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Title

The spread of bovine tuberculosis in Canadian shared pastures: data, model, and simulations

Short title

Bovine TB spread in pastures

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Summary

Bovine tuberculosis (bTB), caused by *Mycobacterium bovis*, is a chronic disease typical of cattle. Nonetheless, it can affect many mammals including humans, making it one of the most widespread zoonotic diseases worldwide. In industrialized countries, the main pathways of introduction of bTB into a herd are animal trade and contact with infected wildlife. In addition, for slow-spreading diseases with a long latent period such as bTB, shared seasonal pastures might be a between-herd transmission pathway, indeed farmers might unknowingly send infected animals to the pasture, since clinical signs are rarely evident in early infection.

In this study, we developed a dynamic stochastic model to represent the spread of bTB in pastures. This was tailored to Canadian cow-calf herds, as we calibrated the model with data sourced from a recent bTB outbreak in Western Canada. We built a model for a herd with seasonal management, characterized by its partition into a group staying in the main facility and the remaining group(s) moving to summer pastures. We used this model to estimate the time of first introduction of bTB into the herd.

Further, we expanded the model to include herds categorized as high-risk contacts with the index herd, in order to estimate the potential for disease spread on shared pastures. Finally, we explored two control scenarios to be applied to high-risk farms after the outbreak detection.

Our results showed that the first introduction likely happened three to five years prior to the detection of the index herd, and the probability of bTB spreading in pastures was low, but not negligible. Nevertheless, the surveillance system currently in place was effective to detect potential outbreaks.

Keywords

bovine tuberculosis, beef herd, pasture land, parameter estimation, simulations

Main text

1. Introduction

Bovine tuberculosis (bTB), caused by *Mycobacterium bovis*, represents a threat for the cattle industry in several regions around the world (Pfeiffer et al., 2013), as well as for humans (Olea-Popelka et al., 2017) and wildlife (Miller et al., 2013). Bovine tuberculosis is characterized by a slow spread dynamics, partly due to the length and high variability of the latency period of infected hosts, which can last months to years (Brooks-Pollock et al., 2014). Infected animals rarely show clinical signs before the final stage of the infection (Morris et al., 1994), but they may become infectious prior to that. In the case of intensively reared herds, such as many dairy farms in high-income countries, cattle trade movements of infected animals represent one of the main pathways of introduction of bTB into a herd (Gilbert et al., 2005). Another source of bTB can be the contact with infected wildlife species, such as wood bison and wapiti (Nishi et al., 2006), as well as European badgers, white-tailed deer, and possums (Pfeiffer et al., 2013, and references therein). Management practices can also play a role in between-herd transmission of bTB. In fact, studies have shown that, both for Canadian and Michigan (US) herds, the sharing of pastures with or in proximity to an infected herd has been associated with a higher probability of testing positive to bTB (Kaneene et al., 2002; Munroe et al., 1999).

Moving animals to seasonal pasture lands is a well-established practice for many livestock industries worldwide, including cattle, horses, sheep, and goats. A common practice in countries such as Canada and the United States is the use of seasonally shared or community pastures. These lands are usually co-managed and they can harbour mixed groups of cow-calf pairs and bulls that are managed separately for the rest of the year (Sheppard et al., 2014; Siegwart et al., 2006). From an epidemiological point of view, seasonal pastures can enhance the spread of infectious diseases between herds (Palisson et al., 2017), as they might facilitate potentially infectious contacts between otherwise separated groups of animals (Waret-Szuka et al., 2011). Pastures have been shown effective

for the spread of diseases transmitted by different types of contacts, including direct (Valle et al., 1999; Kaneene et al., 2002), indirect (Nusinovici et al., 2015), and through vectors (Pioz et al., 2014).

For diseases such as bTB, this represents a challenge for epidemic control and surveillance, as farmers might unknowingly move sub-clinically infected animals to and from community pastures.

This particular problem was evident during a recent outbreak in Western Canada, where fifteen herds had to be destroyed due to high-risk direct contact via commingling on pasture with a cow-calf herd that was found positive to bTB in September 2016 (CFIA, 2018).

Canada is considered officially free from bTB according to domestic criteria in the *Health of Animals Regulations*, with only sporadic localized outbreaks detected over the past decade (El Allaki et al., 2016). Moreover, the epidemiological investigation showed that the strain involved in the 2016 outbreak was different from others previously isolated from Canadian herds or wildlife (CFIA, 2018).

This raised several epidemiological questions regarding the introduction into the index herd, in particular when it could have happened, and how likely the infection could have spread to other herds on shared pastures.

The main objectives of this study were, first, to estimate the time of introduction of bTB in the index herd of the 2016 outbreak, using a stochastic mathematical model representing the spread of bTB within a cow-calf herd characterized by seasonal management. Second, to model the potential spread of bTB to other herds, by extending the model to a framework with multiple herds, in which the main contact between herds is the sharing of pasture land during summer. The last objective was to use the model to explore two different strategies (single whole herd test and depopulation vs. quarantine and repeated whole herd tests) for the detection of potentially infected herds among the high-risk contacts herds.

2. Material and methods

Two mathematical models were developed: the index-herd model and the pasture model. The former was developed to represent the spread of bTB in the index herd and thus to estimate the time of introduction. The pasture model could be considered a meta-population extension of the index-herd model, to which potential for bTB between-farm spread was added. The main between-herd spread mechanism was the use of the same pasture by different herds simultaneously, but another type of high-risk direct contact (shared bull use) identified during the epidemiological investigation in the 2016 outbreak was also included (CFIA, 2018). This model was simulated using the parameters previously estimated with the index-herd model.

Both models were stochastic and simulation-based, with each simulation of bTB spread running from the introduction of a single infected but not yet infectious cow, to the bTB detection by the surveillance system and following testing. In case the bTB outbreak was not detected, the pasture model simulation stopped in September 2016 (the observed outbreak detection time).

Information about all involved herds was obtained from the epidemiological investigation conducted by the Canadian Food Inspection Agency (CFIA) (Table 1). The next sections describe the herd demographic (2.1), the index-herd and pasture models (2.2 and 2.3, respectively), and finally the surveillance system (2.4).

2.1. Herds demographic

The herds demographics parameters (reported in Table 2) were based on the 2014 Western Canada Cow-Calf Survey (WCCCS, Western Beef Development Group, 2015). The respondents to this voluntary survey (411 farmers) accounted for 76,000 breeding females or 2.2% of the 3.45 million cows reported by Statistics Canada to be in Western Canada as of July 1, 2013. The survey was distributed at producer meetings and events, as well as beef industry conferences. Results were assumed to be representative of common management practices in Western Canadian cow-calf herds.

Herds included four sex/age categories of animals: cows, heifers, bulls, and calves. In order to maintain a stable herd population size, the internal replacement rate for cows, i.e. the number of calves maintained as heifers, and the yearly purchase rate for bulls were empirically estimated to restore the starting herds size (see Table 2). As bTB prevalence is currently very low in Canadian herds (El Allaki et al., 2016), it was assumed that the purchased bulls would not be infected with bTB. Commonly to most herds in the study area, cow replacement was assumed to be done entirely with their own stock.

The month of the calving season offset was randomly chosen at the beginning of every simulation's run for each herd, with probabilities corresponding to those described in the WCCCS (Table 2). Based on this survey, the calving season was assumed to start between January and May and spanned three months: 75% of pregnant cows gave birth in the first month, 20% in the second, and 5% in the third. Calves weaning happened once a year, and its timing for each herd was selected from September to December. The probability of selecting each of these months was described in the WCCCS (Table 2). In addition, weaning months were chosen so that calving and weaning could not be less than 6 or more than 12 months apart. For the sake of simplicity, it was assumed that at the time of weaning the retained replacement heifers were moved to the adult cow class. New bulls were purchased between February and April. Natural death rates were as reported in the WCCCS (Table 2). Mortalities for cows, bulls, and heifers were assumed to be homogeneously distributed throughout the year. Calf mortality is generally higher during the neonatal period and, following Wittum et al. (1994), we set it at 1.47% per month for the first two months. From the third month until the calves were weaned (on average, a total of 8 months from calving to weaning), mortality was equally distributed to a cumulative yearly value of 6.9% (Table 2). Removal of cull cows for slaughter was assumed to happen on a quarterly basis (March, June, September, and December), with a higher value at the beginning of December because typical management procedures call for the slaughter of cows failing a pregnancy test before winter feeding begins. Bull culling was assumed to happen once a year, at the end of the breeding season: this would be either September for herds calving earlier in the year (January or February), or December for herds calving later (March to May). A proportion of each herd

was moved to summer pasture during June each year, and bulls and cows returned to the main herd in September and November, respectively. Demographic stochasticity was incorporated by drawing the exact number of animals for each event (e.g., death, removal, birth, replacement, and movement to pasture) from a Poisson distribution.

2.2. The index-herd model

The index-herd model consisted of a dynamic within-herd bTB epidemic model, with the particular characteristic that during summer the herd split into three groups, each with its own transmission dynamics. These three groups represented the cattle going to two pastures (labelled A and B for convenience), and those staying in the main herd facility. The model included three main parts: the herd demographics, the bTB dynamics, and the surveillance system.

Although in the following sections the model is described in a deterministic format, all the results are obtained with stochastic simulations of potential bTB outbreaks using a fixed monthly time step following the τ -leap algorithm (Gillespie & Petzold, 2001; Keeling & Rohani, 2008). This method was chosen for its computational efficiency, and given the slow dynamics of bTB infection, the step was set to 1 month. All models, analyses, and parallel simulations were done in R version 3.4.1 (R Core Team, 2016), using the *mc2d* package for the PERT distribution (Pouillot & Delignette-Muller, 2010), and *ggplot2* for graphic representations (Wickham, 2009).

2.2.1. Within-herd bTB dynamics

The within-herd dynamics of bTB infection were represented by a compartmental model with four compartments: Susceptible (not infected), Occult (latently infected but not reactive to skin test), Reactive (latently infected and reactive to skin test), and Infectious (infected, reactive, and able to infect) (Figure 1, panel A). The set of differential equations for a deterministic model without considering age/sex classes was:

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$$\begin{aligned}
\frac{dS}{dt} &= \mu N - \lambda S - \mu S \\
\frac{dO}{dt} &= \lambda S - \sigma_O O - \mu O \\
\frac{dR}{dt} &= \sigma_O O - \sigma_R R - \mu R \\
\frac{dI}{dt} &= \sigma_R R - \mu I
\end{aligned} \tag{1}$$

For the sake of simplicity, here μ represents all demographic inputs (birth, purchase, or ageing) and outputs (death, removal, and/or ageing). The parameters σ_O and σ_R are the transition rates from Occult to Reactive and from Reactive to Infectious, respectively, with $1/\sigma_O$ and $1/\sigma_R$ representing the average time spent in the Occult and Reactive statuses. The distribution of these two parameters was derived from the literature (Table 3). Since the herds included in this study were large and extensively managed, following Alvarez et al. (2014) the within-herd transmission rate was assumed to be frequency-dependent. Specifically, the within-herd force of infection (λ) was set as $\lambda = \beta I/N$, where β is the effective contact rate, I is the number of infected individuals in the herds, and N is the total number of individuals ($N = S + O + R + I$). Since β has never been estimated in the context of Canadian cow-calf herds at the time of writing, this parameter was estimated from the data (see section 2.2.2). Because calves tend to stay in closer contact with their dams than with the rest of the herd (Brooks-Pollock et al., 2013), their contact rate was scaled down by a factor ϕ .

2.2.2. Estimating the time of introduction

The first objective of this study was to estimate the time of introduction (ToI) of bTB in the index-herd. An Approximate Bayesian Computation - Sequential Monte Carlo (ABC-SMC) like algorithm (Toni et al., 2009), called the pseudo-ABC algorithm hereafter, was used to estimate the duration of the infection in the index herd, from which the ToI probability distribution was derived. The contact rate (β), the β -scaling factor for calves (ϕ), and the slaughterhouse sensitivity for infectious animals (Se_{sla}) were also estimated using this algorithm.

The ABC-SMC method can be used to estimate a set of parameters starting from their prior distributions without explicitly specifying a likelihood function, and has already been used in the bTB modelling literature (Conlan et al., 2012; Brooks-Pollock et al., 2014). With respect to the original ABC algorithm, the idea of SMC is to sample the parameters' populations from a sequence of approximate ABC posteriors with increasingly lower acceptance tolerances (Kypraios et al., 2017). The advantage of this technique is that it concentrates on parameter space regions with relatively high acceptance probabilities, thus making the algorithm more computationally efficient. Generally, the acceptance tolerance is based on the distance (d) between the observed data and their simulated counterpart.

The ToI was estimated based on the following observations gathered during the investigation of the index herd of the 2016 outbreak: (i) the number of infected adults detected at the slaughterhouse D_A ($n = 1$), (ii) the number of infected calves detected at slaughterhouse after fattening D_C ($n = 0$), and (iii) the number of infected adults detected by the follow-up testing F ($n = 5$). Details on the surveillance system and testing can be found in section 2.4. The distance d was calculated as the Euclidean distance between the observations (Obs) and the model simulations ($Simul$):

$$d = \sqrt{(D_A^{Obs} - D_A^{Simul})^2 + (D_C^{Obs} - D_C^{Simul})^2 + (F^{Obs} - F^{Simul})^2}. \quad (2)$$

To obtain the number of detected animals (D_A , D_C , and F), all simulations ran until bTB was detected in the herd. In order to correctly estimate the ToI, two precautions had to be taken. The first one regarded the choice of the number of additional parameters to estimate and their priors. In fact, this was limited to three: ϕ , β , and Se_{sla} . The first parameter, ϕ , was assumed to be uniformly distributed between 0.25 and 0.75. For β , a betaPERT distribution was used, with minimum, maximum, and mode based on estimates from the literature (see Table 3 for the list of references). Since a frequency-dependent transmission model was adopted, only the published works that used this type of transmission were considered. The prior distribution of Se_{sla} was also represented via a betaPERT distribution. However, in this case we set the mode to 0.86, following a study on a similar area (Michigan, US, by Norby et al., 2004), while the minimum and maximum were respectively set equal

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to 0 and 1 to account for a broad range of values. The second precaution was to modify the ABC-SMC algorithm by making it accept only the parameters that could replicate the exact number of infected animals observed in the index herd ($d = 0$). Since tolerance was not decreasing, the main purpose of the steps became to explore the parameters space through a perturbation of the previous steps particle with a Gaussian kernel, with variance set to the observed variance of the previous step, times 0.68 (Brooks-Pollock et al., 2014; Filippi et al., 2013). The estimation was run through five steps, with 60,000 set of parameters per step. The estimated parameters distributions at the end of each step were used as priors in the subsequent step.

2.3. The pasture model

2.3.1. *Between-herd dynamics*

The main between-herd bTB transmission route assumed by this model was through contacts on shared pastures, as described above. Following a common approach in the literature, the pasture model was built as a meta-population (Smith et al., 2013; Rossi et al., 2015; VanderWaal et al., 2017a). Each herd represented an individual sub-population with its own dynamics, corresponding to the within-herd dynamics established by the index herd model (section 2.1). During the pasture season, herds were coming into contact with others by sending some or all of their cattle to a shared pasture (Figure 1, panel B). In this case, the pasture bTB dynamics were represented by the following ordinary differential equations system:

$$\begin{aligned}\frac{dS_i^P}{dt} &= \mu N_i^P - \lambda_b S_i^P - \mu S_i^P \\ \frac{dO_i^P}{dt} &= \lambda_b S_i^P - \sigma_O O_i^P - \mu O_i^P \\ \frac{dR_i^P}{dt} &= \sigma_O O_i^P - \sigma_R R_i^P - \mu R_i^P \\ \frac{dI_i^P}{dt} &= \sigma_R R_i^P - \mu I_i^P\end{aligned}\tag{3}$$

Here S_i^P , O_i^P , R_i^P , and I_i^P corresponded respectively to the proportion of Susceptible, Occult, Reactive, and Infectious animals of herd i sent to pasture P . The pasture force of infection λ_b was calculated as:

$$\lambda_b = \beta I_i^P / N_i^P + \psi \beta (\sum_{j \neq i} I_j^P) / (\sum_{j \neq i} N_j^P), \quad (4)$$

where ψ represents the pasture mixing rate. The summation was done on all j herds except the i^{th} herd, for which within-herd transmission dynamics held. The pasture mixing rate was defined over the interval (0,1), reflecting how well the animals mix in pastures. A value of $\psi=0$ represented no mixing between animals of different herds on pasture (i.e., no potential infectious contacts), while $\psi=1$ implied homogeneous mixing of animals from different herds.

2.3.2. Pasture model simulations

The spread of bTB on pasture lands was simulated using the Canadian 2016 outbreak data (Table 1). Other than the index herd (#1), 15 direct contact high-risk herds identified during the epidemiological investigation conducted by the CFIA were included in the model. Twelve of these herds co-mingled some or all of their cattle with the index herd on one of the two summer pastures (pasture A, n=8 herds and pasture B, n=4 herds; see Table 1). Two herds (#3 and #4; see Table 1) co-mingled cattle with the index herd on winter grazing land from November 2015 to March 2016, while one herd (#2) co-owned and shared bulls with the index herd. The epidemiological investigation showed that bulls were mainly managed by herd #1 during the non-breeding season. Thus, the model was assumed that a group including 30% to 70% of randomly selected bulls from herd #1 was sent to herd #2 for the breeding season each year in May, and returned to herd #1 in October.

The set of parameters β , ϕ , Se_{sla} and ToI used in each pasture model run was randomly drawn from distributions obtained through the index-herd model simulations. For the summer pastures, the pasture mixing rate (ψ) was an unobservable parameter, and a sensitivity analysis was conducted by running 120,000 simulations for each of the following 6 values: 0, 0.125, 0.25, 0.5, 0.75, and 1. On the winter

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pasture animals tend to aggregate at feeding areas, thus we assumed the three herds (#1, #3, and #4) to be in full (homogeneous) contact during this period ($\psi=1$). Pasture model simulations ran from the selected ToI until bTB was detected, or until September 2016 in case the outbreak was not detected earlier.

2.4. Surveillance system

Both the index-herd and pasture models included a surveillance component based on Canada's current national surveillance system and eradication policy for bTB. This includes multiple surveillance components: routine slaughter inspection, tuberculin testing for specific groups of animals, and mandatory reporting of any suspect cases (El Allaki et al., 2016). In the model, slaughterhouse surveillance was applied to all adults removed from herds for slaughter in the next time step, as well as to the calves leaving the herd for fattening, after a delay correspondent to the time necessary to reach 18 months of age, the typical age at slaughter. This test is also identified in the literature as gross necropsy or meat inspection.

The slaughterhouse inspection sensitivity for infectious adults and calves (Se_{sla}) was estimated through the pseudo-ABC algorithm. As occult and reactive animals might not have developed granulomas at the time of slaughter, the slaughterhouse inspection sensitivity was scaled down by a factor κ . It was assumed that occult animals could not be detected at slaughterhouse ($\kappa = 0$). For reactive adults and calves, κ was drawn from a betaPERT distribution, with minimum, mode, and maximum set to 0, 0.05, and 0.25, respectively. The proportion of infected calves that transitioned from compartments O to R and from R to I during the fattening period was calculated from an exponential function with rates σ_O and σ_R , respectively.

In Canada, any confirmed case of bTB detected at slaughter is traced back to every herd that the index animal has resided in from birth to death in order to conduct the investigation and, if the disease is confirmed, take action to eradicate the disease¹. In addition, at-risk livestock herds that are epidemiologically linked (e.g., trace back, trace forward, and contacts) with the infected premises are investigated, and the type of on-farm testing and disease eradication activities conducted will depend on the relationship between each herd and the infected one¹. Animals that are humanely destroyed due to infection, test reactor or suspect status are subjected to an enhanced post-mortem (EPM) examination, during which any abnormalities that may be observed plus a selection of normal tissues are subject to laboratory examination and testing (e.g., histopathology, PCR, bacterial culture), in order to increase the probability that bTB is detected. Animals destroyed based on their high-risk exposure status but negative to on-farm testing are subject to a regular post-mortem examination with sampling and laboratory examination of any observed abnormality. When all destroyed animals in a herd are negative to bTB, no further action is required, and the herd can be released from quarantine.

During the investigation of the 2016 outbreak, the index herd was subject to a whole-herd test (WHT) which, as the name suggests, is applied to all adult cattle (> 12 months of age) in the herd. The WHT was composed of two on-farm diagnostic tests, namely the caudal fold tuberculin (CFT) test and a commercial enzyme-linked immunosorbent assay (ELISA) for the measurement of antibody response to *M. bovis* antigens (IDEXX Laboratories, Westbrook, ME), followed by humane destruction and EPM for any animal with a positive or non-negative (suspect) result to either test, or standard slaughterhouse inspection for cattle that tested negative.

1 <http://www.inspection.gc.ca/animals/terrestrial-animals/diseases/reportable/tuberculosis/farm-under-investigation/eng/1449456995596/1449456996360>

All parameters for the three parts of the WHT were estimated from the literature. The mean [95% confidence interval] individual CFT test sensitivity was 0.76 [0.56 – 0.89] (Nunez-Garcia et al., 2018), and was modelled with a beta-PERT distribution, using the mean as the central value and the confidence interval as the range. The IDEXX Elisa sensitivity was modelled with a beta distribution, with parameters α and β set to 159 and 191, respectively. These parameters were estimated from published data on the test sensitivity in animal populations with a low bTB prevalence (New Zealand and USA) (Buddle et al., 2013; Waters et al., 2011; Trist et al., 2016). Finally, the mean sensitivity [95% confidence interval] of the EPM (necropsy including laboratory bacterial culture and histopathology) was set to 0.96 [0.82 -1.00] (Nunez-Garcia et al., 2018), and it was modelled with a beta-PERT distribution as described above.

Following the first bTB detection, two scenarios were modelled for the index and high-risk direct-contact herds. The first scenario aimed to represent the situation that prevailed during the 2016 outbreak: the detection of at least one infected individual (since the model is stochastic, more than one individual might be detected at the same time in a simulation run) triggered a WHT in all systems' herds. This test included a CFT for all adults, followed by an EPM for all reactors and a gross necropsy (meat and tissues inspection) for all non-reactors. The necropsy implied that all tested herds were subject to depopulation irrespectively of the CFT result, in order to improve the chances of detecting potentially infected animals and thus to evaluate whether to extend the outbreak's tracing investigation further.

In the second scenario, an alternative control policy for the high-risk contact herds was explored. This reflects what is done in countries where the control of bTB includes test-and-removal protocols, such as the US² and Great Britain³. Specifically, this consisted of a repeated WHT (CFT on all adults) that

2 USDA:APHIS:VS. Bovine Tuberculosis Eradication: Uniform Methods and Rules. 2005 Available at http://www.aphis.usda.gov/publications/animal_health/content/printable_version/bovind_turb_errad_1_1_0_5.pdf

was applied to all direct-contact high-risk herds following the initial detection at slaughterhouse.

Whole herd tests were modelled quarterly for a maximum period of three years starting one month after the initial detection, for a maximum of 13 WHT. The output of the surveillance modelling was the proportion of herds detected at the end of the testing period, as well as at each WHT. Once a herd was determined to be infected, it was not subject to WHT anymore. Since the main objective of this alternative scenario analysis was to assess the ability of such control practice to identify infected herds, these herds were not monitored after the detection. It was assumed that herds were quarantined during this period. This implied no possibility of between-herd spread of infection, although within-herd transmission of bTB was allowed to continue. Note that during the quarantine all adults animals leaving the herds for slaughterhouse were subject to an EPM test, while weaned calves underwent first a CFT, followed by a meat inspection for the positive ones.

3. Results

3.1. Description of the outbreak

A five-year old Canadian cow slaughtered in the USA on September 6, 2016 was found to be infected with bovine TB (bTB) following post-mortem examination and isolation of *Mycobacterium bovis* in bacterial culture. The cow was traced to a cow-calf operation in Alberta, and disease eradication and investigation measures were initiated by the CFIA on the index farm. Live animal testing was conducted on all animals aged 12 months or more, which were then subject to post-mortem examination after the whole herd was slaughtered. During the post-mortem examination, five additional infected animals were identified and confirmed by isolation of *M. bovis*.

Moreover, the disease investigation brought to the identification of 15 herds that had high-risk direct contact with the index herd (Table 1 and Figure 1, panel C). All these herds were subject to WHT, depopulation, and post-mortem examination, but no other infected animal was detected. In addition, 130 farms whose animals had been exposed to the index herd were identified. A total of 34,000 animals were tested. Depending on the type of exposure to the index herd, those with a reaction or non-negative result to a screening test were subject to either supplementary testing or enhanced post-mortem examination after slaughter. All test results were negative.

3.2. Index-herd model

According to the index-herd model and the pseudo-ABC algorithm, the introduction of bTB into the index herd (detected in September 2016) most likely occurred in June 2013 (mode). Figure 2 shows a 50% probability that bTB introduction occurred between July 2011 and November 2013 (median: December 2012), and a very low probability (< 5%) of occurrence prior to April 2007 or after January 2015.

Table 3 reports the parameters estimated with the pseudo-ABC algorithm, while their prior and estimated posterior distributions are shown in Figure 3. The median contact rate (β) was 1.92 (new cases/case/year), with the 95% Credible Interval [CI] distributed between 0.68 and 5.07 (Figure 3, panel A). The contact rate was lower for calves, as the median for the scaling factor ϕ was 0.44 [0.26 and 0.72] (Figure 3, panel B). Finally, the median of the slaughterhouse inspection test sensitivity distribution was 0.68 [0.20, 0.98] for infectious individuals.

3.3. Pasture model

The results from the pasture model simulations showed no other infected herd beside the index herd in 41-56% of the simulations, with the percentage decreasing with Ψ . As expected, the percentage of

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simulations with a single infected herd was lower for higher values of Ψ (Figure 4, panel A). As showed in panel B of Figure 4, this significant effect of Ψ on the number of additional infected herds was even more evident when only shared summer pasture contacts were considered (thus, excluding bull sharing and winter quarters contacts). In that case, the probability of no additional infected herd ranged between 88% and 57% for values of Ψ from 0.125 to 1 (by definition it was equal to 100% for $\Psi = 0$). Increasing the value of Ψ increased the probability of finding a higher number of additional herds infected on pasture, but the probability of more than three additional herds infected remained very low, especially for low values of Ψ . By comparing the probability of at least one other infected herd for all contacts (44-59%) versus summer pasture only (12-43%), it emerged that in this model contacts via bull sharing (herd #2 infected in the 19% of simulations) and winter colony (herds #3 and #4 both infected in 17% of the simulations, only one of the two infected in 20% of simulations) were also important in the potential spread of the disease between herds.

The median [2.5th – 97.5th percentiles] number of maximum occult (O), reactive (R), and infectious (I) animals in the index herd was respectively 2 [0 – 11], 2 [1 – 19], and 3 [0 – 23]. For all other herds combined, the number of O, R, and I individuals, respectively, was 0 [0 – 5], 0 [0 – 7], and 0 [0 – 6] if $\Psi = 0$, and 1 [0 – 10], 1 [0 – 11], and 0 [0 – 8] if $\Psi = 1$.

On average, 12.3% of the simulated outbreaks faded out naturally without being detected (Figure 5, panel A and Table 4). The slaughterhouse inspection-based surveillance could detect on average 75.2% of the remaining outbreaks (66.0% over all simulations), while 24.8% (21.7% overall simulations) were still ongoing without detection at the end of the simulation. The share of detected outbreaks slightly increased with Ψ , while both faded-out and undetected outbreaks decreased. As shown in Figure 5 (panel B), the naturally faded outbreaks involved a very low number of infected herds, while the detected and ongoing outbreaks were characterized by similar size.

The detected outbreaks were subject to the follow-up whole-herd testing (WHT) for herds not already detected by the slaughterhouse surveillance (between 59.6% and 40.5% of all infected herds). In the first control scenario (live animal CFT testing followed by EPM for reactors and gross necropsy for non-reactors), it was estimated that the WHT could have missed between 8.3% ($\Psi = 0$) and 10.2% ($\Psi = 1$) of the infected herds, while another 6.5% ($\Psi = 0$) and 13.1% ($\Psi = 1$) of infected herds were non-detectable, meaning that all their bTB infected animals were at the occult stage (Table 4). The single WHT test was able to identify on average 64.0% of the bTB infected herds, ranging from 67.3% ($\Psi = 0$) to 62.6% ($\Psi = 1$).

As for the second scenario (quarantine and repeated live animal testing), Figure 6 shows the average cumulative probability of escaping detection after repeated WHT. The average probability of escaping detection ranged between 8.4% ($\Psi = 0$) and 14.5% ($\Psi = 1$) for the first test, between 2.3% ($\Psi = 0$) and 4.4% ($\Psi = 1$) for the second, between 0.8% ($\Psi = 0$) and 1.4% ($\Psi = 1$) for the third, and 0.4% or less for the fourth WHT, which occurred nine months after the first detection at the slaughterhouse. In fact, about three quarters of the detections happened during the first test (77.4% at $\Psi = 0$, and 75.0% $\Psi = 1$). The remaining bTB infected herds were detected mostly during the first year of quarantine (22.2% to 24.6%), while very few were detected during the second year (0.1-0.2%) or cleared out the infection unnoticed (0.2%). Only 4 [3 to 7] infected herds reached the 9th test of the series (two years after the first detection) undetected, while no one reached the 10th test.

4. Discussion

One of the main objectives of this study was to estimate the time of bTB introduction into the only infected herd of the 2016 Western Canada outbreak. Our results showed that the introduction most likely happened three years and three months before detection. This is consistent with another simulation-based model study on North-American cow-calf herds (Smith et al., 2013), as well as with

the epidemiology of the disease, considering the long and highly variable latency period of bTB (see references in Table 3).

Thanks to the National Bovine Tuberculosis Eradication Program started in 1923, Canada's domestic livestock herd is officially bTB-free as per the *Health of Animals Regulations* (Minister of Justice, 2017). Prior to the September 2016 outbreak, the previous one occurred in British Columbia in 2011 and involved one herd only (El Allaki et al., 2016). To the best of our knowledge, bTB dynamic parameters have never been estimated in the context of Canadian herds. In general, North-American cow-calf herds and management practices are poorly represented in the published bTB modelling literature, with one of the few exceptions being Smith et al. (2013). Since the parameters governing transmission dynamics could be strongly affected by management practices, we decided to estimate the effective contact rate (β), the contact rate scaling factor for calves (ϕ), and the baseline slaughterhouse test sensitivity (Se_{sla}) for infectious animals.

The estimated effective contact rate (β) was 1.92, thus falling in the range of what found in the published literature, but slightly lower than the median value (median 2.2 and range 0.61 – 5.2, references in Table 3). This could reflect the fact that our model only considers extensive cow-calf herds, while most existing studies include multiple production types.

The effective contact rate for calves, which for a long part of the year represents almost half of the herd, was estimated to be 44% that of adult cattle. This could partly explain the findings by Brooks-Pollock et al. (2013), who showed that reactor rates to the comparative cervical test for bTB increased with age for the first 2-3 years of age of beef and dairy cattle in Great Britain. Other explanations include less exposure time, lower number of tests received, and less time to move from O to R when infected. This result also supports other authors who opted for a lower relative risk of infection to calves as compared to adults in their surveillance models (El Allaki et al., 2016; Sergeant et al., 2011). In fact, this was expected for cow-calf herds, since calves spend most of their time with their dam before being weaned and moved.

The slaughterhouse inspection sensitivity estimate for infectious animals (68%) was close to other estimates in recent literature (71% in EFSA, 2012 and Nuñez-Garcia et al., 2018). Other studies carried out in low bTB prevalence countries, such as Australia and Uruguay, found lower sensitivity values: 53% and 42% in Corner et al. (1990) and VanderWaal et al. (2017a), respectively. It has to be noted that in the latter case the authors assigned to the reactive animals a 50% probability of being detected with respect to the infectious animals. Our model assigned a lower value (betaPERT with minimum 0, mode 5%, and maximum 25%), and thus the difference could be explained by a different balance between these parameters. El Allaki et al. (2016) found a slaughterhouse sensitivity of 30% for Canadian slaughterhouses. In this case the estimate was comprehensive of all infected animals, and not infectious only like in our case. This distinction is important because, since infectious animals shed the pathogen, they are more likely to have developed visible granulomas.

For all three estimated parameters, the 95th credible interval did not substantially differ from the prior distribution range. This was a consequence of the limited data available for summary statistics, which constrained the parameters' estimation power. As a result, the obtained Se_{sla} posterior distribution (coefficient of variation 0.32) was broader than the informed prior (coefficient of variation 0.22). Also, we had to provide a set of informed prior distributions for the parameters of interest, as well as find a stricter algorithm for parameter estimation. In particular, the prior distribution for ϕ needed to be restricted to 0.25 and 0.75 in order to ensure the algorithm convergence. This was possible because the previous literature already reported values restricted to this range for this parameter (Brooks-Pollock et al., 2013; El Allaki et al., 2016). The Se_{sla} prior distribution mode was set to the literature estimate in a similar rearing system (86%, Norby et al., 2004). Although this value was higher than other literature estimates (see above cited references), it was counterbalanced by using a very wide range (from 0 to 100%) to incorporate variability. Moreover, a betaPERT model was chosen for the prior distribution, resulting in a mean and median of 74% and 77% respectively, that is, values similar to existing estimates. Finally, as described above, the parameter that we estimated referred to the slaughterhouse inspection sensitivity applied to infectious (i.e. shedding) animals only. Nevertheless, the shape of the posterior distributions added information to the model as compared with the prior

distributions. By accepting only parameters that produced no distance between the observed and simulated summary statistics, our algorithm was *de facto* a hybrid between ABC and Exact Bayesian Computation. This was done following Kypraios et al. (2017), who showed how EBC could be effective in case of limited data, although the model developed here was too complex to use a Selke construction, as the reference method.

The pasture model simulated the potential transmission of bTB from the index herd to 15 herds that were classified as “high-risk contacts” by the CFIA during the investigation of the 2016 Western Canada bTB outbreak. These herds have been depopulated to avoid potential further spread in Alberta, as they were considered to have had significant and recurrent contacts with the index herd. Before being depopulated, the high-risk herds underwent a whole herd test (WHT) that included two live animal tests and an EPM examination of CFT reactor and ELISA positive animals, as well as a meat inspection for the non-reactors. The pre-depopulation test was done with the purpose of ruling out other potentially infected herds, in which case the control measures need to be extended to their high-risk contacts. The estimated value of CFT sensitivity in similar herds and areas (Farnham et al., 2012; Norby et al., 2004) was higher than that used in the simulations (Nuñez-Garcia et al., 2018). The reasons supporting this decision were to use a more conservative approach toward the effectiveness of WHT, as well as to use a more recent estimate. As reported above, no infected cattle was identified in any of the 15 herds, but given the typically long incubation period of bTB and imperfect test sensitivities, the infection of these herds could not be completely ruled out.

The simulations showed that the probability of spread through pasture was limited but non-negligible, and that most infected herds would have had a very low number of infected animals at the time of the outbreak detection. In addition, the simulation results showed that the probability of an infected herd failing the follow-up single WHT was below or equal to 10% (depending on the pasture mixing rate). However, there was a further probability of 6.5–13.1% that the infection in the herd was at an early stage (only occult animals) and thus non detectable. This is important because these herds could go undetected for long time before an individual develops the symptoms or

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becomes responsive to a test. Nonetheless, if we take into account gross numbers, it was estimated a 2.5% probability of observing at least two occult herds and at least one undetected infected herd.

By adopting a different control scheme (quarantine and series whole-herd CFT) we observed that most detections occurred during the first test (whose performance was very similar to the WHT test in the current control scenario), while the other infections were detected within the second to fifth test. As expected, increasing the pasture mixing rate increased the probability of the infection being spread to other herds, but it had no substantial effect on the number of faded-out outbreaks. The number of natural elimination events was due to the demographic stochasticity, as the introduced latent cow can be removed before infecting other animals. To support this, we observed that, in the great majority of faded outbreaks, no other herd beside the index one was infected, and we found only few cases with one or two other infected herds. The number of undetected (ongoing) outbreaks was negatively affected by the pasture mixing rate value, because the probability of outbreak detection increased with the number of infected herds.

Given the impact of potentially having multiple infected herds in a previously bTB-free country, as well as the potential for spread to susceptible wildlife (such as elk or cervids) which may be present in the outbreak area, Canada has implemented an aggressive depopulation and testing strategy in case of bTB detection.

The regular surveillance strategy currently in place in Canada consists of slaughterhouse inspection, the most common method for bTB surveillance in many countries (Fisher et al., 2005; Alvarez et al., 2014; Smith et al., 2014; Rossi et al., 2015; VanderWaal et al., 2017a). Our results showed that this method was able to detect about two thirds of the total simulated outbreaks. Similar results were found by Rossi et al. (2015) for dairies in Northern Italy, by assuming slaughterhouse inspection as the only detection method in place. The undetected outbreaks (21-22% of the total simulated outbreaks) usually involved the index herd and at most one other herd. Given the rareness of bTB in Canada, adopting further methods for surveillance might not be economically feasible. However, as

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VanderWaal et al. (2017a) pointed out, increasing the sensitivity of the carcass inspection by enhancing veterinarians' training can substantially improve surveillance performances. This might be valuable for systems such as the one we studied, in which bTB surveillance relies heavily on carcass inspection for detection.

There has been growing attention toward between-herd disease transmission pathways other than animal movements for trade, such as wildlife (Porphyre et al., 2008), farms visitors (Noremark et al., 2013), veterinarians (Rossi et al., 2017), and summer pastures (Vidondo & Voelkl, 2018). Previous work by Palisson et al. (2017) showed how seasonal pasture can represent a viable regional transmission path for infectious diseases by calculating the connectedness of the spatial network of pastures and farms based on distance thresholds. Our analysis came to similar conclusions with a different method, showing how sharing a pasture can be a viable transmission route for slow-spreading diseases such as bTB, based on simulation of herd management practices. Despite having very detailed data on pasture sharing, our results were obtained by focusing on the network defined by the index herd and its high-risk contacts only (i.e., egocentric network). With a local cluster of only 16 involved herds, running a network analysis would have not provided meaningful results. Assuming the availability of similar data for a wider area or region, we could implement a deeper analysis, assuming pastures and herds as two different types of nodes, and thus provide further insights for epidemic surveillance and control. In fact, another study of a local network of 49 cattle herds in a pastoralist management system in Kenya showed how the contact structure, and thus the potential epidemic spread, could be strongly affected by seasonality (VanderWaal et al., 2017b).

One important question when considering the potential spread of diseases on community pasture is the level of mixing between animals coming from different herds during pasture grazing. Our analysis showed that the level of mixing on pasture might have a non-negligible effect on bTB spread. Cattle usually graze in small rather than large groups (Harris et al., 2007), and Stephenson et al. (2016) showed that the stability of the contacts depends on the herd size, with cattle from

smaller herds tending to have more stable connection with other cows. However, the amount of association between cattle from different herds remains unclear. More observation studies are needed to provide a valuable estimate of the mixing pattern between individuals from different herds, including the use of GPS tracking systems (Stephenson et al., 2016). Another viable option could be the constitution of a panel of experts (e.g. farmers, veterinarians, animal behaviour experts) to provide an estimation of the pasture mixing rate. This method has already proved to be effective to deal with unknown parameters in other livestock contexts (Bates et al., 2003; Kinsley et al., 2016).

In conclusion, while mathematical modelling might have a limited use as a stand-alone tool for epidemic risk management, this work showed how it could help address specific questions when it is used alongside epidemiological investigations. The model estimated crucial information about the outbreak of bTB in Western Canada during the fall of 2016, in particular the time of introduction. This information could be used to conduct further epidemiological investigation, by focusing on the contacts of the index herd during the most likely introduction time. This modelling framework was also able to estimate the probability of bTB spread to high-risk contact herds, which was not negligible, showing how summer pastures represent a potential transmission pathway for infectious diseases in livestock. In particular, this could be a problem for elusive infections such as bTB, which, despite being characterized by slow transmission dynamics, can still represent a threat for systems entailing seasonal management. Finally, the findings of this study could enhance the understanding of the bTB spread in cow-calf herds managed seasonally, as well as provide a state-of-the-art tool for bTB preparedness and response.

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Conflict of interests statement

The authors declare no conflict of interests in relation to this work.

References

- Álvarez, J., A.M. Perez, J. Bezós, C. Casal, B. Romero, S. Rodríguez-Campos, J.L. Saez-Llorente, R. Díaz, J. Carpintero, L. de Juan, and L. Domínguez, 2012: 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, DOI: 10.1186/1746-6148-8-100.
- Álvarez, J., J. Bezós, M.L. de la Cruz, C. Casal, B. Romero, L. Domínguez, L. de Juan, and A. Pérez, 2014: Bovine tuberculosis: Within-herd transmission models to support and direct the decision-making process. *Res. Vet. Sci.* **97**, S61–S68, DOI: 10.1016/j.rvsc.2014.04.009.
- Barlow, N.D., J.M. Kean, G. Hickling, P.G. Livingstone, and a B. Robson, 1997: A simulation model for the spread of bovine tuberculosis within New Zealand cattle herds. *Prev Vet Med* **32**, 57–75, DOI: 10.1016/S0167-5877(97)00002-0.
- Bates, T.W., M.C. Thurmond, and T.E. Carpenter, 2003: Description of an epidemic simulation model for use in evaluating strategies to control an outbreak of foot-and-mouth disease. *Am. J. Vet. Res.* **64**, 195–204, DOI: 10.2460/ajvr.2003.64.195.
- Brooks-Pollock, E., G.O. Roberts, and M.J. Keeling, 2014: A dynamic model of bovine tuberculosis spread and control in Great Britain. *Nature* **511**, 228–31, DOI: 10.1038/nature13529.
- Buddle, B.M., T. Wilson, D. Luo, H. Voges, R. Linscott, E. Martel, J.C. Lawrence, and M.A. Neill, 2013: Evaluation of a commercial enzyme-linked immunosorbent assay for the diagnosis of bovine tuberculosis from milk samples from dairy cows. *Clin. Vaccine Immunol.* **20**, 1812–1816, DOI: 10.1128/CVI.00538-13.
- CFIA, 2018: Bovine Tuberculosis (Bovine TB) investigation – Western Canada. Retrieved from <http://www.inspection.gc.ca/animals/terrestrial-animals/diseases/reportable/tuberculosis/investigation-western-canada/overview/eng/1529621742332/1529621742743>
- Conlan, A.J.K., T.J. McKinley, K. Karolemeas, E.B. Pollock, A.V. Goodchild, A.P. Mitchell, C.P.D. Birch, R.S. Clifton-Hadley, and J.L.N. Wood, 2012: Estimating the hidden burden of bovine tuberculosis in Great Britain. *PLoS Comput. Biol.* **8**, e1002730, DOI: 10.1371/journal.pcbi.1002730.
- European Food Safety Authority (EFSA) Panel on Animal Health and Welfare, 2012: Scientific Opinion on the use of a gamma interferon test for the diagnosis of bovine tuberculosis 1. *EFSA J.* **10**, 2975, DOI: 10.2903/j.efsa.2012.2975.

European Food Safety Authority; Modelling the impact of a change in MI sensitivity on the surveillance of bTB at the country level. Supporting Publications 2013:EN-450. [40 pp.]. Available online: www.efsa.europa.eu/publications

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

Farnham, M.W., B. Norby, T.J. Goldsmith, and S.J. Wells, 2012: Meta-analysis of field studies on bovine tuberculosis skin tests in United States cattle herds. *Prev. Vet. Med.* **103**, 234–242, DOI: 10.1016/j.prevetmed.2011.08.009.

Filippi, S., C.P. Barnes, J. Cornebise, and M.P.H. Stumpf, 2013: On optimality of kernels for approximate Bayesian computation using sequential Monte Carlo. *Stat. Appl. Genet. Mol. Biol.* **12**, 87–107, DOI: 10.1515/sagmb-2012-0069.

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

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

Gilbert, M., A. Mitchell, D. Bourn, J. Mawdsley, R. Clifton-Hadley, and W. Wint, 2005: Cattle movements and bovine tuberculosis in Great Britain. *Nature* **435**, 491–6, DOI: 10.1038/nature03548.

Gillespie, D.T., and L.R. Petzold, 2003: Improved lead-size selection for accelerated stochastic simulation. *J. Chem. Phys.* **119**, 8229–8234, DOI: 10.1063/1.1613254.

Harris, N.R., D.E. Johnson, N.K. McDougald, and M.R. George, 2007: Social Associations and Dominance of Individuals in Small Herds of Cattle. *Rangel. Ecol. Manag.* **60**, 339–349, DOI: 10.2111/1551-5028(2007)60[339:SAADOI]2.0.CO;2.

Kaneene, J.B., C.S. Bruning-Fann, L.M. Granger, R. Miller, and B. a Porter-Spalding, 2002: Environmental and farm management factors associated with tuberculosis on cattle farms in northeastern Michigan. *J. Am. Vet. Med. Assoc.* **221**, 837–842, DOI: doi:10.2460/javma.2002.221.837.

Kao, R.R., M.G. Roberts, and T.J. Ryan, 1997: A model of bovine tuberculosis control in domesticated cattle herds. *Proc. R. Soc. B Biol. Sci.* **264**, 1069–1076, DOI: 10.1098/rspb.1997.0148.

Keeling, M.J., and P. Rohani, 2008: Modeling Infectious Diseases in Humans and Animals. Princeton University Press.

Kinsley, A.C., G. Patterson, K.L. VanderWaal, M.E. Craft, and A.M. Perez, 2016: Parameter Values for Epidemiological Models of Foot-and-Mouth Disease in Swine. *Front. Vet. Sci.* **3**, 44, DOI: 10.3389/fvets.2016.00044.

This article is protected by copyright. All rights reserved.

- Kypraios, T., P. Neal, and D. Prangle, 2017: A tutorial introduction to Bayesian inference for stochastic epidemic models using Approximate Bayesian Computation. *Math. Biosci.* **287**, 42–53, DOI: 10.1016/j.mbs.2016.07.001.
- Miller, R.S., M.L. Farnsworth, and J.L. Malmberg, 2013: Diseases at the livestock–wildlife interface: Status, challenges, and opportunities in the United States. *Prev. Vet. Med.* **110**, 119–132, DOI: 10.1016/j.prevetmed.2012.11.021.
- Minister of Justice, 2015. Health of Animals Regulations (C.R.C., c. 296). Enabling Act: Health of Animals Act. Last amended on July 1, 2015. Available at http://laws-lois.justice.gc.ca/eng/regulations/C.R.C.,_c._296/index.html
- Morris, R.S., D.U. Pfeiffer, and R. Jackson, 1994: The epidemiology of *Mycobacterium bovis* infections. *Vet. Microbiol.* **40**, 153–77.
- Munroe, F.A., I.R. Dohoo, W.B. McNab, and L. Spangler, 1999: Risk factors for the between-herd spread of *Mycobacterium bovis* in Canadian cattle and cervids between 1985 and 1994. *Prev. Vet. Med.* **41**, 119–133, DOI: 10.1016/S0167-5877(99)00051-3.
- Nishi, J.S., T. Shury, and B.T. Elkin, 2006: Wildlife reservoirs for bovine tuberculosis (*Mycobacterium bovis*) in Canada: Strategies for management and research. *Vet. Microbiol.* **112**, 325–338, DOI: 10.1016/j.vetmic.2005.11.013.
- Norby, B., P.C. Bartlett, S.D. Fitzgerald, L.M. Granger, C.S. Bruning-Fann, D.L. Whipple, and J.B. Payeur, 2004: The sensitivity of gross necropsy, caudal fold and comparative cervical tests for the diagnosis of bovine tuberculosis. *J. Vet. Diagnostic Investig.* **16**, 126–131, DOI: 10.1177/104063870401600206.
- Nöremark, M., J. Frössling, and S.S. Lewerin, 2013: A survey of visitors on Swedish livestock farms with reference to the spread of animal diseases. *BMC Vet. Res.* **9**, 184, DOI: 10.1186/1746-6148-9-184.
- Núñez-García, J., S.H. Downs, J.E. Parry, D.A. Abernethy, J.M. Broughan, A.R. Cameron, A.J. Cook, R. de la Rua-Domenech, A. V. Goodchild, J. Gunn, S.J. More, S. Rhodes, S. Rolfe, M. Sharp, P.A. Upton, H.M. Vordermeier, E. Watson, M. Welsh, A.O. Whelan, J.A. Woolliams, R.S. Clifton-Hadley, and M. Greiner, 2018: Meta-analyses of the sensitivity and specificity of ante-mortem and post-mortem diagnostic tests for bovine tuberculosis in the UK and Ireland. *Prev. Vet. Med.* **153**, 94–107, DOI: 10.1016/j.prevetmed.2017.02.017.
- Nusinovici, S., T. Hoch, M.L. Brahim, A. Joly, and F. Beaudeau, 2017: The Effect of Wind on *Coxiella burnetii* Transmission Between Cattle Herds: a Mechanistic Approach. *Transbound. Emerg. Dis.* **64**, 585–592, DOI: 10.1111/tbed.12423.
- O’Hare, A., R.J. Orton, P.R. Bessell, and R.R. Kao, 2014: Estimating epidemiological parameters for bovine tuberculosis in British cattle using a Bayesian partial-likelihood approach. *Proc. R. Soc. B Biol. Sci.* **281**, DOI: 10.1098/rspb.2014.0248.

Okafor, C.C., D.L. Grooms, C.S. Bruning-Fann, J.J. Averill, and J.B. Kaneene, 2011: Descriptive Epidemiology of Bovine Tuberculosis in Michigan (1975–2010): Lessons Learned. *Vet. Med. Int.* **2011**, 1–13, DOI: 10.4061/2011/874924.

Olea-Popelka, F., A. Muwonge, A. Perera, A.S. Dean, E. Mumford, E. Erlacher-Vindel, S. Forcella, B.J. Silk, L. Ditiu, A. El Idrissi, M. Raviglione, O. Cosivi, P. LoBue, and P.I. Fujiwara, 2017: Zoonotic tuberculosis in human beings caused by *Mycobacterium bovis*—a call for action. *Lancet Infect. Dis.* **17**, e21–e25, DOI: 10.1016/S1473-3099(16)30139-6.

Palisson, A., A. Courcoul, and B. Durand, 2017: Analysis of the Spatial Organization of Pastures as a Contact Network, Implications for Potential Disease Spread and Biosecurity in Livestock, France, 2010. *PLoS One* **12**, e0169881, DOI: 10.1371/journal.pone.0169881.

Pfeiffer, D.U., 2013: Epidemiology caught in the causal web of bovine tuberculosis. *Transbound. Emerg. Dis.* **60**, 104–110, DOI: 10.1111/tbed.12105.

Pioz, M., H. Guis, D. Pleydell, E. Gay, D. Calavas, B. Durand, C. Ducrot, and R. Lancelot, 2014: Did vaccination slow the spread of bluetongue in France? *PLoS One* **9**, DOI: 10.1371/journal.pone.0085444.

Porphyre, T., J. McKenzie, and M. Stevenson, 2007: A descriptive spatial analysis of bovine tuberculosis in intensively controlled cattle farms in New Zealand. *Vet. Res.* **38**, 465–479, DOI: 10.1051/vetres:2007003.

Pouillot, R., and M.L. Delignette-Muller, 2010: Evaluating variability and uncertainty separately in microbial quantitative risk assessment using two R packages. *Int. J. Food Microbiol.* **142**, 330–340, DOI: 10.1016/j.ijfoodmicro.2010.07.011.

R Core Team, 2016: R: A Language and Environment for Statistical Computing. . Vienna, Austria.

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

Rossi, G., G.A. De Leo, S. Pongolini, S. Natalini, L. Zarengi, M. Ricchi, and L. Bolzoni, 2017: The Potential Role of Direct and Indirect Contacts on Infection Spread in Dairy Farm Networks. *PLoS Comput. Biol.* **13**, DOI: 10.1371/journal.pcbi.1005301.

Sergeant, E. S. G., et al. (2011). Evaluation of Australian surveillance for freedom from bovine tuberculosis. *Épidémiologie et Santé Animale* (No.59/60): 325-327. Sheppard, S.C., S. Bittman, G. Donohoe, D. Flaten, K.M. Wittenberg, J.A. Small, R. Berthiaume, T.A. McAllister, K.A. Beauchemin, J. McKinnon, B.D. Amiro, D. MacDonald, F. Mattos, and K.H. Ominski, 2014: Beef cattle husbandry practices across Ecoregions of Canada in 2011. *Can. J. Anim. Sci.* **1–17**, DOI: 10.4141/cjas-2014-158.

Siegwart, N., M. Hilbe, M. Hässig, and U. Braun, 2006: Increased risk of BVDV infection of calves from pregnant dams on communal Alpine pastures in Switzerland. *Vet. J.* **172**, 386–388, DOI: 10.1016/j.tvjl.2005.07.018.

This article is protected by copyright. All rights reserved.

- Smith, R.L., 2016: Proposing a Compartmental Model for Leprosy and Parameterizing Using Regional Incidence in Brazil. *PLoS Negl. Trop. Dis.* **10**, 1–14, DOI: 10.1371/journal.pntd.0004925.
- Smith, R.L., L.W. Tauer, M.W. Sanderson, and Y.T. Grohn, 2014: Minimum cost to control bovine tuberculosis in cow-calf herds. *Prev. Vet. Med.* **115**, 18–28, DOI: 10.1016/j.prevetmed.2014.03.014.
- Smith, R.L., L.W. Tauer, Y.H. Schukken, Z. Lu, and Y.T. Grohn, 2013: Minimization of bovine tuberculosis control costs in US dairy herds. *Prev. Vet. Med.* **112**, 266–275, DOI: 10.1016/j.prevetmed.2013.07.014.
- Stephenson, M.B., D.W. Bailey, and D. Jensen, 2016: Association patterns of visually-observed cattle on Montana, USA foothill rangelands. *Appl. Anim. Behav. Sci.* **178**, 7–15, DOI: 10.1016/j.applanim.2016.02.007.
- Toni, T., D. Welch, N. Strelkowa, A. Ipsen, and M.P.H. Stumpf, 2009: Approximate Bayesian computation scheme for parameter inference and model selection in dynamical systems. *J. R. Soc. Interface* **6** 187–202, DOI: 10.1098/rsif.2008.0172.
- Trost, B., T. Stuber, O. Surujballi, J. Nelson, S. Robbe-Austerman, N.H. Smith, L. Desautels, S.K. Tikoo, and P. Griebel, 2016: Investigation of the cause of geographic disparities in IDEXX ELISA sensitivity in serum samples from Mycobacterium bovis-infected cattle. *Sci. Rep.* **6**, 1–11, DOI: 10.1038/srep22763.
- Valle, P.S., S.W. Martin, R. Tremblay, and K. Bateman, 1999: Factors associated with being a bovine-virus diarrhoea (BVD) seropositive dairy herd in the More and Romsdal County of Norway. *Prev. Vet. Med.* **40**, 165–177, DOI: 10.1016/S0167-5877(99)00030-6.
- VanderWaal, K., E.A. Enns, C. Picasso, J. Alvarez, A. Perez, F. Fernandez, A. Gil, M. Craft, and S. Wells, 2017(a): Optimal surveillance strategies for bovine tuberculosis in a low-prevalence country. *Sci. Rep.* **7**, 4140, DOI: 10.1038/s41598-017-04466-2.
- VanderWaal, K., M. Gilbertson, B.F. Allan, and M.E. Craft, 2017 (b): Seasonality and pathogen transmission in pastoral cattle contact networks. *R. Soc. Open Sci.* **4**, 170808, DOI: 10.1098/rsos.170808.
- Vidondo, B., and B. Voelkl, 2018: Dynamic network measures reveal the impact of cattle markets and alpine summering on the risk of epidemic outbreaks in the Swiss cattle population. *BMC Vet. Res.* **14**, 1–11, DOI: 10.1186/s12917-018-1406-3.
- Waret-Szkuta, A., A. Ortiz-Pelaez, D.U. Pfeiffer, F. Roger, and F.J. Guitian, 2011: Herd contact structure based on shared use of water points and grazing points in the Highlands of Ethiopia. *Epidemiol. Infect.* **139**, 875–885, DOI: 10.1017/S0950268810001718.
- Waters, W.R., B.M. Buddle, H.M. Vordermeier, E. Gormley, M. V. Palmer, T.C. Thacker, J.P. Bannantine, J.R. Stabel, R. Linscott, E. Martel, F. Milian, W. Foshaug, and J.C. Lawrence, 2011: Development and evaluation of an enzyme-linked immunosorbent assay for use in the

detection of bovine tuberculosis in cattle. *Clin. Vaccine Immunol.* **18**, 1882–1888, DOI: 10.1128/CVI.05343-11.

Western Beef Development Centre, 2015: 2014 Western Canadian Cow-Calf Survey (WCCCS).

Wickham, H., 2009: ggplot2: Elegant Graphics for Data Analysis. Springer New York.

Wittum, T.E., M.D. Salman, M.E. King, R.G. Mortimer, K.G. Odde, and D.L. Morris, 1994: Individual animal and maternal risk factors for morbidity and mortality of neonatal beef calves in Colorado, USA. *Prev. Vet. Med.* **19**, 1–13, DOI: 10.1016/0167-5877(94)90010-8.

Table 1

Characteristics of the herds categorized as high-risk during the observed bTB outbreak, including type and size of contacts with the index herd (#1).

<i>Herds</i>	<i>#cows</i>	<i>#heifers</i>	<i>#bulls</i>	<i>Total size</i>	<i>Contact type</i>	<i>% of herd in contact</i>
#1 (index herd)	385	47	51	483	index herd	17% to A and 26% to B
#2	604	205	0	809	Bulls sharing	bulls
#3	279	0	0	279	Winter colony (2015-2016)	100%
#4	209	2	11	222	Winter colony (2015-2016)	100%
#5	89	10	3	102	Pasture A	37%
#6	148	13	8	169	Pasture A	32%
#7	88	17	6	111	Pasture B	27%
#8	64	10	3	77	Pasture A	33%
#9	304	100	22	426	Pasture A	7,5%
#10	236	45	22	303	Pasture A	6,5%
#11	104	41	0	145	Pasture B	27,5%
#12	222	41	13	276	Pasture A	7%
#13	537	120	21	678	Pasture B	10%
#14	569	120	23	712	Pasture B	15%
#15	437	140	22	599	Pasture A	17%
#16	1204	310	0	1514	Pasture A	1,25%

Table 2

Cow-calf herds demographic parameters used in the study.

<i>Demographic parameters</i>		<i>Value</i>	<i>Unit</i>	<i>Source</i>
Cows (and heifers) mortality		1,4%	year	WCCCS
Bulls mortality		2,4%	year	WCCCS
Calves mortality		6,9%	year	WCCCS
Cows culling		10,3%	year	WCCCS
Bulls culling		22,4%	year	WCCCS
Pregnancy		93,0%	year	WCCCS
Late abortions		3,0%	year	WCCCS
Calves retained as replacements		14,2%	year	estimated
Bulls purchases rate (% of bulls present at purchase)		29,0%	year	estimated
Probability calving onset:	January	15,0%	-	Adapted from WCCCS
	February	19,0%		
	March	36,0%		
	April	24,0%		
	May	5,0%		
Probability of weaning onset:	September	11,0%	-	WCCCS
	October	42,0%		
	November	32,0%		
	December	15,0%		

Table 3

The list of parameters used in the infection models.

<i>Parameter</i>	<i>Unit</i>	<i>Original parameters distribution or prior (in italic)</i>	<i>References</i>	<i>Posterior estimate (median [credible interval])</i>
<i>bTB infection</i>				
Contact rate (β)	New cases/ case/year	<i>BetaPERT (min = 0.61, mode = 2.2, max = 5.2)</i>	Alvarez et al, 2012; Brooks-Pollock et al., 2014; Fisher et al., 2005; Perez et al., 2002; Rossi et al., 2015; Smith et al., 2013	1.91 [0.68 – 5.07]
β -scaling factor for calves (ϕ)		<i>U(0.25 – 0.75)</i>	assumed	0.44 [0.26 – 0.72]
Occult period length ($1/\sigma_O$)	month	BetaPERT (min = 0.03, mode = 1.15, max = 17)	Barlow et al., 1997; Conlan et al., 2012; Fisher et al., 2005; Kao et al., 1997; O'Hare et al., 2014; Smith et al., 2014; VanderWaal et al., 2017	NA
Reactive period length ($1/\sigma_R$)	month	BetaPERT (min = 3, mode = 7.15, max = 36)	Barlow et al., 1997; Conlan et al., 2012; Fisher et al., 2005; Kao et al., 1997; O'Hare et al., 2014; Smith et al., 2014; VanderWaal et al., 2017	NA
<i>bTB surveillance</i>				
Slaughterhouse inspection sensitivity for infectious (I) adults and calves (Se_{sla})		<i>BetaPERT (min = 0, mode = 0.93, max = 1.00)</i>	Norby et al., 2004	0.68 [0.20 – 0.98]
Scaling factor κ for Se_{sla} in occult animals		0	Assumed	NA
Scaling factor κ for Se_{sla} in reactive animals		BetaPERT (min = 0, mode = 0.05, max = 0.25)	Assumed	NA
Caudal Fold Test (CFT) skin test sensitivity		BetaPERT (min = 0.56, mode = 0.76, max = 0.89)	Nuñez-Garcia et al., 2018; EFSA, 2012	NA
IDEXXX Elisa sensitivity		Beta ($\alpha = 159$, $\beta = 191$; mean = 0.45, 95 th confidence interval = 0.40 – 0.51)	Buddle et al., 2013; Trist et al., 2016; Waters et al., 2011;	NA
Enhanced post-mortem (EPM)		BetaPERT (min = 0.96, mode = 0.82, max = 1.00)	Nuñez-Garcia et al., 2018; EFSA, 2012	NA

Table 4

Surveillance system performance in pasture model simulations (C.I.: confidence interval).

	Pasture mixing rate (ψ)					
	0.00	0.125	0.25	0.50	0.75	1.00
<i>Slaughterhouse inspection surveillance performance</i>						
Faded-out outbreaks (%)	12.4	12.4	12.4	12.3	12.2	12.2
Detected outbreaks (%)	65.4	65.4	65.7	66.1	66.5	66.8
Non-detected (ongoing) outbreaks (%)	22.2	22.2	22.0	21.6	21.3	21.0
<i>Detected outbreaks¹</i>						
# infected herds at detection (median [95 th C.I.])	1 [1 – 4]	2 [1 – 5]	2 [1 – 5]	2 [1 – 6]	2 [1 – 7]	2 [1 – 8]
# detected by surveillance (median [95 th C.I.])	1 [1 – 2]	1 [1 – 2]	1 [1 – 2]	1 [1 – 2]	1 [1 – 2]	1 [1 – 2]
# detected by surveillance (%)	59.6	54.9	51.6	46.5	43.1	40.5
# total infected herds to WHT (median [95 th C.I.])	0 [0 – 3]	1 [0 – 3]	1 [0 – 4]	1 [0 – 5]	1 [0 – 6]	1 [0 – 6]
total infected herds to WHT (%)	40.4	45.1	48.4	53.5	56.9	59.5
<i>Current scenario (whole-herd test and depopulation of high-risk contact herds)²</i>						
# herds detected by WHT (median [95 th C.I.])	0 [0 – 3]	0 [0 – 3]	0 [0 – 3]	1 [0 – 4]	1 [0 – 5]	1 [0 – 5]
herds detected by WHT (%)	67.3	65.0	63.7	62.9	62.8	62.6
# infected herds faded-out ³ (median [95 th C.I.])	0 [0 – 1]	0 [0 – 1]	0 [0 – 1]	0 [0 – 2]	0 [0 – 2]	0 [0 – 2]
infected herds faded-out ³ (%)	17.8	17.1	16.5	15.4	14.7	14.2
# occult herds ⁴ (median [95 th C.I.])	0 [0 – 1]	0 [0 – 1]	0 [0 – 1]	0 [0 – 2]	0 [0 – 2]	0 [0 – 2]
occult herds ⁴ (%)	6.5	58.9	10.4	12.0	12.7	13.1
# herds escaping WHT (median [95 th C.I.])	0 [0 – 1]	0 [0 – 1]	0 [0 – 1]	0 [0 – 1]	0 [0 – 1]	0 [0 – 1]

# herds escaping WHT (%)	8.4	9.0	9.4	9.7	9.8	10.1
<i>Alternative scenario (quarantine and quarterly whole-herd test of high-risk contact herds)</i>						
# detected herds at 1 st WHT (median 95 th [C.I.])	0 [0 – 2]	0 [0 – 2]	0 [0 – 3]	0 [0 – 3]	1 [0 – 3]	1 [0 – 4]
detected at 1 st WHT (%)	77.5	76.4	75.6	75.1	75.1	75.0
# detected herds at 2 nd to 5 th WHT (median 95 th [C.I.])	0 [0 – 1]	0 [0 – 1]	0 [0 – 1]	0 [0 – 1]	0 [0 – 2]	0 [0 – 2]
detected herds at 2 nd to 5 th WHT (%)	22.2	23.2	24.0	24.5	24.5	24.6
# detected herds at 6 th to 13 th WHT (median [95 th C.I.])	0 [0 – 0]	0 [0 – 0]	0 [0 – 0]	0 [0 – 0]	0 [0 – 0]	0 [0 – 0]
detected herds at 6 th to 13 th WHT (%)	0.1	0.2	0.2	0.2	0.2	0.2
infected herds faded-out (%)	0.2	0.2	0.2	0.2	0.2	0.2
¹ : percentages calculated on the total number of infected herds at detection ² : percentages calculated on the number of infected herds not detected by slaughterhouse surveillance ³ : herds that cleared out infection between detection and WHT (infected animal/s dead or slaughtered) ⁴ : herds with susceptible or bTB infected but occult animals only						

Figure 1

Conceptual scheme of the within-herd bovine TB spread model, including the surveillance system (Panel A). This model was then extended to a meta-population framework to simulate the spread in shared pastures, where herds send a group of their animals to pastures at the beginning of the summer and move it back in during the fall (scheme in panel B). The index herd of the 2016 outbreak had 15 high-risk contacts: one through bulls exchanging, two through winter grazing sharing, and 12 through pasture sharing, either A or B (panel C).

Figure 2

Estimated distribution of the Time of Introduction (ToI) of bTB in the index-herd (thick line).

Mode/median/mean: June 2013, December 2012, and June 2012; 50th quantile (dark grey area): July 2011 – November 2013; 75th quantile (medium grey area): April 2010 – May 2014; 95th quantile (light grey area): April 2007 – January 2015.

Figure 3

Prior and posterior distributions of the parameters estimated with the pseudo-ABC algorithm: the within-herd contact rate (β , panel A), the contact scaling factor for calves (ϕ , panel B), and the slaughterhouse inspection sensitivity for infectious adults (Se_{sla} , panel C).

Figure 4

Probability of secondarily infected herds during a simulated bTB outbreak. This includes all types of contact during the 2016 Northern Alberta outbreak (panel A), and the summer pasture contacts only

(panel B). All probabilities are shown for the six assumed values of pasture mixing rate ψ (0, 0.125, 0.25, 0.5, 0.75, 1).

Figure 5

Simulated bTB outbreak dynamics, including the portion of naturally extinct (green), detected (blue), and undetected and ongoing (red) simulated outbreaks (Panel A) and comparison of the maximum outbreaks size reached (in number of herds, Panel B) for the outbreaks extinct (green), detected (blue), and undetected but ongoing (red), for six different values of pasture mixing rate ψ : 0, 0.125, 0.25, 0.5, 0.75, 1 (grey panels on top).

Figure 6

Cumulative probability of an infected herd remaining undetected after each quarterly whole herd tests (WHT). Panels show the mean (blue line) and the range (grey shade) for the six different values of pasture mixing rate ψ (0, 0.125, 0.25, 0.5, 0.75, 1).

A

B

C