71, 4-11.

Ciaravino, G., Ibarra, P., Casal, E., Lopez, S., Espluga, J., Casal, J., Napp, S., Allepuz, A., 2017. Farmer and Veterinarian Attitudes towards the Bovine Tuberculosis Eradication Programme in Spain: What Is Going on in the Field? Frontiers in Veterinary Science 4.

Crozet, G., Dufour, B., Rivière, J., 2019. Investigation of field intradermal tuberculosis test practices performed by veterinarians in France and factors that influence testing. Research in veterinary science 124, 406-416.

Delavenne, C., Pandolfi, F., Girard, S., Réveillaud, S., Jabert, P., Boschiroli, M.L., Dommergues, L., Garapin, F., Keck, N., Martin, F., Moussu, M., Philizot, S., Rivière, J., Tourette, I., Calavas, D., Dupuy, C., Dufour, B., Chevalier, F., 2019. Tuberculose bovine : bilan et évolution de la situation épidémiologique entre 2015 et 2017 en France métropolitaine. Bull Epid Santé Anim Alim Sous presse.

European Commission (EC), 1964. Council Directive of 26 June 1964 on animal health problems affecting intra-Community trade in bovine animals and swine. Official Journal of the European Communities. 164-184.

European Food Safety Authority (EFSA), European Centre for Disease Prevention and Control (ECDC), 2018. The European Union summary report on trends and sources of zoonoses, zoonotic agents and food-borne outbreaks in 2017. EFSA Journal 16, e05500.

Food and Agriculture Organization (FAO), 2014. Risk-based disease surveillance – A manual for veterinarians on the design and analysis of surveillance for demonstration of freedom from disease. FAO Animal Production and Health Manual No. 17. Rome, Italy.

French General Directorate for Food, 2017. Note de service DGAL/SDSPA/2017-863 modifiant la note DGAL/SDSPA/N2006-8051 relative aux dérogations aux tests de dépistage brucellose et

tuberculose lors de mouvements de bovins afin d'allonger la durée de validité de l'IDC dans les cheptels à risque.
French General Directorate for Food, 2018a. French national bovine tuberculosis action plan 2017-2022. pp. 12.
French General Directorate for Food, 2018b. Instruction technique DGAL/SDSPA/2018-598 du 06 août 2018 : Modalités techniques et financières de mise en œuvre de la campagne de surveillance de la tuberculose bovine 2018-2019.
French Ministry of Agriculture, 2003. Arrêté du 15 septembre 2003 fixant les mesures techniques et administratives relatives à la prophylaxie collective et à la police sanitaire de la tuberculose des bovinés et des caprins.
Grange, J.M., Yates, M.D., 1994. Zoonotic aspects of Mycobacterium bovis infection. Veterinary microbiology 40, 137-151.
Hénaux, V., Ngwa-Mbot, D., Memeteau, S., Touratier, A., Bronner, A., Calavas, D., 2017. Première estimation des coûts vétérinaires et de laboratoire de la surveillance et de la lutte vis-à-vis des maladies réglementées chez les ruminants en France en 2014. Bull Epid Santé Anim Alim 79, 2-11.
Huneau-Salaun, A., Stark, K.D., Mateus, A., Lupo, C., Lindberg, A., S, L.E.B.-L., 2015. Contribution of Meat Inspection to the surveillance of poultry health and welfare in the European Union. Epidemiology and infection 143, 2459-2472.
Maddock, E.C., 1933. Studies on the Survival Time of the Bovine Tubercle Bacillus in Soil, Soil and Dung, in Dung and on Grass, with Experiments on the Preliminary Treatment of Infected Organic Matter and the Cultivation of the Organism. The Journal of hygiene 33, 103-117.
Martin, P.A., Cameron, A.R., Greiner, M., 2007. Demonstrating freedom from disease using multiple complex data sources 1: a new methodology based on scenario trees. Preventive veterinary medicine 79, 71-97.
McKay, M.D., Beckman, R.J., Conover, W.J., 1979. A comparison of three methods for selecting values of input variables in the analysis of output from a computer code. Technometrics 21, 239-245.
Menzies, F.D., Neill, S.D., 2000. Cattle-to-cattle transmission of bovine tuberculosis. Vet J 160, 92-106.
Michelet, L., de Cruz, K., Karoui, C., Hénault, S., Boschiroli, M.L., 2017. Mycobacterium microti infection in a cow in France. Veterinary Record 180, 429.
Monaghan, M.L., Doherty, M.L., Collins, J.D., Kazda, J.F., Quinn, P.J., 1994. The tuberculin test. Veterinary microbiology 40, 111-124.
Nuñez-Garcia, J., Downs, S.H., Parry, J.E., Abernethy, D.A., Broughan, J.M., Cameron, A.R., Cook, A.J., de la Rua-Domenech, R., Goodchild, A.V., Gunn, J., More, S.J., Rhodes, S., Rolfe, S., Sharp, M., Upton, P.A., Vordermeier, H.M., Watson, E., Welsh, M., Whelan, A.O., Woolliams, J.A., Clifton-Hadley, R.S., Greiner, M., 2018. Meta-analyses of the sensitivity and specificity of ante-mortem and post-mortem diagnostic tests for bovine tuberculosis in the UK and Ireland. Preventive veterinary medicine 153, 94-107.
Olea-Popelka, F., Muwonge, A., Perera, A., Dean, A.S., Mumford, E., Erlacher-Vindel, E., Forcella, S., Silk, B.J., Ditiu, L., El Idrissi, A., Raviglione, M., Cosivi, O., LoBue, P., Fujiwara, P.I., 2017. Zoonotic tuberculosis in human beings caused by Mycobacterium bovis—a call for action. The Lancet Infectious Diseases 17, e21-e25.
Palisson, A., Courcoul, A., Durand, B., 2016. Role of Cattle Movements in Bovine Tuberculosis Spread in France between 2005 and 2014. PLoS One 11, e0152578.
Phillips, C.J., Foster, C.R., Morris, P.A., Teverson, R., 2003. The transmission of Mycobacterium bovis infection to cattle. Research in veterinary science 74, 1-15.
Poirier, V., Rivière, J., Bouveret, A., Gardon, S., Dufour, B., 2019. Cost-effectiveness assessment of three components of the bovine tuberculosis surveillance system by intradermal tuberculin testing in French cattle farms by a scenario tree approach. Preventive veterinary medicine 166, 93-109.

Prodinger, W.M., Brandstatter, A., Naumann, L., Pacciarini, M., Kubica, T., Boschiroli, M.L., Aranaz, A., Nagy, G., Cvetnic, Z., Ocepek, M., Skrypnyk, A., Erler, W., Niemann, S., Pavlik, I., Moser, I., 2005. Characterization of Mycobacterium caprae isolates from Europe by mycobacterial interspersed repetitive unit genotyping. Journal of clinical microbiology 43, 4984-4992.
R Core Team, 2018. R: A language and environment for statistical computing., R Foundation for Statistical Computing. Vienna, Austria.
Réveillaud, É., Desvaux, S., Boschiroli, M.-L., Hars, J., Faure, É., Fediaevsky, A., Cavalerie, L., Chevalier, F., Jabert, P., Poliak, S., Tourette, I., Hendrikx, P., Richomme, C., 2018. Infection of Wildlife by Mycobacterium bovis in France Assessment Through a National Surveillance System, Sylvatub. Frontiers in Veterinary Science 5.
Rivière, J., Carabin, K., Le Strat, Y., Hendrikx, P., Dufour, B., 2014. Bovine tuberculosis surveillance in cattle and free-ranging wildlife in EU Member States in 2013: a survey-based review. Veterinary microbiology 173, 323-331.
Rivière, J., Le Strat, Y., Dufour, B., Hendrikx, P., 2015. Sensitivity of Bovine Tuberculosis Surveillance in Wildlife in France: A Scenario Tree Approach. PLoS One 10, e0141884.
Sala, C., Vinard, J.L., Perrin, J.B., 2019. Cattle herd typology for epidemiology, surveillance, and animal welfare: method and applications in France. Preventive veterinary medicine 167, 108-112.
Srinivasan, S., Jones, G., Veerasami, M., Steinbach, S., Holder, T., Zewude, A., Fromsa, A., Ameni, G., Easterling, L., Bakker, D., Juleff, N., Gifford, G., Hewinson, R.G., Vordermeier, H.M., Kapur, V., 2019. A defined antigen skin test for the diagnosis of bovine tuberculosis. Science Advances 5, eaax4899.
Villarreal-Ramos, B., Berg, S., Whelan, A., Holbert, S., Carreras, F., Salguero, F.J., Khatri, B.L., Malone, K., Rue-Albrecht, K., Shaughnessy, R., Smyth, A., Ameni, G., Aseffa, A., Sarradin, P., Winter, N., Vordermeier, M., Gordon, S.V., 2018. Experimental infection of cattle with Mycobacterium tuberculosis isolates shows the attenuation of the human tubercle bacillus for cattle. Scientific reports 8, 894.
World Organisation for Animal Health (OIE) 2009. Chapter 3.4.6. Bovine tuberculosis. In: Edition., M.o.D.T.a.V.f.T.A.t. (Ed.).

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

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

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

		≥ 24 months old: 67% [50-100] ≥ 18 months old: 78% [60-100] ≥ 12 months old: 100% [67-100] ≥ 6 weeks old: 100% [100-100]			
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 ± Standard error**	**Median [interquartile interval]**
≥ 24 months old	67.6 ± 24.2	71.5 [47.4-89.4]
≥ 18 months old	71.5 ± 23.6	76.7 [52.7-93.1]
≥ 12 months old	76.4 ± 22.0	83.5 [60.6-95.9] *
≥ 6 weeks old	82.9 ± 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 ± Standard error**	**Median [interquartile interval]**
Previously TB-infected herds + herds with an epidemiological link	1.4 ± 0.8	1.2 [0.7-1.8]
Previously TB-infected herds + herds with an epidemiological link + all herds located in RPZ	29.1 ± 14.1	26.5 [18.1-37.9] *

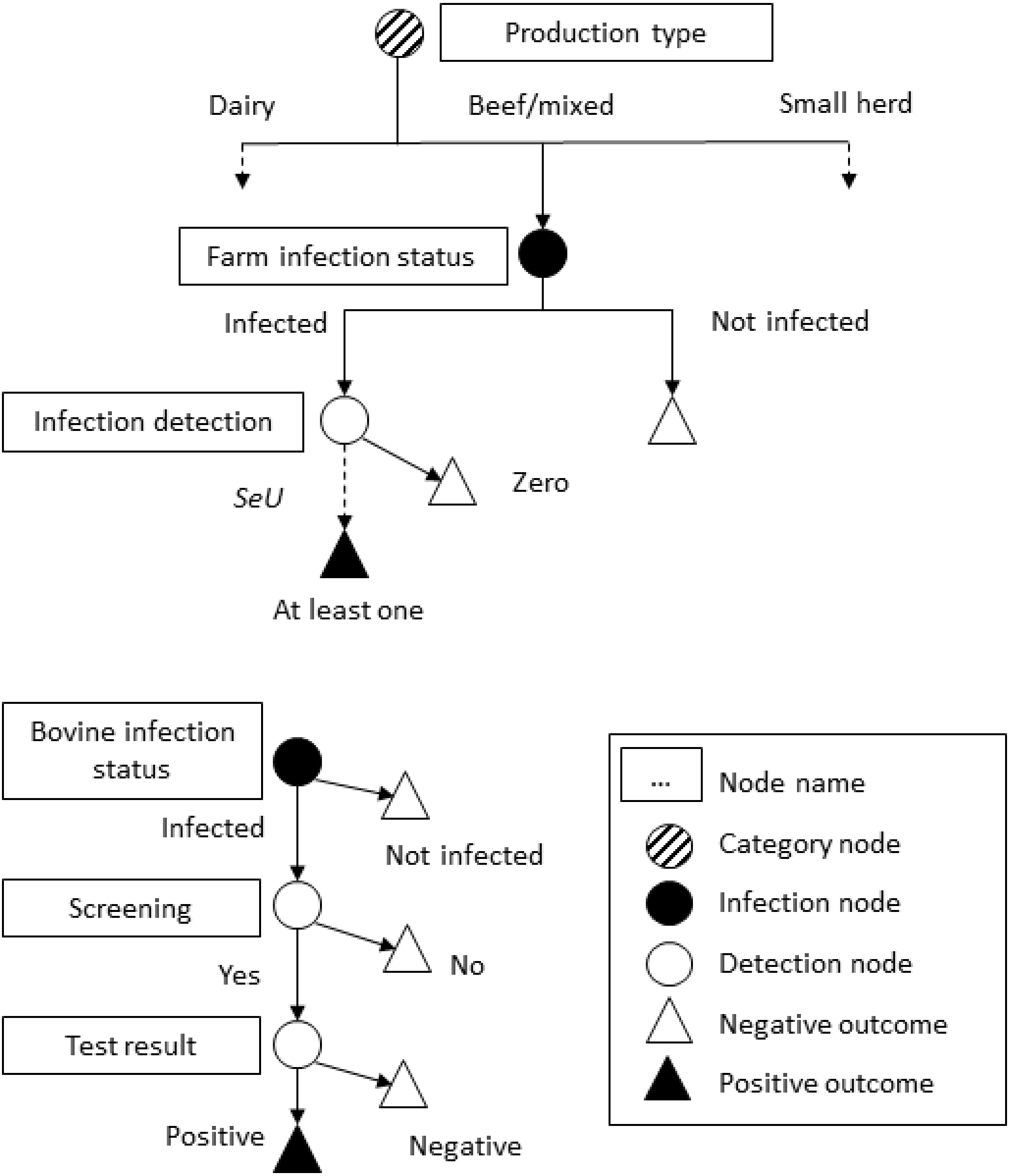
* Significant gain in comparison to current pre-movement surveillance

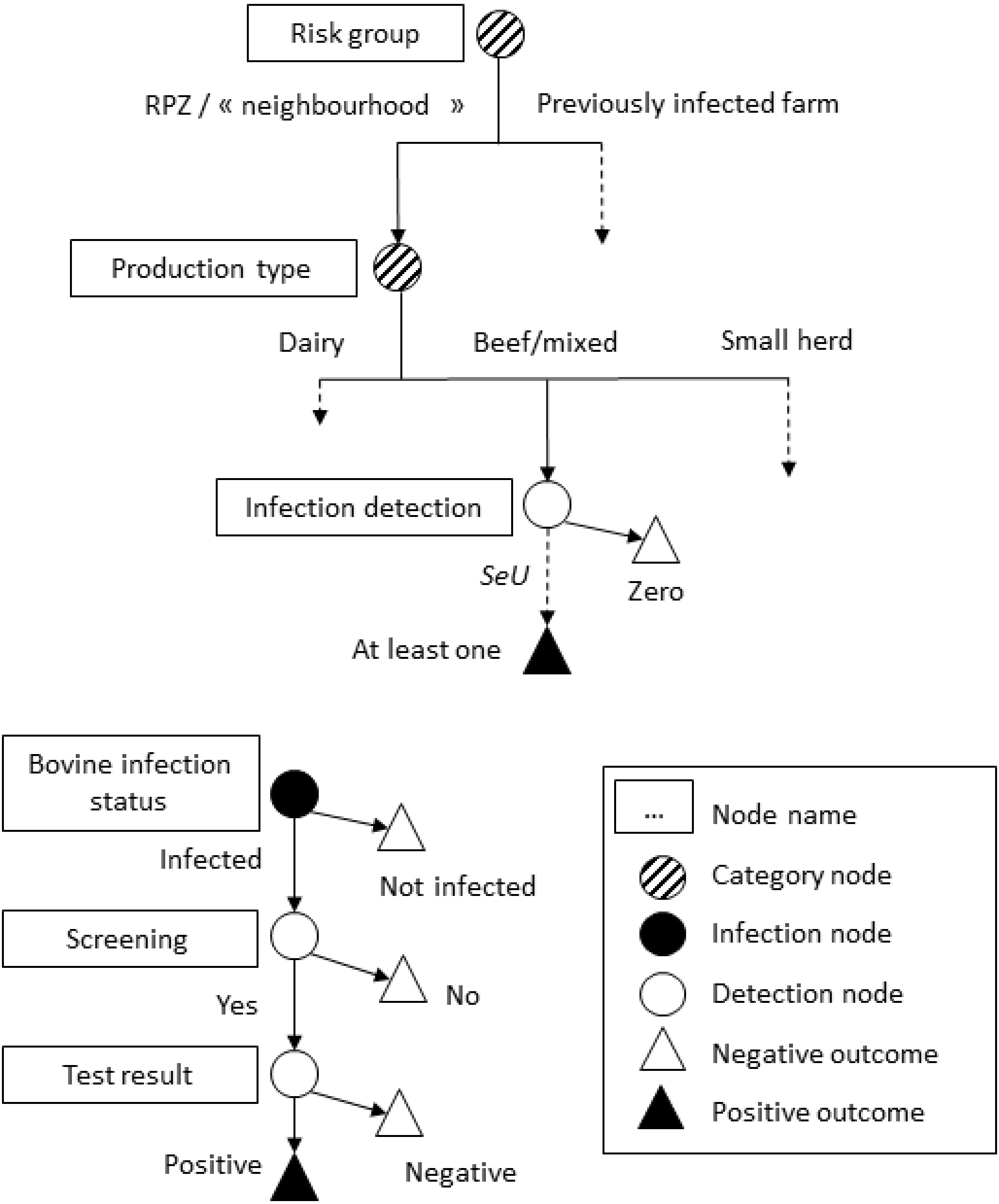
Table 4: Sensitivity analysis (influence of input parameter values on the detection fraction) of the models evaluating the effectiveness of TB detection by the current surveillance components (programmed surveillance with a minimum age of testing of 24 months old, pre-movement surveillance in previously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

	Programmed surveillance		**Pre-movement surveillance**	
Paramètre	**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


Production type
Dairy
Beef/mixed
Small herd
Farm infection status
Infected
Not infected
Infection detection
SeU
Zero
At least one
Bovine infection status
Infected
Not infected
Screening
Yes
No
Test result
Positive
Negative
...
Node name
Category node
Infection node
Detection node
Negative outcome
Positive outcome


Risk group
RPZ / « neighbourhood »
Previously infected farm
Production type
Dairy
Beef/mixed
Small herd
Infection detection
SeU
Zero
At least one
Bovine infection status
Infected
Not infected
Screening
Yes
No
Test result
Positive
Negative
...
Node name
Category node
Infection node
Detection node
Negative outcome
Positive outcome