Preventive Veterinary Medicine 173 (2019) 104805

Contents lists available at ScienceDirect

Preventive Veterinary Medicine

journal homepage: www.elsevier.com/locate/prevetmed

Evaluation of the effectiveness of the surveillance system for tuberculosis in cattle in Spain

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ARTICLE INFO

Keywords:
Surveillance
Animal tuberculosis
Bovine tuberculosis
Cattle
Stochastic model

ABSTRACT

In Spain, the eradication of tuberculosis (TB) in cattle has had some setbacks and therefore we need to re-evaluate the current surveillance strategies. The Spanish cattle TB surveillance system consists of three components: a) routine skin testing, b) slaughterhouse surveillance, and c) pre-movement controls. Our objectives were to assess the effectiveness of the whole surveillance system and evaluate the relative contribution of each of those components, both at national and at the province level. The effectiveness was estimated based on both the sensitivity of detection per year and the time until detection. Moreover, we evaluated the impact of different factors on that effectiveness. We used a stochastic model that simulated the spread of *Mycobacterium tuberculosis*-complex (*MTC*) infection within cattle herds that was modified to incorporate the three components of TB surveillance. Input data, at the province level, on cattle movements off-farm or the frequency of the routine screening were provided by the Spanish Ministry for Agriculture, Fisheries and Food.

Under the current conditions, 96.1% of Spanish herds were detected within one year after their infection (i.e. mean sensitivity of TB surveillance), although that detection took on average 178 days. The surveillance system effectiveness was highly dependent on the routine skin testing, responsible for the detection of almost 90% of the infected herds, while slaughterhouse surveillance and pre-movement controls contributed only to the identification of a small proportion of infected herds. We observed substantial differences in the effectiveness of the surveillance components among Spanish provinces, although in general, the sensitivities were high. The most influential factor on the efficiency of TB detection in Spain was, by far, the frequency of routine controls, followed by the sensitivity of the test used.

In a context of reduced funding for cattle TB eradication, the frequency of testing should be adapted based on risk-based surveillance strategies, i.e. efforts should focus on herds more likely to be infected, but also in herds more likely to infect other herds. While slaughterhouse surveillance seems a cost-effective strategy, the use of pre-movement testing at least in areas of low incidence should be further evaluated.

1. Introduction

Tuberculosis (TB) in cattle, formerly known as bovine TB, is defined as a chronic infectious disease caused by any of the three mycobacterial species within the *Mycobacterium tuberculosis*-complex (*MTC*): *M. bovis*, *M. caprae* and *M. tuberculosis* (EU - DG SANCO, 2013; EU - DG SANTE (European Commission, Directorate-General for Health & Food Safety), 2018; OIE, 2018). In addition to cattle, other domestic species, mainly goats, may be affected. Also wildlife, of which wild boars and red deer are considered the main reservoirs in Spain (De Mendoza et al., 2006). *M. bovis* and *M. caprae* also pose a risk of infection to humans (known as zoonotic TB) which makes the disease a public health concern (Cosivi et al., 1998; Thoen et al., 2010). Traditionally, zoonotic TB was considered to have a much higher impact on low-income countries, whereas in high-income countries with mandatory eradication programmes in place TB cases in humans were infrequent (Müller et al., 2013; Olea-Popelka et al., 2017). However, recent studies have highlighted that the real burden of zoonotic TB may be underestimated in both developing and developed countries, mainly due to technical constrains in the isolation and differentiation of the *MTC* members (Lombardi et al., 2017; Palacios et al., 2016; Olea-Popelka et al., 2017; WHO, 2019).

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https://doi.org/10.1016/j.prevetmed.2019.104805
Received 3 June 2019; Received in revised form 5 September 2019; Accepted 10 October 2019

In Spain, according to official reports, the number of confirmed cases of tuberculosis in humans due to *M. bovis/M. caprae* were 33 in 2014, 38 in 2015, 35 in 2016 and 55 in 2017 (European Food Safety Authority and European Centre for Disease Prevention and Control (EFSA and ECDC, 2018). Given the zoonotic potential and its high economic impact, the objective in the EU countries is the eradication of TB in cattle (Reviriego Gordejo and Vermeersch, 2006). In Spain, eradication programs with "test-and-slaughter" strategies have been implemented for decades, but despite the progressive reinforcement of the program the disease has not yet been eliminated. Between 2005 and 2013, the cattle TB eradication program only achieved a slight reduction in herd prevalence (from 1.52% to 1.39%). However, between 2013 and 2016, apparent herd prevalence increased from 1.39% to 2.87%. (Anonymous, 2019v). Moreover, the distribution of the disease in Spain is highly heterogeneous, with herd prevalences close to zero in the majority of the northern regions, but above 10% in most of the south-central areas (Anonymous, 2019v). In this context, the measures currently implemented within the eradication program need to be re-evaluated.

In Spain, the detection of infected cattle herds relies mainly on the periodic screening of the Officially Tuberculosis Free (OTF) herds (whole-herd tests) with the single intradermal tuberculin test (SITT) followed by the culling of positive cattle and the establishment of movement restrictions for infected herds. Herd-testing interval varies between once every two years and twice a year depending on the prevalence in the area where the herd is located (Anonymous, 2019v). Regular TB testing is complemented by slaughterhouse surveillance, as all cattle intended for human consumption undergo *post-mortem* examination at the slaughterhouse (Anonymous, 2019v). If lesions compatible with *MTC* infection are detected, samples are collected and sent for laboratory confirmation. Moreover, since 2006, the Spanish eradication program established measures to prevent *MTC* spread by cattle trade. Thus, with a few exceptions, such as some movements to calf-fattening units, cattle are subject to SITT before their transportation to other holdings, which also contributes to the detection of infected herds. Consequently, three major components: a) routine (skin) testing, b) slaughterhouse surveillance, and c) pre-movement controls, can be considered within the cattle TB surveillance system in Spain. While it is clear that the three contribute to the detection of infected herds, their relative impact has never been evaluated. Once cattle TB has been detected in a herd by any of these components and the *MTC* infection has been confirmed, control measures are established. They include the culling of all positive cows and the implementation of movement restrictions until the herd has been cleared (for which two consecutive negative whole-herd tests are required) (Anonymous, 2019v). In infected herds, SITT is used in parallel with the the interferon-γ assay (IFN-γ) to increase the probability of detection of the infected animals. The success of TB eradication relies not only on the identification of infected herds but also on the clearance of the herds identified as infected. In Spain, the persistence of TB in cattle herds, in particular in southern and central regions, poses an important challenge to the eradication program (Guta et al., 2014). Movement restrictions impose a significant burden for farmers, which adds to the direct cost of the eradication program, estimated in 30.7 million euros (19.6 for testing and 11.1 for compensation), of which 50% is co-financed by the EU (Anonymous, 2017).

For surveillance and control of TB in cattle herds, understanding the dynamics of *MTC* spread within Spanish cattle herds is essential (Ciaravino et al., 2018). However, the study of cattle TB dynamics is hampered by factors such as the long incubation periods, the lack of clinical symptoms in infected animals, or the uncertainty about the mechanisms of transmission. That is why mathematical modelling offers a practical option for the study of *MTC* spread in cattle herds (Brooks-Pollock et al., 2014). To evaluate the effectiveness of the surveillance system for tuberculosis in cattle in Spain, a model previously developed to simulate the spread of *MTC* infection within Spanish cattle herds (Ciaravino et al., 2018), was combined with another dynamic model that simulated detection by the different components of surveillance. The within-herd spread model was fed with transmission parameters obtained from Spanish herds (see Ciaravino et al., 2018), while the model that simulated detection was fed with real data from Spanish cattle herds provided by the Ministry for Agriculture, Fisheries and Food (MAPA).

Our objectives were to assess the effectiveness of the whole cattle TB surveillance system, and evaluate the relative contribution of each of its components, both at national and at provincial level. The effectiveness was estimated based on both a) the sensitivity of detection per year and b) the time until detection of infected herds. Finally, we evaluated the impact of different factors on the effectiveness of cattle TB surveillance. Ultimately, the aim is to use those results for the improvement of the surveillance and control strategies implemented in Spain for the eradication of cattle TB.

2. Materials and methods

2.1. Within-herd spread model

The *MTC* infection spread within-herds was simulated using a compartmental stochastic SOEI (Susceptible, Occult, Exposed and Infectious) model (Ciaravino et al., 2018). Occult animals (O) represented animals that were infected but were not yet detectable by SITT and were not infectious. Exposed animals (E) represented animals that were infected and were detectable by SITT but were not yet infectious. Finally, infectious animals (I) represented animals that were infected, were detectable by SITT and were infectious. It was assumed that the occult and exposed sojourn states followed the Erlang distribution; thus, the O and E compartments were divided into 3 sequential sub-compartments each (see Ciaravino et al., 2018 for further details). Animals susceptible to *MTC* infection (S) became occult (O), by contact with infectious cattle at a rate β, the transmission coefficient. Occult cattle became exposed (E), at a rate α_1. Exposed animals became infectious and detectable by SITT (I) at a rate α_2. Animals were born into the susceptible class at a rate μ (Fig. 1).

The model was run in continuous time (with days as units) and transitions between compartments occurred according to the corresponding differential equations using the Gillespie's direct algorithm (see Ciaravino et al., 2018 for further details) (Keeling and Rohani, 2007). The values of the transmission parameters (α_1, α_2 and β) used in the simulations were randomly drawn from the probability distributions estimated by Ciaravino et al. (2018) for Spanish cattle herds. Regardless of the mechanism of introduction of *MTC* within the herd, infection was assumed to start with a single infected (occult) animal (time 0) and the model was run for 5 years.

2.2. Modifications to include the surveillance components

2.2.1. Modelling detection at slaughterhouses

Province-level data on cattle movements to slaughterhouses in 2017 was provided by the MAPA. Data included the average number of batches sent to the slaughterhouse per herd per year, and the average number of animals in those batches ($size_{Si}$). Therefore, for province i, given the average frequency of movement of cattle to the slaughterhouse, measured in batches transported per year ($rate_{Si}$), the time of the first movement from a herd to the slaughterhouse ($t_{S_{1i}}$) was simulated as:

$$t_{S_{1i}} \sim uniform\ (0,\ 365/rate_{Si})$$

At time t_{S_1}, the spread of the infection within the herd determined the number of animals in the different compartments (S, O, $E$and I). The composition of the herd at time $t_{S_{1i}}$ and the average size of the batches ($size_{Si}$) defined the composition of the batch ($S_{S_{1i}}$, $O_{S_{1i}}$, $E_{S_{1i}}$ and $I_{S_{1i}}$).

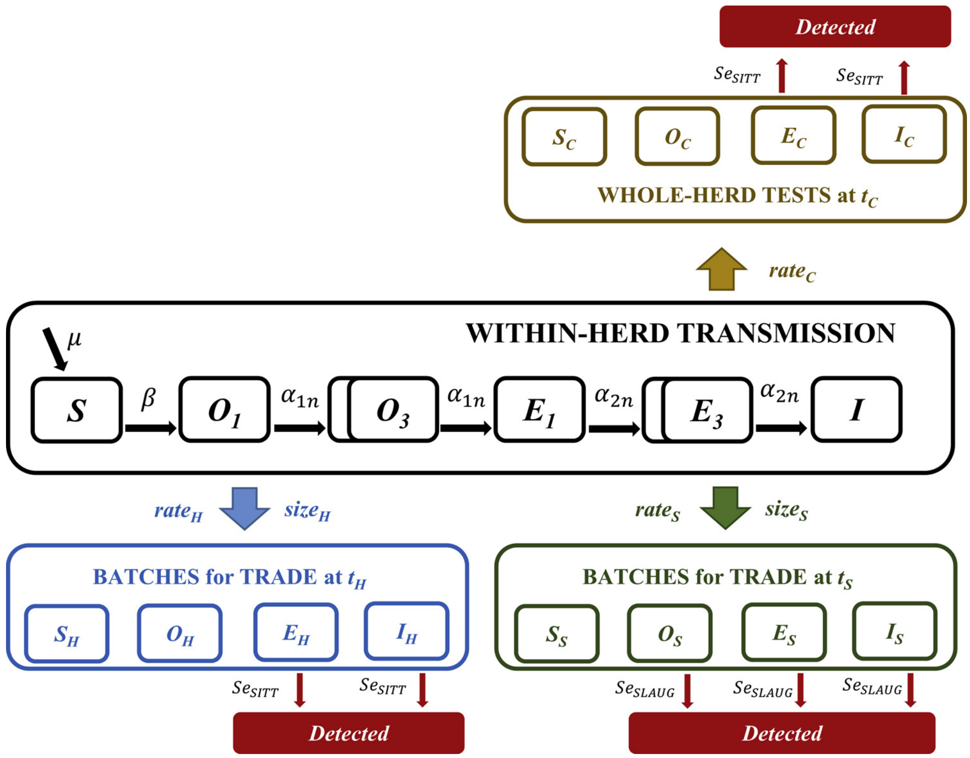

Fig. 1. Modifications of the within-herd transmission model developed by Ciaravino et al., 2018 to include births (with birth rate μ), plus models for the different components of the TB surveillance system: a) whole-herd tests (i.e. routine testing), b) Batches for trade (i.e. pre-movement testing), and c) Batches for slaughter (i.e. slaughterhouse surveillance). The black main box represent the herd composition and simulate the spread of the disease in the herd. Cattle are distributed in the following compartments: S for susceptible animals, O for occult, E for exposed and I for infectious cattle.

The probability of detection (by slaughterhouse surveillance) for that batch at time $t_{S_{1i}}$ ($Se_{S_{1i}}$) was given by the probability that at least one of the infected animals was detected at the post-mortem inspection:

$$Se_{S_{1i}} \sim binomial\ ((O_{S_{1i}} + E_{S_{1i}} + I_{S_{1i}}),\ Se_{slaug})$$

where Se_{slaug} was the sensitivity of *post-mortem* detection at the slaughterhouse for a single infected cow (Fig. 1). The value of Se_{slaug} used in the model was 31.4%, which was derived from a study carried out in North-Eastern Spain (Catalonia) (Garcia-Sáenz et al., 2015). The estimated sensitivity of slaughterhouse for a *MCT*-infected cow was the product of three probabilities: first, the probability that a *MCT*-infected cow from an OTF herd arrived at the slaughterhouse with TB-Macroscopically Detectable Lesions (MDL); second, the probability that those MDL were detected by the routine meat inspection; and third, the probability that the Veterinary Officer suspected of TB and sent a sample to the laboratory for confirmation or directly notified the authorities (Garcia-Sáenz et al., 2015).

After the movement to the slaughterhouse, the composition of the herd was re-adjusted by subtracting the number of cattle in the different compartments in the batch ($S_{S_{1i}}$, $O_{S_{1i}}$, $E_{S_{1i}}$ and $I_{S_{1i}}$) from the number of animals in the different compartments in the herd (S, O, $E$and I). If an infected animal (O, Eor I) remained in the herd, within-herd spread was resumed. If further movements to slaughterhouses fell within the period considered for the simulation (5 years), the whole process was repeated (Fig. 2).

2.2.2. Modelling of TB detection by pre-movement testing

Province-level data on cattle movements to other holdings in 2017 was also provided by the MAPA. Data included, for province i, the average number of batches transported to other holdings per herd per year and the average number of animals in those batches ($size_{Hi}$). Given the frequency of movements to other herds ($rate_{Hi}$), the time of the first movement ($t_{H_{1i}}$) was simulated, and the composition of the batch ($S_{H_{1i}}$, $O_{H_{1i}}$, $E_{H_{1i}}$ and $I_{H_{1i}}$) was calculated taking into account the average size of the batch ($size_{Hi}$) and the composition of the herd at time $t_{H_{1i}}$.

The probability of detection (by pre-movement tests) for that batch at time $t_{H_{1i}}$ ($Se_{H_{1i}}$) was be given by:

$$Se_{H_{1i}} \sim binomial\ ((E_{H_{1i}} + I_{H_{1i}}),\ Se_{SITT})$$

where $E_{H_{1i}}$ and $I_{H_{1i}}$ were the number of exposed and infectious cattle on the batch subject to pre-movement tests at time $t_{H_{1i}}$. And where Se_{SITT} was the sensitivity of the SITT for a single animal. As in (Ciaravino et al., 2018), the value of Se_{SITT} was set at 94%. After the movement, the composition of the herd was also re-adjusted, and if any infected animal (O, Eor I) remained, within-herd spread was resumed. If further movements to other herds fell within period considered, the whole process was repeated (Fig. 2).

2.2.3. Routine testing by SITT

In Spain, the frequency of routine controls on OTF herds varies between once every two years and twice a year depending on the prevalence in the area (province and county) where the herd is located (Anonymous, 2019v).

Therefore, given the frequency of routine controls per year in a herd in province i ($rate_{Ci}$), the time of the first routine control ($t_{C_{1i}}$) was simulated. At time $t_{C_{1i}}$, the spread of *MTC* within the herd determined the number of animals in the different compartments ($S_{C_{1i}}$, $O_{C_{1i}}$, $E_{C_{1i}}$ and $I_{C_{1i}}$), and therefore the probability of detection for that first control ($Se_{C_{1i}}$):

$$Se_{C_{1i}} \sim binomial\ ((E_{C_{1i}} + I_{C_{1i}}),\ Se_{SITT})$$

where $E_{C_{1i}}$ and $I_{C_{1i}}$ were the number of exposed and infectious cattle in the herd at the time of the first routine control ($t_{C_{1i}}$), and Se_{SITT} was the sensitivity of the SITT for a single animal, which was set at 94%, as in Ciaravino et al. (2018).

The times for the subsequent routine controls followed a regular

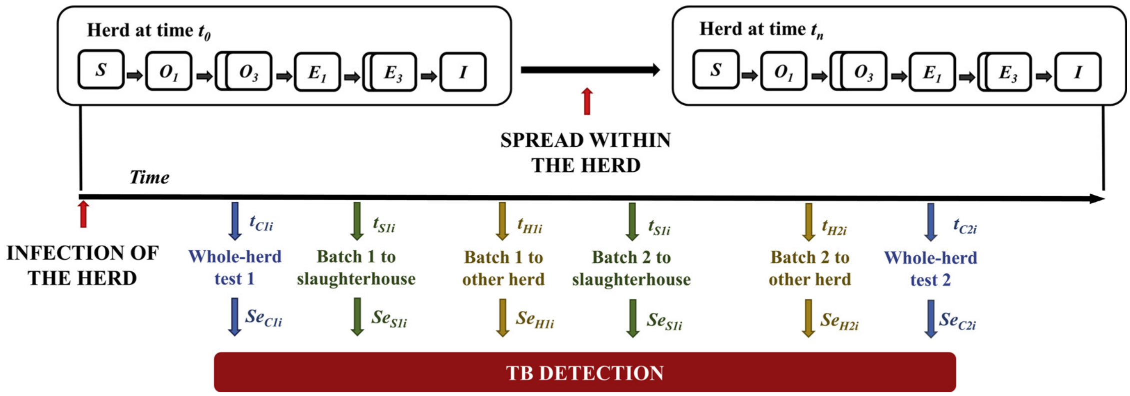

Fig. 2. Timeline summarizing the disease spread and control activities. Since the introduction of TB, infection progresses within the herd. That progress determines the composition of the herd at each point in time, which will influence on the probability of detection by the different components of the TB surveillance system.

pattern, where:

$$t_{C2i} = t_{C1i} + (365/rate_{Ci})$$

$$t_{C3i} = t_{C2i} + (365/rate_{Ci})$$

For any further routine controls that fell within the period considered for the simulation of within-herd spread, the process was repeated (Fig. 2).

2.2.4. Further modifications of the TB within-herd model

The inclusion of animal movements to both slaughterhouses and other holdings implied the progressive decrease of the number of animals in the herd. To avoid that, a crude birth rate (μ) term (Keeling and Rohani, 2007) was included in the equation that determines the variation in the number of susceptible animals, therefore implying that all animals were born as susceptible. The differential equation for susceptibles was then modified to:

$$\frac{dS}{dt} = \mu - \frac{\beta S(t)I(t)}{N(t)}$$

To allow the maintenance of a more or less constant number of animals, μ was estimated as a function of the number and size of the batches sent to both slaughterhouses and to other herds. As those parameters vary per province, the values of μ also vary:

$$\mu_i = (rate_{Si} \times size_{Si}) + (rate_{Hi} \times size_{Hi})$$

2.3. Evaluation of the effectiveness of TB surveillance at province level and nationally

At each iteration, the model simulated the spread of *MTC* infection within a cattle herd, as well as movements to other holdings or slaughterhouses and routine SITT controls (Fig. 2). The results of whether detection by any of the components occurred, were recorded, and the effectiveness of surveillance, either of the whole system or the different components individually, was evaluated based on the sensitivity of surveillance and time between infection and detection.

As the input values fed to the model (e.g. frequency of movements to slaughterhouses and to other herds, or frequency of routine SITT controls) represented the average values for the different provinces in Spain in 2017, we were able to estimate the effectiveness of each of the surveillance components and of the whole system at province level. That allowed the assessment of the spatial variation in the effectiveness of TB surveillance among the different provinces in Spain (objective 2). Then, by combining the province-level results, weighted by the number of cattle herds in each province, the average values of effectiveness of surveillance for Spain, for each component and overall (objective 1) were obtained.

Then, we also compared how well the overall sensitivity of TB surveillance in a province correlated with the TB herd prevalences in that province. In order to do that, we standardized the overall sensitivities of TB surveillance and TB prevalences in the different provinces (i.e. we set both values in a scale from 0 to 100):

$$Prev.\ ST_i = \frac{Prev_i}{max(Prev_i)} \times 100$$

Where, $Prev.\ ST_i$ was the standardized prevalence for province i, and $Prev_i$ the prevalence for province i.

$$Se.\ ST_i = \frac{Se_{ALLi}}{max(Se_{ALLi})} \times 100$$

Where, $Se.\ ST_i$ was the standardized sensitivity for province i, and Se_{ALLi} was the overall sensitivity of the surveillance (i.e. including all components) for province i.

Then, we estimated, for each province, a parameter that we called discrepancy as:

$$Discrepancy_i = Se.\ ST_i - Prev.\ ST_i$$

That allowed provinces to be identified where sensitivity of TB surveillance was lower than expected according to their prevalence of herds infected with *MTC*.

2.4. Evaluation of the factors influencing the effectiveness of TB surveillance

Finally, by allowing different model parameters to vary within their range of values, the influence of those factors on the effectiveness of TB detection (objective 3) were evaluated. The parameters assessed included:

Sensitivity of the routine test: A value of 94% was the average estimate given in the review carried out by the European Food Safety Authority (EFSA) (EFSA, 2012). However, in field conditions, the difficulties of carrying out the skin tests in extensively-reared cattle (Álvarez et al., 2012a), or the pressure faced by the veterinarians when performing the tests in the presence of farmers (Ciaravino et al., 2017), may result in much lower sensitivities. Therefore, in addition to the value of 94%, we included another two scenarios in which the sensitivity of the SITT was reduced to 70% and 50%. Furthermore, in Spain, the use of the single intradermal comparative cervical test (SICCT) with a severe interpretation can be authorized for TB detection in areas with herd prevalences below 1% (Anonymous, 2019v). The SICCT requires the simultaneous injection of bovine and avian tuberculin, and its interpretation is based on the observation that *MTC*-infected cattle tend to show a greater response to the bovine tuberculin than to the avian tuberculin (De la Rua-Domenech et al., 2006). It allows minimizing the risk of false-positive results caused by other mycobacteria, but increases the risk of false-negative results, giving an average sensitivity of 61%

Table 1
Data inputs for models. For objective 1 and 2 we used the range of values for the different provinces (*minimum* and *maximum* values represented in the table). For objective 3 we also used the median values for the parameters related to movements to slaughterhouses and other herds.

	Average herds size	Routine SITT controls (per year)	Movements to slaughterhouses (per year)	Average size batches to slaughterhouses	Movements to other holdings (per year)	Average size batches to other holdings
Minimum (provinces)	6	0.5	0,1	1	0.01	1
Maximum (provinces)	217	2	61,5	4	14.2	8
Median (provinces)	72	1.1	0.68	2	2.5	4

(with a severe interpretation) (EFSA, 2012). This value of 61% was also incorporated in the evaluation.

Frequency of routine controls: In most Spanish provinces OTF herds are tested once a year. In the provinces of Tenerife, Las Palmas, Islas Baleares, Pontevedra and Guipúzcoa the majority of OTF herds are tested once every two years, while in Extremadura and Andalucía regions most OTF herds are tested twice a year. Therefore, for the assessment of the influence of the frequency of routine controls, we included three scenarios: once every two years, once a year and twice a year.

Frequency of movements and size of the batches: For the frequency of cattle movements to slaughterhouses ($rate_S$), the frequency of cattle movements to other herds ($rate_H$), the average size batches to slaughterhouses ($size_S$) and the average size batches to other herds ($size_H$), three scenarios corresponding to low, medium and high frequency, were considered. They correspond to the minimum, maximum and 50th percentile of the values provided by the MAPA for the different provinces (Table 1).

2.5. Specifications of the models

Iterations were carried out in the following way:

- Input selection: First, the values of the transmission parameters (α_1, α_2 and β) were randomly selected from their probability distributions. Second, a Spanish province was randomly chosen and its inputs (herd size, rates of movements to slaughterhouses or other herds, or batch sizes) selected.
- Then, *MTC* spread as well as movements to slaughterhouses or other holdings were simulated.
- Finally, detection by routine SITT, slaughterhouse detection and pre-movement tests were also simulated.

To achieve the convergence of the output parameters, a large number of iterations were run (100,000 for objectives 1 and 2, and 240,000 for objective 3). Moreover, convergence was later assessed by splitting iterations in two and comparing the variation in the average output values (Gelman and Rubin, 1992). All models were implemented within the R environment version 3.2.1 (R Core Team et al., 2015).

3. Results

3.1. The effectiveness of the cattle TB surveillance system in Spain (Objective 1)

The results of the evaluation of the effectiveness of the different components and the overall surveillance system in Spain are shown in Table 2. Routine testing was by far the most effective component, whereas slaughterhouse surveillance and pre-movement testing components had a much lower contribution to the effectiveness of the system. Given the current conditions in Spain, we estimated that more than ninety-six percent of herds would be detected within the first year after their infection (i.e. > 96% sensitivity), and detection would take, on average, 178 days.

3.2. The effectiveness of the TB surveillance system among Spanish provinces (Objective 2)

3.2.1. Effectiveness of the TB surveillance by province

The values of sensitivity for the different components of the TB surveillance system varied significantly among provinces (Table 3; Fig. 3).

There was a significant variation in the effectiveness of the slaughterhouse surveillance by province (Table 3; Fig. 3A). The provinces with the highest sensitivities were León, Salamanca, Ciudad Real and Cáceres (Fig. 3A), which reached values above 25%. The sensitivity of pre-movement detection also varied significantly among provinces (Table 3; Fig. 3B). The provinces with the highest sensitivities (above 20%) were located mainly in south-western Spain (e.g. Huelva, Cáceres, Ciudad Real and Albacete) (Fig. 3B). The sensitivities of routine testing were considerably higher than the other two components, with values greater than or equal to 95% in 25 out of 50 Spanish provinces (Fig. 3C); only in five provinces (Guipúzcoa, Pontevedra, the Balearic Islands, Tenerife and Las Palmas) sensitivities were in the range of 50% (Fig. 3C) but those provinces were actually free of TB. The overall sensitivity of the TB surveillance system in Spain was above 95% for the majority of provinces (Table 3; Fig. 3D).

Accordingly, the times to detection of infected herds also varied significantly among provinces, for both the whole system and for each of the different components (Table 3; Fig. 4) and, as expected, the times were inversely correlated to the sensitivities of the surveillance components. The times to detection of infected herds by slaughterhouse surveillance were more than 600 days for all Spanish provinces, and for 38 out of 50 provinces times were more than 800 days (Fig. 4A). The times to detection by pre-movement testing were more than 900 days in most of the Spanish provinces, and only a few provinces could detect the infection of their herds by this component in less than 700 days on average (Fig. 4B). On the other hand, times to detection by the routine (skin) testing were much lower, and the 80% of provinces were able to detect infected herds by this component in less than 250 days (Fig. 4C). Considering the whole surveillance system for TB, the mean times to detection were even lower (Fig. 4D), and only in the five provinces that

Table 2
Average values of effectiveness of TB surveillance in Spain. Results for the different components, as well as for the overall surveillance system.

	Sensitivity (%)	Mean time to detection (days)	First detected by (%)	Not detected within 5 years (%)
Slaughterhouse detection	9.5%	1124	4.5%	24.6%
Pre-movement testing	10.8%	1173	5.7%	30.7%
Routine testing	94.3%	208	89.0%	2.8%
Overall TB surveillance	96.1%	178	NA	1.2%

Table 3
Average values of effectiveness of TB surveillance at herd level in the different Spanish provinces (objective 2). Results for the different components, as well as for the overall surveillance system.

		Sensitivity (%)	Mean time to detection (days)
Slaughterhouse detection	*Minimum*	1.1%	678
	Maximum	32.1%	1684
Pre-movement testing	*Minimum*	1.4%	454
	Maximum	44.6%	1725
Routine testing by SITT	*Minimum*	46%	85
	Maximum	99.7%	489
Overall TB surveillance	*Minimum*	50.7%	82
	Maximum	99.8%	367

were free of cattle TB in 2017 (Guipúzcoa, Pontevedra, the Balearic islands, Tenerife and Las Palmas) detection of infected herds took longer than 300 days.

3.2.2. Discrepancy between sensitivity of detection and cattle TB herd prevalence

We also evaluated whether the intensity of surveillance efforts in each province was adequate to its TB herd prevalence (i.e. the proportion of infected herds), by calculating the parameter called discrepancy (Fig. 5).

In the majority of Spanish provinces, the high overall sensitivity of the TB surveillance system prevented negative discrepancy values, which would be indicative of a high TB herd prevalence together with a relatively low sensitivity for the detection of infected herds. We identified only one province with negative discrepancy (Guadalajara, with a value of -5) (Fig. 5). This was the result of a relatively high sensitivity of TB detection (95.1%) combined with an extremely high TB herd prevalence (28.6%), the highest in Spain in 2017. Eleven provinces were associated to very high values of discrepancy (above 95) because of the combination of high overall sensitivities of the surveillance system (above 95%) and very low herd prevalences (below 0.5% in 2017). Those provinces were located mainly in northern Spain (Fig. 5).

3.3. Factors influencing the effectiveness of TB surveillance in Spain (Objective 3)

The higher the sensitivity of the diagnostic test used, the higher the efficiencies of both the routine herd testing and pre-movement detection components. For a test-sensitivity of 50%, the overall sensitivity of TB surveillance was 74.6% and the mean time for detection was 227 days, while for a test-sensitivity of 94%, the overall sensitivity of TB surveillance was 88.1% and the mean time for detection was 153 days (Table 4).

The higher the frequency of routine controls, the higher the sensitivity of herd testing and the overall sensitivity of TB surveillance. For one control every two years, the overall sensitivity of TB surveillance was 64.3%, while under a testing interval of six months, the overall sensitivity of TB surveillance was 93.7% (Table 4). That allowed reducing the time to detection from 280 days with one control every two years, to only 115 days with two controls per year.

The increase in the frequency of cattle movements to the slaughterhouse had a huge effect on the sensitivity of slaughterhouse detection, but the effect on the overall sensitivity was quite limited (Table 4). On the other hand, an increase in the average size of the batches sent to slaughterhouses resulted in a slight increase in the sensitivity of slaughterhouse detection, while it did not affect the overall system sensitivity. The increase of the frequency of cattle movements to other holdings had a very large effect on the sensitivity of pre-movement testing, but also a significant effect on the overall sensitivity of TB detection (11.0% difference) (Table 4). The increase in the average size of the batches sent to other herds also resulted in a large increase in the sensitivity of pre-movement testing and some effect on the overall sensitivity of TB detection (Table 4).

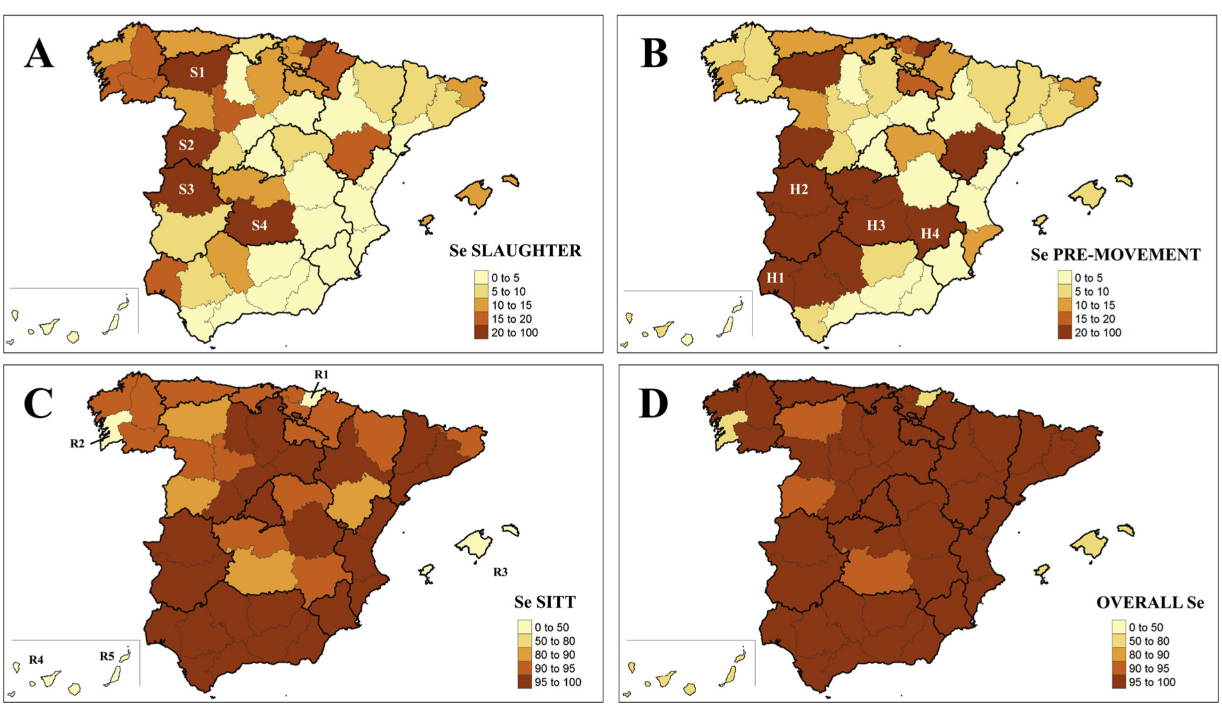

Fig. 3. Maps of sensitivities of the different TB surveillance components and overall sensitivity by province. A: Slaughterhouse detection; in the map, the following provinces are indicated: León (S1), Salamanca (S2), Cáceres (S3) and Ciudad Real (S4). B: Pre-movement detection; in the map, the following provinces are indicated: Huelva (H1), Cáceres (H2), Ciudad Real (H3) and Albacete (H4). C: Routine SITT test detection; in the map, the following provinces are indicated: Guipúzcoa (R1), Pontevedra (R2), the Balearic Islands (R3), Tenerife (R4) and Las Palmas (R5). D: Whole TB surveillance system (overall sensitivity). ** *Be aware that the scales for the maps are different* **.

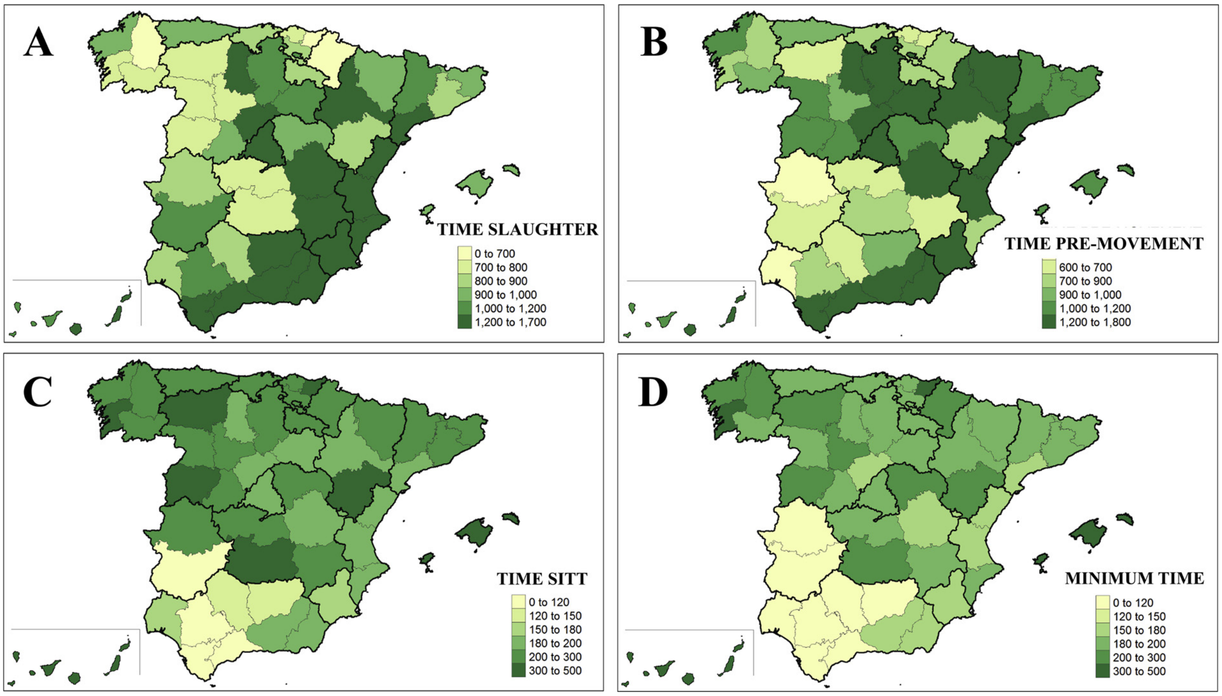

Fig. 4. Maps of times to detection for the different components of the TB surveillance system. A: Slaughterhouse detection. B: Pre-movement detection. C: Routine SITT test detection. D: Whole TB surveillance system. ** Be aware that the scales for the maps are different **.

Convergence of output values was demonstrated by splitting iterations in two and comparing the variation in the average sensitivities. For objective 1 (whole of Spain) the mean sensitivities differed in 0.013%, for objective 2 (provinces) 0.86%, and for objective 3 (parameters) 0.17%.

4. Discussion

In recent years, the progress towards the eradication of cattle TB in Spain has had some setbacks, particularly in some regions where the prevalence has increased significantly. Given such difficulties, there is a need to re-evaluate the strategies currently implemented.

Our results indicate that, under the present conditions in Spain, the sensitivity of the TB surveillance system was quite high (96.1%). However, it should be noted that the evaluation of the sensitivity of a surveillance system requires the definition of the period over which data are analysed (Cameron et al., 2014), and for cattle TB we chose a relatively long period (one year). Choosing a long time period increases the apparent sensitivity of the surveillance system (Cameron et al., 2014). In fact, the detection of infection in the herds took on average 178 days, and during that period transmission to other herds may occur.

Despite that 96.1% sensitivity, between 2013 and 2016, the cattle TB herd prevalence in Spain went from 1.39% to 2.87%. That apparent increase is likely to have been associated with the improvement of the sensitivity of the surveillance system after the implementation of a series of reinforcement measures (EU, 2015, 2019a). Measures included: compulsory training courses for the veterinarians who perform the SITT controls, official control of field veterinarians, training courses for official veterinarians, audits of the implementation of the eradication program by the different regions carried out by the MAPA, random post-movement tests or additional control measures to herds sharing pastures. In fact, a recent survey of farmers and veterinarians indicated that they perceived an improvement in the application of the Spanish cattle TB eradication programme in recent years, which they mainly attributed to the organization of the mandatory training courses (Ciaravino et al., 2017). They acknowledged that some bad practices in the field were largely caused by lack of knowledge and training among veterinarians.

Another factor that has influenced the lack of progress in TB eradication is the time it takes to clear the infected herds once they have been detected. In Spain, the persistence of *MTC* in cattle herds, in particular in southern and central regions, poses an important challenge to the eradication of cattle TB (Guta et al., 2014). Residual infection could be the result of the presence of false negatives to the skin test, reviewed by De Mendoza et al. (2006), or be the consequence of the incorrect application of the test (Humblet et al., 2009). Indirect transmission caused by the persistence of the microorganism in the environment could also result in residual infections (Courtenay et al., 2006). Moreover, the presence of infected goats on the farm could contribute to the recirculation of *MTC* within cattle herds (Crawshaw et al., 2008).

The evaluation of the relative contribution of the three components evidenced that routine testing was by far the most sensitive surveillance component (94.3% sensitivity). Almost 90% of the infected herds were first detected by this component, and that took on average 208 days after the infection of the herd. Therefore, the detection of *MTC*-infected herds in Spain seems to be highly dependent on routine testing. This is consistent with the fact that in the countries where TB in cattle has been eradicated, that was achieved mainly through the regular skin testing of cattle and the elimination of infected animals. In all Spanish provinces, the routine testing was the most sensitive surveillance component and it strongly influenced the overall sensitivity of the system in the province. In general, routine testing sensitivities were relatively high, with values above 90% in more than 80% of provinces. Those sensitivity values were clearly associated with the frequencies of testing. In fact, the only five provinces with sensitivities of routine testing below 50% were those that had a prevalence of zero in 2017, and where most cattle herds were tested only once every two years. This was further confirmed by the results of objective 3, which indicated that the frequency of testing was the most influential factor on the effectiveness of the routine testing component, and therefore of the whole TB surveillance system. As a matter of fact, changing from two controls per year to one control every two years reduced the overall sensitivity of TB

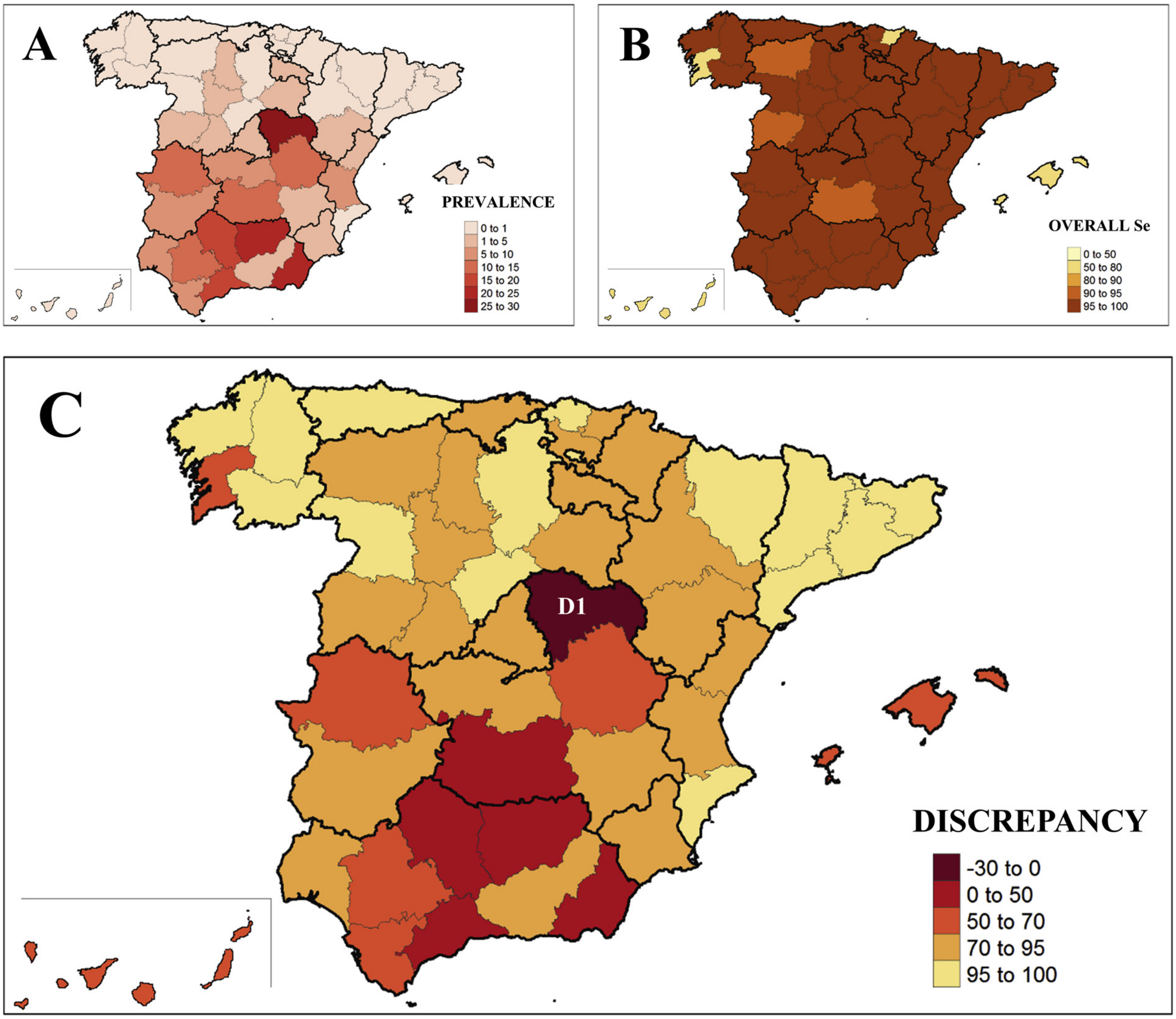

Fig. 5. Map showing the results obtained for the parameter discrepancy by provinces. A: Map of prevalence of herds infected with *MTC* in 2017 in Spain. B: Map of the overall sensitivity for TB in 2017. C: Map of discrepancy; the province of Guadalajara (D1) is indicated in the map.

surveillance by almost 30%, and increased the time to detection from 115 to 280 days. That was in agreement with previous studies (Fischer et al., 2005; Rossi et al., 2015) that found that the variations in the sensitivity of TB surveillance were primarily related to the frequency of testing. Routine testing represents a significant part of the cost of the eradication program in Spain (23.7 out of the 38.8 million euros) (Anonymous, 2019v), and that figure is clearly dependent on the frequency of testing of herds. However, any increase in the time between SITT controls will come at the cost of a significant reduction in the effectiveness of cattle TB detection.

The sensitivity of the test used for the detection of *MTC*-infected herds had a significant influence on the sensitivity of the routine testing, but also on the pre-movement component, and as a result, affected the overall sensitivity of surveillance. However, in comparison with the frequency of controls, the sensitivity of the test used had a much lower impact. The sensitivity of the SITT is generally considered as high, in fact, a value of 94% (based on the review by EFSA) was used for the evaluation of the cattle TB surveillance (at national and provincial levels). However, much lower values have been reported when the SITT is applied in field conditions (Álvarez et al., 2012b; Humblet et al., 2011b). Among the reasons for the reduction of the sensitivity is the management and on-farm testing conditions, which can make the SITT difficult to perform, in particular in some production types such as extensively managed beef herds and fighting bulls (Álvarez et al., 2014; Humblet et al., 2009; Meskell et al., 2013). Furthermore, it has been pointed out that in Spain the correct execution and interpretation of the SITT results might be influenced by the pressure linked with the "patronage relationship" between farmers and private veterinarians, because the latter carry out other duties besides TB testing, and are paid by farmers (Ciaravino et al., 2017). Also, factors related to the professional skills and awareness of veterinarians may compromise the application of the SITT in the field (Ciaravino et al., 2017; Humblet et al., 2011a, 2011b; Meskell et al., 2013). Also, exposure to the parasite *Fasciola hepatica* is known to interfere with the diagnosis of cattle TB (Claridge et al., 2012). *F. hepatica* is considered widespread in Europe but with a heterogeneous spatial distribution and significant regional variations in prevalence (Beesley et al., 2018). In Spain, the spatial distribution and prevalence of *F. hepatica* are not known, and therefore its influence on TB detection is difficult to predict. Spatial models indicate relatively high risks in areas of northern Spain (Ducheyne et al., 2015) where the prevalence of cattle TB is quite low.

The estimates of the effectiveness of cattle TB surveillance in Spain were based on the assumption of a sensitivity of 94% for the SITT, so any reduction of that value, for whatever reason, would result in a lower sensitivity of the cattle TB surveillance and longer times for the detection of infected herds.

In countries such as the UK and Ireland, the single intradermal comparative cervical test (SICCT) is the primary screening test for TB in

Table 4
Results of the evaluation of the influence of different factors on the effectiveness of TB surveillance (objective 3). Where Se_{TEST} was the sensitivity of routine testing, Se_{HERD} was the sensitivity of pre-movement testing and Se_{SLAUG} was the sensitivity of slaughterhouse detection.

	Categories	Value	Overall Se (Se_{ALL})	Se specific component
Sensitivity of the routine test	Minimum	50%	74.6%	Se_{TEST} = 56.0% & Se_{HERD} = 22.9%
	Other (SICCT)	61%	79.0%	Se_{TEST} = 61.6% & Se_{HERD} = 25.8%
	Medium	70%	82.0%	Se_{TEST} = 65.3% & Se_{HERD} = 28.0%
	Maximum	94%	88.1%	Se_{TEST} = 73.9% & Se_{HERD} = 32.7%
Frequency of the routine controls (per year)	Minimum	0.5	64.3%	Se_{TEST} = 35.4%
	Medium	1	84.8%	Se_{TEST} = 70.5%
	Maximum	2	93.7%	Se_{TEST} = 86.8%
Frequency of cattle movements to slaughterhouses (per year)	Minimum	0.1	80.3%	Se_{SLAUG} = 0.4%
	Medium	2.5	80.1%	Se_{SLAUG} = 2.4%
	Maximum	61.5	82.4%	Se_{SLAUG} = 58.4%
Average size batches to slaughterhouses	Minimum	1	81.4%	Se_{SLAUG} = 16.3%
	Medium	2	80.9%	Se_{SLAUG} = 21.0%
	Maximum	4	80.4%	Se_{SLAUG} = 23.6%
Frequency of cattle movements to other herds (per year)	Minimum	0.01	75.9%	Se_{HERD} = 0.2%
	Medium	0.7	80.0%	Se_{HERD} = 23.3%
	Maximum	14.2	86.9%	Se_{HERD} = 59.1%
Average size batches to other herds	Minimum	1	78.3%	Se_{HERD} = 13.8%
	Medium	4	81.6%	Se_{HERD} = 30.0%
	Maximum	8	82.9%	Se_{HERD} = 38.3%

cattle (De la Rua-Domenech et al., 2006; Frankena et al., 2007). In Spain, the SICCT can be authorized in areas of low herd prevalence (Anonymous, 2019v). While the use of the SICCT increases the specificity as compared with the SITT, it comes at the price of a reduced sensitivity (EFSA, 2012). In fact, in our scenarios, the average time to detection of TB infected herds was estimated to be 153 days with the SITT assuming a 94% sensitivity, while it increased to 204 days with a test sensitivity of 61% (SICCT with the severe interpretation) and to 227 days when the test sensitivity decreased to 50% (SICCT with the standard interpretation). In Spain, given the difficulties in the later stages of cattle TB eradication, the objective should be the maximization of sensitivity, and therefore the use of SITT rather than SICCT is recommended.

One alternative for increasing the sensitivity of routine testing would be the use of the IFN-γ in combination with the SITT. However, there are several factors that limit the systematic use of IFN-γ for routine testing, among them, its highest cost, the logistic difficulties for sending blood samples to the laboratory on time from remote areas, as well as the increased risk of false positives (Ciaravino et al., 2017). That is why in Spain the routine testing of herds is carried out using the tuberculin test (usually the SITT), while the IFN-γ is used as a complementary test to the tuberculin, but only in TB-positive herds (Anonymous, 2019v). Given its importance, any measure to increase the sensitivity of the test in the field would improve the effectiveness of cattle TB detection. Therefore, initiatives such as compulsory training courses for the veterinarians who perform the SITT controls or official control of field veterinarians seem a cost-effective alternative to improve cattle TB detection.

The slaughterhouse surveillance component also contributed to the detection of *MTC* infected herds, although its average sensitivity was 9.5% and the mean time to detection was longer than three years. We estimated that the slaughterhouse was responsible for the first detection of only 4.5% of TB infected herds. In 2017, according to the MAPA, lesions compatible with cattle TB were observed in animals from 282 OTF-herds, of which 119 herds were confirmed as infected by *MTC* by the laboratory (Anonymous, 2017).The conclusions of the audit carried out by the European Commission on the progress of the Spanish program to eradicate bovine tuberculosis indicated that the optimization of the sensitivity of this component was still far for being accomplished (EU - DG SANTE, 2016). Reasons that may have contributed to the low rate of detection include the lack of competence/awareness of meat inspectors and veterinarians or inadequate facilities/conditions (e.g. lighting or line speed) (EU - DG SANCO, 2013; Garcia-Sáenz et al., 2015; Hadorn and Stärk, 2008). Moreover, in Spain, some deficiencies in the coordination between the authorities responsible for the TB eradication programme (animal health authorities) and those responsible for slaughterhouse inspection (food safety authorities) have also been identified (EU - DG SANTE, 2016).

At the provincial level, the sensitivities of slaughterhouse detection were quite heterogeneous, although no clear spatial pattern was observed. While the number of movements to the slaughterhouse had a large effect on the sensitivity of the slaughterhouse detection and limited on the sensitivity of the whole system, the size of the slaughterhouse batches only had a moderate influence on the slaughterhouse component. In any case, even in those provinces where the sensitivities of slaughterhouse detection were highest (around 30% in several provinces), it took around two years for this component to detect infected herds. However, despite its apparent limited contribution to the overall sensitivity of the TB surveillance system, the slaughterhouse detection may still play an import role in the detection of “anergic” animals (Domingo et al., 2014). These are chronically infected animals in which cell-mediated immune response may be depressed, and therefore may not be detectable by skin test or gamma-interferon, but which are likely to have developed macroscopic lesions and therefore be detected by *post-mortem* inspection at the slaughterhouses (De la Rua-Domenech et al., 2006). Moreover, according to the EU report, slaughterhouse surveillance is in place for the detection of diseases other than TB, and it has proven its capacity to find *MCT*-infected animals that otherwise would have been missed (EU - DG SANTE (European Commission, Directorate-General for Health & Food Safety), 2016).

Contrary to our findings, studies carried out in Belgium (Welby et al., 2012), Denmark (Calvo-Artavia et al., 2013) or Canada (El Allaki et al., 2016) estimated that the slaughterhouse surveillance was highly effective. However, those countries were OTF and therefore their surveillance systems did not include the same components as in Spain. In fact, some of them (Calvo-Artavia et al., 2013; El Allaki et al., 2016) did not consider periodic tuberculin screenings but only the testing of imported animals, while other (Welby et al., 2012) considered reduced herds screenings. Furthermore, in the Belgian study (Welby et al., 2012) the sensitivity of detection at the slaughterhouse for an individual animal (Se_{slaug}) was assumed to range between 50% and 99%, with a most likely value of 70%, while in our study we used a value of 31.4%, derived from the study carried out in North-Eastern Spain (Garcia-Sáenz et al., 2015). In agreement with our results, other studies (Fischer et al., 2005; Rossi et al., 2015; Schöning et al., 2013; Van Asseldonk et al., 2005) have highlighted the limitations of the slaughterhouse surveillance for TB detection. In any case, the comparison with studies carried out in other countries is difficult due to the variability in the methodologies applied and therefore interpretations should take with caution.

Our estimates indicated that in Spain the sensitivity of pre-movement testing was 10.8%, and it took over 3 years for this component to detect the infection of a herd. That meant that 5.7% of infected herds were first detected by tests prior to the movement of cattle to other herds. That result is in line with the proportion of herds estimated to be detected by this component in the report of the EU on the progress of the Spanish eradication program for the period 2012–2014, 5.2% in 2012, 3.9% in 2013, and 3.7% in 2014 (EU - DG SANTE (European Commission, Directorate-General for Health, 2016). The sensitivities of pre-movement detection varied significantly among provinces (between 1.4 and 44.6%), with larger values generally observed in south-western Spanish provinces. In the case of pre-movement detection, both the number of movements and the size of the batches had an effect on the sensitivity of the whole surveillance system. In Spain, the low sensitivity of pre-movement testing is the result of a) the small size of the batches (median value of 4) as compared to the size of the herds (median value of 72); and b) the low prevalence in infected herds as a result of the combination of the slow spread of *MTC* infection and the implementation of regular controls for many years. That results in a small probability that the batch of animals selected to be transported to other herd contains an infected animal. Furthermore, if we also take into account that in many areas of Spain the incidence (i.e. probability of appearance of newly infected herds) (Anonymous, 2019v) is very low (way below 1% for all the northern regions), the contribution of pre-movement testing to the overall system is limited. In fact, according to the MAPA, in 2017, pre-movement tests were carried out in 16,202 herds and 203,989 animals, resulting in 72 positive herds (8 confirmed) and 103 positive animals (Anonymous, 2017). Therefore, the cost-effectiveness of pre-movement testing, at least in areas of low incidence, should be evaluated taking into account not only its contribution to the detection, but also its cost, and that should be compared to the cost-effectiveness of alternative options (e.g. increasing the frequency of routine testing).

The distribution of TB in Spain is highly heterogeneous (Allepuz et al., 2011; Garcia-Sáenz et al., 2014), and in fact, the Spanish eradication program is designed to account for that heterogeneity by allowing changes in the frequency of routine testing according to the prevalence in the area (Anonymous, 2019v). Our results evidence that, in general, the sensitivities of cattle TB detection in the provinces with the highest TB herd prevalences were also quite high. The exception was the province of Guadalajara, which had the highest TB herd prevalence in Spain in 2017 (28.6%), but the sensitivity of TB detection (95.1%) was not among the highest. However, in several provinces with very low TB prevalence, the frequencies of SITT, and therefore the overall sensitivities, were quite high resulting in large positive discrepancy values. The budget provided by the EU for cofinancing the Spanish eradication programme has progressively decreased (14.4 million in 2016, 13.2 in 2017, 13.4 in 2018 and 11.9 in 2019) (EU, 2016, 2017; EU, 2018, 2019b). To cope with this reduction, a straightforward solution could be to decrease the frequency of testing in areas of low prevalence. However, that would increase the time to the detection of the infected herds facilitating the spread of the infection, which may compromise cattle TB eradication in those areas where the disease was close to elimination. Surveillance of low-prevalence diseases is problematic because large sample sizes are required to achieve an acceptable level of sensitivity, but at the same time, surveillance needs to be affordable (Cameron et al., 2014). In this context, the only option may be to use risk-based surveillance strategies, i.e. reducing the surveillance efforts in those animal populations that are less likely to be affected, while increasing the efforts in those populations that are more likely to be infected. That requires good knowledge of the risk factors for cattle TB. Risk-based surveillance strategies may be applied based on area-level or herd-level risk factors. In Spain, area-level risk factors are better known. For example, a large number of movements from counties with high incidence (> 1%) or the presence of bullfighting cattle herds are known to increase the risk of cattle TB at the county level (Garcia-Sáenz et al., 2014). Some herd-level risk factors were identified in previous studies, e.g. a previous infection of the herd or sharing of pastures (Guta et al., 2014). Those factors have already been incorporated into the Spanish eradication program, so that in areas of low prevalence, herds receiving animals from high incidence areas, bullfighting herds, herds previously infected or those sharing pastures are tested more frequently than other herds (Anonymous, 2019v). In addition to the risk of infection of the herds, the consequences also need to be taken into account for the prioritization of the surveillance effort (Cameron, 2012). Some factors that make herds more likely to infect other herds (e.g. large number of movements to other herds) are also considered in the program, and therefore those herds are tested more regularly (Anonymous, 2019v). While some herd-level factors related to the risk of infection and further transmission are known, further studies are needed for their proper quantification. That would allow a better estimation of the most cost-effective frequency of testing depending on the characteristics of the herds.

For the estimation of discrepancy, we used provinces as units because they were the smallest geographical unit for which we had complete data. However, in reality, there may be significant differences in the prevalence of infected herds, as well as in the frequency of testing among the smaller geographical units (called *comarcas*) within provinces, and that may have some influence on the results.

The understanding of the efficacy of the different components of TB surveillance and their drivers allows adjusting the level of surveillance to the risk of infection in the area, maximizing the cost-effectiveness of cattle TB detection and contributing to the eradication of the disease in the long term. An improved characterization of the risk of cattle TB at herd level, based not only in the prevalence in the area, but in other characteristics of the herd (e.g. type of production or size) would allow an even better allocation of resources for the surveillance of TB.

A stochastic model was used to simulate the spread of *MTC* infection within herds, which allowed the estimation of the effectiveness of cattle TB surveillance. Therefore, the model assumptions (e.g. homogeneous-mixing model with frequency-dependent transmission) may have had an influence on the results.

5. Conclusions

- Under the current conditions in Spain, and considering a sensitivity of 94% for the SITT, 96.1% of herds were detected within one year after their infection (i.e. mean sensitivity of TB surveillance), although that detection took on average 178 days after the infection of the herd.
- Variations in the efficiency of the components and overall surveillance were observed at the provincial-level, although in general, the sensitivities were high, with the exception of OTF provinces where the frequency of routine testing was reduced to one control every two years.
- Routine testing was by far the most sensitive surveillance component (94.3% sensitivity). Almost 90% of infected herds were first detected with routine testing; on average it took 208 days until infected herds were detected using this method. Therefore, the detection of *MTC*-infected herds in Spain was highly dependent on routine testing by SITT.
- The frequency of testing was the most influential factor in the efficiency of routine testing. However, in the context of reduced funding for cattle TB eradication, rather than a straightforward decrease in the frequency of testing, risk-based surveillance strategies should be promoted. Surveillance efforts should focus not only in those herds more likely to be infected, but also in those herds more likely to infect other herds.
- The sensitivity of the test used for TB detection had an important influence on the sensitivity of the routine testing component but also on the pre-movement detection, and as a result, affected the overall sensitivity of the system. Therefore, improving the sensitivity through initiatives such as compulsory training courses for the veterinarians in charge of the testing seems a cost-effective alternative to improve cattle TB surveillance.
- Slaughterhouse surveillance also contributed to detection of *MTC*-infected herds with an average sensitivity of 9.5% and a mean time to detection longer than three years. Despite this relatively low effectiveness, this component is important as it allows the detection of diseases other than TB, and it has proven its capacity to find *MCT*-infected animals that otherwise would have been missed (i.e. “anergic” animals) although those cases are less and less frequent in Spain.
- In Spain, 10.8% of infected herds were detected by pre-movement

testing within the first year following infection, and on average detection took over 3 years. The cost-effectiveness of pre-movement testing, at least in areas of low incidence, should be evaluated taking into account not only its contribution to the detection, but also its cost, and should be compared to the cost-effectiveness of alternative options.

Funding

This research was funded by the Ministerio de Economía y Competitividad (MINECO) of Spain (Ministry of Economy and Competitiveness, EPITUBER Project, number AGL2013-49159-C2-1-R) and was supported by “Integrated epidemiological models for risk-based surveillance approaches (Epi-risk)” Era-Net ANIHWA Project. The PhD of Giovanna Ciaravino was funded by the Universitat Autònoma de Barcelona (UAB) of Spain (Autonomous University of Barcelona, grant number D045702/B14P0024).

Acknowledgments

The authors express their thanks to all the field veterinarians and Veterinary officers involved in the Spanish Bovine Tuberculosis Eradication Programme for their dedication and effort in implementing the campaign. We would also like to acknowledge the animal health and administrative staff of the Spanish Ministry for Agriculture, Fisheries and Food (MAPA) for their constructive assistance in the management of the database and for facilitating the data. Databases on cattle movements and routine controls are propriety of the Ministry for Agriculture, Fisheries and Food (MAPA) and subjected to confidentiality issues.

References

Allepuz, A., Casal, J., Napp, S., Saez, M., Alba, A., Vilar, M., Domingo, M., González, M.A., Duran-Ferrer, M., Vicente, J., Álvarez, J., Muñoz, M., Saez, J.L., 2011. Analysis of the spatial variation of Bovine tuberculosis disease risk in Spain (2006–2009). Prev. Vet. Med. 100, 44–52. https://doi.org/10.1016/j.prevetmed.2011.02.012.

Álvarez, J., Bezos, J., de la Cruz, M.L., Casal, C., Romero, B., Domínguez, L., de Juan, L., Pérez, A., 2014. Bovine tuberculosis: within-herd transmission models to support and direct the decision-making process. Res. Vet. Sci. 97, S61–S68. https://doi.org/10.1016/j.rvsc.2014.04.009.

Álvarez, J., Perez, A.M., Bezos, J., Marqués, S., Grau, A., Saez, J.L., et al., 2012a. Evaluation of the sensitivity and specificity of bovine tuberculosis diagnostic tests in naturally infected cattle herds using a Bayesian approach. Vet. Microbiol. 155, 38–43. https://doi.org/10.1016/j.vetmic.2011.07.034.

Álvarez, J., Perez, A.M., Bezos, J., Casal, C., Romero, B., Rodriguez-Campos, S., Saez-Llorente, J.L., Diaz, R., Carpintero, J., de Juan, L., Domínguez, L., 2012b. Eradication of bovine tuberculosis at a herd-level in Madrid, Spain: study of within-herd transmission dynamics over a 12 year period. BMC Vet. Res. 8, 100. https://doi.org/10.1186/1746-6148-8-100.

Anonymous, 2017. Informe Final Técnico-Financiero Programa Nacional de la Tuberculosis Bovina año 2017. Available at:. Ministerio de Agricultura Pesca y Alimentación (MAPA) - Dirección General de Sanidad de la Producción, Madrid, Spain. https://www.mapa.gob.es/es/ganaderia/temas/sanidad-animal-higiene-ganadera/informefinaltecnicotb2017_tcm30-496047.pdf.

Anonymous, 2019v. Programa Nacional de Erradicación de Tuberculosis Bovina presentado por España para el año 2019. Available at:. Ministerio de Agricultura Pesca y Alimentación (MAPA) - Dirección General de Sanidad de la Producción, Madrid, Spain. https://www.mapa.gob.es/es/ganaderia/temas/sanidad-animal-higiene-ganadera/programatb2019verdefinitiva_tcm30-500265.pdf.

Beesley, N.J., Caminade, C., Charlier, J., Flynn, R.J., Hodgkinson, J.E., Martinez-Moreno, A., Martinez-Valladares, M., Perez, J., Rinaldi, L., Williams, D.J.L., 2018. Fasciola and fasciolosis in ruminants in Europe: identifying research needs. Transbound. Emerg. Dis 65, 199–216.

Brooks-Pollock, E., Roberts, G.O., Keeling, M.J., 2014. A dynamic model of bovine tuberculosis spread and control in Great Britain. Nature 511, 228–231. https://doi.org/10.1038/nature13529.

Calvo-Artavia, F., Alban, L., Nielsen, L., 2013. Evaluation of surveillance for documentation of freedom from bovine tuberculosis. Agriculture 3, 310–326. https://doi.org/10.3390/agriculture3030310.

Cameron, A.R., 2012. The consequences of risk-based surveillance: developing output-based standards for surveillance to demonstrate freedom from disease. Prev. Vet. Med. 105, 280–286.

Cameron, A., Njeumi, F., Chibeu, D., Martin, T., 2014. Risk-Based Disease Surveillance. Available at:. FAO. http://www.fao.org/3/a-i4205e.pdf.

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? Front. Vet. Sci. 4, 1–28. https://doi.org/10.3389/fvets.2017.00202.

Ciaravino, G., García-Saenz, A., Cabras, S., Allepuz, A., Casal, J., García-Bocanegra, I., De Koeijer, A., Gubbins, S., Sáez, J.L., Cano-Terriza, D., Napp, S., 2018. Assessing the variability in transmission of bovine tuberculosis within Spanish cattle herds. Epidemics 23, 110–120. https://doi.org/10.1016/j.epidem.2018.01.003.

Claridge, J., Diggle, P., McCann, C.M., Mulcahy, G., Flynn, R., McNair, J., Strain, S., Welsh, M., Baylis, M., Williams, D.J., 2012. *Fasciola hepatica* is associated with the failure to detect bovine tuberculosis in dairy cattle. Nat. Commun. 3, 853.

Cosivi, O., Grange, J.M., Daborn, C.J., Raviglione, M.C., Fujikura, T., Cousins, D., Robinson, R.A., Huchzermeyer, H.F.A.K., de Kantor, I., Meslin, F.X., 1998. Zoonotic tuberculosis due to *Mycobacterium bovis* in developing countries. Emerg. Infect. Dis. 4, 59–70. https://doi.org/10.3201/eid0401.980108.

Courtenay, O., Reilly, L.A., Sweeney, F.P., Hibberd, V., Bryan, S., Ul-Hassan, A., Newman, C., Macdonald, D.W., Delahay, R.J., Wilson, G.J., Wellington, E.M.H., 2006. Is *Mycobacterium bovis* in the environment important for the persistence of bovine tuberculosis? Biol. Lett. 2, 460–462.

Crawshaw, T., Daniel, R., Clifton-Hadley, R., Clark, J., Evans, H., Rolfe, S., De La Rua-Domenech, R., 2008. TB in goats caused by Mycobacterium bovis. Vet. Rec. 163 127-127.

De la Rua-Domenech, R., Goodchild, A.T., Vordermeier, H.M., Hewinson, R.G., Christiansen, K.H., Clifton-Hadley, R.S., 2006. Ante mortem diagnosis of tuberculosis in cattle: a review of the tuberculin tests, γ-interferon assay and other ancillary diagnostic techniques. Res. Vet. Sci. 81, 190–210. https://doi.org/10.1016/j.rvsc.2005.11.005.

Domingo, M., Vidal, E., Marco, A., 2014. Pathology of bovine tuberculosis. Res. Vet. Sci. 97, S20–S29. https://doi.org/10.1016/j.rvsc.2014.03.017.

Ducheyne, E., Charlier, J., Vercruysse, J., Rinaldi, L., Biggeri, A., Demeler, J., Brandt, C., de Waal, T., Selemetas, N., Höglund, J., Kaba, J., 2015. Modelling the spatial distribution of *Fasciola hepatica* in dairy cattle in Europe. Geospat. Health 9, 261–270.

El Allaki, F., Harrington, N., Howden, K., 2016. Assessing the sensitivity of bovine tuberculosis surveillance in Canada's cattle population, 2009–2013. Prev Vet Med. 134, 145–152. https://doi.org/10.1016/j.prevetmed.2016.10.012.

EFSA AHAW Panel (EFSA Panel on Animal Health and Welfare), 2012. Scientific opinion on the use of a gamma interferon test for the diagnosis of bovine tuberculosis. EFSA J. 10 (12), 2975. https://doi.org/10.2903/j.efsa.2012.2975.

EU, 2015. Animal Health - Regulatory Committee–Presentations. Evolution of the National Eradication Programme on Bovine tb 2014 in Spain. 2015. Available at:. https://ec.europa.eu/food/sites/food/files/animals/docs/reg-com_ahw_20150506_pres_bovine-tuberculosis_spain.pdf.

EU, 2019a. Animal Health - Regulatory Committee–Presentations. Evolution of the National Eradication Programme on Bovine tb 2018 in Spain. 2019. Available at:. https://ec.europa.eu/food/sites/food/files/animals/docs/reg-com_ahw_20190612_pres_bov-tub_esp.pdf.

EU, 2016. Animal Health - Regulatory Committee–Presentations. Final Outcome of the Evaluation Procedure of Eradication, Control and Surveillance Programmes Submitted by the MSs for Union Financial Contribution for 2016 and Following Years. Available at:. https://ec.europa.eu/food/sites/food/files/animals/docs/reg-com_ahw_20160112_pres_eval-procedure_ecsp.pdf.

EU, 2017. Animal Health - Regulatory Committee–Presentations. Outcome of the Evaluation Procedure of the 2017 EU Co-financed Veterinary Programmes. Available at:. https://ec.europa.eu/food/sites/food/files/animals/docs/reg-com_ahw_20170117_pres_erad-2017_eur.pdf.

EU, 2018. Animal Health - Regulatory Committee–Presentations. Outcome of the Evaluation Procedure of the 2019 Veterinary Programmes for Which MSs Request EU Co-financing. Available at:. https://ec.europa.eu/food/sites/food/files/animals/docs/reg-com_ahw_20181123_progs-2019.pdf.

EU, 2019b. Animal Health - Regulatory Committee–Presentations. Outcome of the Evaluation Procedure of the 2019 Veterinary Programmes for Which MSs Request EU Co-financing. Available at:. https://ec.europa.eu/food/sites/food/files/animals/docs/reg-com_ahw_20190116_2019-vet-finance-progs_eur.pdf.

EU - DG SANCO (European Comission, Directorate-Generale for Health & Consumers Protection), 2013. Working Document on Eradication of Bovine Tuberculosis in the EU Accepted by the Bovine Tuberculosis Subgroup of the Task Force on Monitoring Animal Disease Eradication. Brussels, SANCO/10067/2013. Available at:. https://ec.europa.eu/food/sites/food/files/animals/docs/diseases_erad_tb_workingdoc2006_en.pdf.

EU - DG SANTE (European Commission, Directorate-General for Health & Food Safety), 2018. Commission Delegated Regulation 2018/1629/ EU of 25 July 2018 Amending the List of Diseases Set Out in Annex II to Regulation (EU) 2016/429 of the European Parliament and of the Council on Transmissible Animal Diseases and Amending and Repealing Certain Acts in the Area of Animal Health ('Animal Health Law'). Brussels. Available at:. http://data.europa.eu/eli/reg_del/2018/1629/oj.

EU - DG SANTE (European Commission, Directorate-General for Health & Food Safety), 2016. Final Report of an Audit Carried Out in Spain from 01 February 2016 to 12 February 2016 in Order to Evaluate the Effectiveness of, and the Progress Made by the Programme Co-financed by the European Union to Eradicate Bovine Tuberculosis. Available at:. . http://ec.europa.eu/food/audits-analysis/audit_reports/details.cfm?rep_id=3711.

European Food Safety Authority and European Centre for Disease Prevention and Control (EFSA and ECDC), 2018. The European Union summary report on trends and sources of zoonoses, zoonotic agents and food-borne outbreaks in 2017. EFSA J. 16 (12). https://doi.org/10.2903/j.efsa.2018.5500. p.e05500. Available at:.

Fischer, E.A., van Roermund, H.J.W., Hemerik, L., van Asseldonk, M.A.P.M., de Jong, M.C.M., 2005. Evaluation of surveillance strategies for bovine tuberculosis (*Mycobacterium bovis*) using an individual based epidemiological model. Prev. Vet. Med. 67, 283–301. https://doi.org/10.1016/j.prevetmed.2004.12.002.

Frankena, K., White, P.W., O'Keeffe, J., Costello, E., Martin, S.W., Van Grevenhof, I., More, S.J., 2007. Quantification of the relative efficiency of factory surveillance in the disclosure of tuberculosis lesions in attested Irish cattle. Vet. Rec. 161, 679–684. https://doi.org/10.1136/vr.161.20.679.

Garcia-Sáenz, A., Napp, S., Lopez, S., Casal, J., Allepuz, A., 2015. Estimation of the individual slaughterhouse surveillance sensitivity for bovine tuberculosis in Catalonia (North-Eastern Spain). Prev. Vet. Med. 121, 332–337. https://doi.org/10.1016/j.prevetmed.2015.08.008.

Garcia-Sáenz, A., Saez, M., Napp, S., Casal, J., Saez, J.L., Acevedo, P., Guta, S., Allepuz, A., 2014. Spatio-temporal variability of bovine tuberculosis eradication in Spain (2006–2011). Spat. Spatiotemporal. Epidemiol. 10, 1–10. https://doi.org/10.1016/j.sste.2014.06.002.

Gelman, A., Rubin, D.B., 1992. Inference from iterative simulation using multiple sequences. Stat. Sci. 7 (4), 457–472. https://doi.org/10.1214/ss/1177011136.

Guta, S., Casal, J., Garcia-Saenz, A., Saez, J.L., Pacios, A., Garcia, P., Napp, S., Allepuz, A., 2014. Risk factors for bovine tuberculosis persistence in beef herds of Southern and Central Spain. Prev. Vet. Med. 115, 173–180.

Hadorn, D.C., Stärk, K.D.C., 2008. Evaluation and optimization of surveillance systems for rare and emerging infectious diseases. Vet. Res. 39, 57. https://doi.org/10.1051/vetres:2008033.

De Mendoza, J.H., Parra, A., Tato, A., Alonso, J.M., Rey, J.M., Pena, J., García-Sánchez, A., Larrasa, J., Teixidó, J., Manzano, G., Cerrato, R., 2006. Bovine tuberculosis in wild boar (*Sus scrofa*), red deer (*Cervus elaphus*) and cattle (*Bos taurus*) in a Mediterranean ecosystem (1992–2004). Prev. Vet. Med. 17 (74), 239–247. https://doi.org/10.1016/j.prevetmed.2005.10.005.

Humblet, M.-F., Boschiroli, M.L., Saegerman, C., 2009. Classification of worldwide bovine tuberculosis risk factors in cattle: a stratified approach. Vet. Res. 40, 50. https://doi.org/10.1051/vetres/2009033.

Humblet, M.-F., Moyen, J.-L., Bardoux, P., Boschiroli, M.L., Saegerman, C., 2011a. The importance of awareness for veterinarians involved in cattle tuberculosis skin testing. Transbound. Emerg. Dis. 58, 531–536. https://doi.org/10.1111/j.1865-1682.2011.01228.x.

Humblet, M.-F., Walravens, K., Salandre, O., Boschiroli, M.L., Gilbert, M., Berkvens, D., Fauville-Dufaux, M., Godfroid, J., Dufey, J., Raskin, A., Vanholme, L., Saegerman, C., 2011b. Monitoring of the intra-dermal tuberculosis skin test performed by Belgian field practitioners. Res. Vet. Sci. 91, 199–207. https://doi.org/10.1016/j.rvsc.2010.12.004.

Keeling, M.J., Rohani, P., 2007. Modeling Infectious Diseases in Humans and Animals. Princeton university presshttps://doi.org/10.1097/01.ede.0000254692.80550.60. 408 pp.

Lombardi, G., Botti, I., Pacciarini, M.L., Boniotti, M.B., Roncarati, G., Dal Monte, P., 2017. Five-year surveillance of human tuberculosis caused by *Mycobacterium bovis* in Bologna, Italy: an underestimated problem. Epidemiol. Infect. 145, 3035–3039. https://doi.org/10.1017/S0950268817001996.

Meskell, P., Devitt, C., More, S.J., 2013. Challenges to quality testing for bovine tuberculosis in Ireland; Perspectives from major stakeholders. Vet. Rec. 173, 94. https://doi.org/10.1136/vr.101676.

Müller, B., Dürr, S., Alonso, S., Hattendorf, J., Laisse, C.J.M., Parsons, S.D.C., van Helden, P.D., Zinsstag, J., 2013. Zoonotic *Mycobacterium bovis* –induced Tuberculosis in humans. Emerg. Infect. Dis. 19, 899–908. https://doi.org/10.3201/eid1906.120543.

OIE (World Organisation for Animal Health), 2018. Infection with *Mycobacterium tuberculosis* complex, 27th ed. OIE, Terrestrial Animal Health Code, vol. 2 session 8, chapter 8.11. Paris. Available at: http://www.oie.int/en/standard-setting/terrestrial-code/access-online/.

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. Lancet Infect. Dis. 17, e21–e25. https://doi.org/10.1016/S1473-3099(16)30139-6.

Palacios, J.J., Navarro, Y., Romero, B., Penedo, A., González, Á.M., Hernández, M.D.P., Fernández-Verdugo, A., Copano, F., Torreblanca, A., Bouza, E., Domínguez, L., 2016. Molecular and epidemiological population-based integrative analysis of human and animal *Mycobacterium bovis* infections in a low-prevalence setting. Vet. Microbiol. 195, 30–36. https://doi.org/10.1016/j.vetmic.2016.08.019.

R Core Team, core Team, R, Team, R.D.C, 2015. R: a language and environment for statistical computing. R A Lang. Environ. Stat. Comput Available from: https://www.r-project.org/.

Reviriego Gordejo, F.J., Vermeersch, J.P., 2006. Towards eradication of bovine tuberculosis in the European Union. Vet. Microbiol. 112, 101–109. https://doi.org/10.1016/j.vetmic.2005.11.034.

Rossi, G., De Leo, G.A., Pongolini, S., Natalini, S., Vincenzi, S., Bolzoni, L., 2015. Epidemiological modelling for the assessment of bovine tuberculosis surveillance in the dairy farm network in Emilia-Romagna (Italy). Epidemics 11, 62–70. https://doi.org/10.1016/j.epidem.2015.02.007.

Schöning, J.M., Cerny, N., Prohaska, S., Wittenbrink, M.M., Smith, N.H., Bloemberg, G., Pewsner, M., Schiller, I., Origgi, F.C., Ryser-Degiorgis, M.P., 2013. Surveillance of bovine tuberculosis and risk estimation of a future reservoir formation in wildlife in Switzerland and Liechtenstein. PLoS One 8, e54253. https://doi.org/10.1371/journal.pone.0054253.

Thoen, C.O., Lobue, P.A., de Kantor, I.N., 2010. Why has zoonotic tuberculosis not received much attention? Int. J. Tuberc. Lung Dis. 14, 1073–1074.

Van Asseldonk, M.A.P.M., van Roermund, H.J.W., Fischer, E.A.J., de Jong, M.C.M., Huirne, R.B.M., 2005. Stochastic efficiency analysis of bovine tuberculosis-surveillance programs in the Netherlands. Prev. Vet. Med. 69, 39–52. https://doi.org/10.1016/j.prevetmed.2005.01.012.

Welby, S., Govaerts, M., Vanholme, L., Hooyberghs, J., Mennens, K., Maes, L., Van Der Stede, Y., 2012. Bovine tuberculosis surveillance alternatives in Belgium. Prev. Vet. Med. 106, 152–161. https://doi.org/10.1016/j.prevetmed.2012.02.010.

WHO (World Health Organization), 2019. Zoonotic TB. In: Tuberculosis (TB). Available from:. WHO. https://www.who.int/tb/areas-of-work/zoonotic-tb/en/.