



# Epidemiological modelling for the assessment of bovine tuberculosis surveillance in the dairy farm network in Emilia-Romagna (Italy)



Gianluigi Rossi<sup>a,\*</sup>, Giulio A. De Leo<sup>b</sup>, Stefano Pongolini<sup>c</sup>, Silvano Natalini<sup>d</sup>,  
Simone Vincenzi<sup>e,f</sup>, Luca Bolzoni<sup>c,g</sup>

<sup>a</sup> Dipartimento di Bioscienze, Università di Parma, Parco Area delle Scienze 11/A, I-43124 Parma, Italy

<sup>b</sup> Stanford University, Hopkins Marine Station, Pacific Grove, CA 93950, USA

<sup>c</sup> Istituto Zooprofilattico Sperimentale della Lombardia e dell'Emilia-Romagna, Via dei Mercati, 13/A, Parma I-43122, Italy

<sup>d</sup> Servizio Veterinario e Igiene Alimenti Assessorato Politiche per la Salute Regione Emilia-Romagna, Viale Aldo Moro 21, Bologna I-40127, Italy

<sup>e</sup> Center for Stock Assessment Research, Department of Applied Mathematics and Statistics, University of California, Santa Cruz, CA 95064, USA

<sup>f</sup> Dipartimento di Elettronica, Informazione e Bioingegneria, Politecnico di Milano, Via Ponzio 34/5, I-20133 Milan, Italy

<sup>g</sup> Department of Biodiversity and Molecular Ecology, Research and Innovation Centre – Fondazione Edmund Mach, San Michele all'Adige, Trento, Italy

## ARTICLE INFO

### Article history:

Received 17 March 2014

Received in revised form 11 February 2015

Accepted 25 February 2015

Available online 6 March 2015

### Keywords:

Epidemiological model

Disease surveillance

Network model

Bovine tuberculosis

SEI model

## ABSTRACT

Assessing the performance of a surveillance system for infectious diseases of domestic animals is a challenging task for health authorities. Therefore, it is important to assess what strategy is the most effective in identifying the onset of an epidemic and in minimizing the number of infected farms.

The aim of the present work was to evaluate the performance of the bovine tuberculosis (bTB) surveillance system in the network of dairy farms in the Emilia-Romagna (ER) Region, Italy. A bTB-free Region since 2007, ER implements an integrated surveillance strategy based on three components, namely routine on-farm tuberculin skin-testing performed every 3 years, tuberculin skin-testing of cattle exchanged between farms, and *post-mortem* inspection at slaughterhouses. We assessed the effectiveness of surveillance by means of a stochastic network model of both within-farm and between-farm bTB dynamics calibrated on data available for ER dairy farms. Epidemic dynamics were simulated for five scenarios: the current ER surveillance system, a no surveillance scenario that we used as the benchmark to characterize epidemic dynamics, three additional scenarios in which one of the surveillance components was removed at a time so as to outline its significance in detecting the infection. For each scenario we ran Monte Carlo simulations of bTB epidemics following the random introduction of an infected individual in the network. System performances were assessed through the comparative analysis of a number of statistics, including the time required for epidemic detection and the total number of infected farms during the epidemic.

Our analysis showed that slaughterhouse inspection is the most effective surveillance component in reducing the time for disease detection, while routine surveillance in reducing the number of multi-farms epidemics. On the other hand, testing exchanged cattle improved the performance of the surveillance system only marginally.

© 2015 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## 1. Introduction

Bovine tuberculosis (bTB) caused by *Mycobacterium bovis* is among the major disease threats to farm animals worldwide (Skuce et al., 2012). bTB is a chronic disease characterized by a variable and generally long incubation period, and its aetiological agent has an exceptionally wide range of hosts, including humans, domestic

and wild animals, as well as high persistence in the environment (Morris et al., 1994). Besides its direct impact to the cattle industry, bTB is a zoonotic disease of great concern. For these reasons, regulatory restrictions are in place to prevent the trade of infected animals and their products within and between countries and to reduce the risk of spillover from the animal to the human compartment. Most countries and transnational areas (such as the European Union) with a thriving cattle industry have developed surveillance systems to prevent bTB outbreaks (Cousins, 2001). Despite the control efforts, bTB is still endemic in many countries, both developed and developing (World Organization for Animal Health, 2008) and

\* Corresponding author.

E-mail address: [gianluigi.rossi@nemo.unipr.it](mailto:gianluigi.rossi@nemo.unipr.it) (G. Rossi).

its eradication has proved to be very challenging (Fitzgerald and Kaneene, 2013; Independent Scientific Group, 2007). Therefore, it is essential to develop surveillance strategies that allow for a rapid detection of infected animals both in endemic and bTB-free areas.

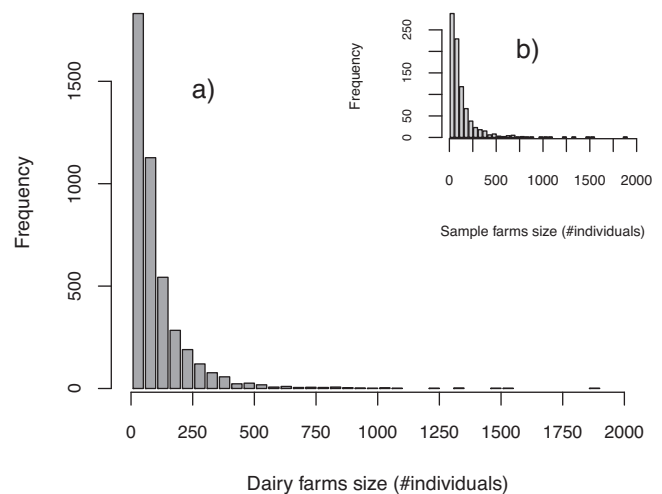
The organization and the components needed for an effective surveillance system in a given territory depend on bTB epidemiology, which is largely determined by the characteristics of the farming system in place. How these factors may interplay to determine the risk of outbreaks in the specific case of bTB has been well documented in the UK and Ireland, where the rising incidence of the infection in the last 20 years has caused significant economic losses (Abernethy et al., 2013; Reynolds, 2006). The direct costs of bTB for UK taxpayers in 2009 were estimated in around £63M (about 95M USD) and over 25,000 cattle were culled (Johnston et al., 2011). Outdoor farming, a common breeding system in the UK and Ireland, favours contacts between animals of different herds, one of the pathways for bTB transmission. In addition, this farming system exposes cattle to the possibly infected wildlife, such as the European badger (*Meles meles*) whose population is endemically infected by *M. bovis* in large areas of the British isles (Cheeseman et al., 1989; Griffin et al., 2005; Morris et al., 1994). Another factor associated with recurrent bTB outbreaks in the UK is between-farm movement of live animals (Johnston et al., 2011; Reilly and Courtenay, 2007). Therefore, preventing contacts between cattle of different herds and between cattle and wildlife are considered effective measures to control bTB risk in the UK and Ireland (Johnston et al., 2011; Phillips et al., 2003; Reilly and Courtenay, 2007).

In countries where indoor farming is the most common breeding practice, such as Italy, bTB transmission rarely occurs through contacts with infected wildlife. A study on bTB risk factors in Northern Italy showed that the main risk factor for bTB breakdown was cattle movement between farms (Marangon et al., 1998). bTB is still endemic, though at very low prevalence, in some Italian regions while it has been eradicated in others.

Among the latter, Emilia-Romagna (ER), located on the right side of the river Po valley (Northern Italy), has been declared officially free from bovine tuberculosis (UE Decision n° 2007/174/CE). This Region has an important food-farming industry characterized by an intensive dairy production, and is the region of origin of Parmigiano-Reggiano cheese. According to the latest official statistics (Italian National Statistics Institute, 2010), about 550,000 cattle are reared in 7343 farms in ER. As an epidemic of bTB in this Region would have severe economic consequences, the regional health authorities have implemented, in compliance with EU regulations (UE Decision 2002/677/CE), an integrated surveillance system to prevent bTB re-emergence in dairy cattle (Regional decision GPG/2010/1049). The system is based on three detection methods, namely: (i) periodic routine skin-test on all animals aged over 24 months (RS); (ii) systematic skin-test on all exchanged cattle (ECT) at the destination farm; and (iii) inspection for bTB lesions of all slaughtered animals (SI). While ER Region has managed to remain bTB-free so far, the effectiveness of the integrated surveillance system (and its individual components) in the case of re-introduction of the infection has never been assessed.

The goal of this work is to quantitatively assess the performance of the current surveillance system and its individual components in terms of (i) time needed to detect a prospective newly introduced bTB epidemic in the dairy farms of ER, and (ii) the magnitude of the epidemic, in terms of number of farms infected before the detection of the epidemic.

Since ER has been free from bTB for many years, no empirical data on the epidemiological dynamics of the infection is available. Therefore, in order to test the performance of the three surveillance methods currently in place in the Region, we developed an individual-based epidemic model capable of simulating the spread



**Fig. 1.** Distribution of Emilia-Romagna dairy farms size. Every bar corresponds to a size interval of 50 individuals (0–50, 51–100, etc.). (a) All dairy farms size distribution (Min = 1, Median = 63, Mean = 101.9, Max = 1889); (b) sampled dairy farms size distribution (Min = 1, Median = 74, Mean = 126.6, Max = 1889).

of bTB in the regional network of dairy farms following the random introduction of infected animals in the system.

Considering that the rearing system in place in ER and that the components of bTB surveillance described above are largely widespread in several developed countries, our findings can be applicable to many farming and surveillance systems worldwide.

## 2. Materials and methods

To assess the performance of the current surveillance system and each of its components, we built a data-driven, stochastic network model that simulates both within-farm and between-farm bTB dynamics. We assumed that the contribution of transmission routes other than cattle exchanges – such as airborne transmission or transmission mediated by wildlife or fomites – was negligible within the regional system of industrial indoor farms. Thus, we considered cattle exchanges as the only transmission route for bTB among dairy farms.

Since bTB is a chronic disease characterized by slow transmission dynamics (see Augusto et al., 2011; Huang et al., 2013; Brooks-Pollock et al., 2014) the assumption of endemic equilibrium within a given farm is unrealistic. Then, we explicitly accounted for within-farm disease dynamics describing how epidemics evolve inside farms following the introduction of infected animals.

We represented the system of cattle exchanges of ER as a contact network where nodes represent farms and directional edges represent between-farm animal movements. We reproduced the network of 4353 dairy farms and 20 intermediary trader farms (ITF) by using information from the cattle movement dataset as described hereafter.

All statistical analyses and model simulations were performed using the software R with “MASS”, “triangle” and “poilog” packages (<http://www.r-project.com>).

### 2.1. Cattle trade movement data

Cattle movement data were provided by the Italian National Bovine database. At the end of 2010, 4353 dairy farms and 20 intermediary trader farms (ITF) were in operation in ER. For all of them we collected the farm size, i.e. number of animals per farm (Fig. 1). For all the ITF and a subset of 837 dairy farms we also collected individual records of every cattle movement, incoming and outgoing, over a 100-week time span (from the beginning of February

**Table 1**  
Detailed data on sampled dairy farms and intermediary trader farms (ITF).

Cattle movement dairy farms data (February-2009/December-2010)		Cattle movement ITF data (February-2009/December-2010)	
Total dairy farms in Emilia-Romagna	4353	Total ITF in Emilia-Romagna	20
Samples dairy farms	837	Sample ITF	20
Sample individual records	106,499	Sample individual records	3571
Incoming individuals		Incoming individuals	
Total	9173	Total	3571
From ER dairy farms	7036	From ER dairy farms	1774
From other regions/countries	2137	From other regions/countries	1797
Outgoing individuals		Outgoing individuals	
Total	28,954	Total	3476
Total to farms	6328	Total to farms	3211
To other ER dairy farms	5597	To other ER dairy farms	2136
To other regions/countries	731	To other regions/countries	1075
Total to slaughterhouse	21,851	Total to slaughterhouse	230
To ER slaughterhouse	10,195	To ER slaughterhouse	147
To other regions slaughterhouse	11,656	To other regions slaughterhouse	83
Death/other destinations	775	Death/other destinations	35
Sample farms mean in-degree	1.91 (SE ± 0.096)	ITF mean in-degree	24.50 (SE ± 7.185)
Sample farms mean out-degree	1.67 (SE ± 0.075)	ITF mean out-degree	19.25 (SE ± 5.537)

2009 to the end of December 2010). The farms were sampled stratified by province and the obtained sample is representative of the farms size distribution observed in the region (Fig. 1 and Supplementary materials S1.1 for details). Each individual record had a unique identifier code for the animal, the birth date, sex and race of the animal, identifier codes for the farms of origin and destination, codes for farms production sector (beef, dairy or mixed), and the movement date. We considered the movements between dairy farms only, and we excluded the movements of young calves or end-of-life cattle sent to beef farms or directly to the slaughterhouse. The final dataset was composed of 15,501 individual records reporting animal movement (Table 1).

ITF activity consists in trading cattle, not in rearing them. As a consequence, animals stay in ITF for just a few days (median 2 days, lower [upper] quartile 1 [8] days) before being moved to a destination dairy farm, a much shorter time compared to the time that individuals spend in dairy farms (1815 days, on average). In addition, the number of animals simultaneously held in ITFs is usually very low (median 0, lower [upper] quartile 0 [5] animals). Given the limited number of animals and the short time that individuals spend inside them, we assumed that the bTB transmission inside ITFs was negligible compared to dairy farms (a sensitivity analysis on the effect of this assumption on bTB dynamics and the effectiveness of surveillance is shown in the Supplementary materials, Section S3.4).

We defined the in-degree and the out-degree for farm  $i$  as the number of farms from which farm  $i$  receives and the number of farms to which farm  $i$  sends cattle, respectively. Altogether, the joint sets of in- and out-degrees are referred to as the in- and out-degree distributions of the network of dairy farms. Since movement data were available for all ITFs in operation in ER, we directly derived the in- and out-degree of each ITF in the network as well as their distributions.

Regarding farms other than ITFs, movement data were available only for a subset of 837 farms out of the total 4353 in the ER network. Thus, we derived the in- and out-degree distributions of this subset. Then, we estimated the parameters of a set of candidate probability distributions (namely: power-law, log-normal, Poisson and Yule) on the available data and selected the distribution that best fitted the data by using log-likelihood ratio (LLR) test as shown in Vuong (1989) and Clauset et al. (2009). Finally, we used the selected probability distribution to generate a synthetic network of 4353 farms having the same topological properties (i.e. the in- and out-degree distributions) observed in the subset of 837 dairy farms. The procedure for network generation is described in the following section.

## 2.2. Network model

To generate a network of 4353 farms with the same topological properties observed in the subset of 837 dairy farms, we first assigned in- and out-degrees independent of each other to the 4353 nodes in the network (as in- and out- degrees were weakly correlated, see Supplementary materials S1.3). Moreover, as both in-degrees and out-degrees were very weakly correlated with farm size in the observed dataset, they were assigned to nodes irrespective of farm size (see Supplementary materials S1.3). According to the available movement data, we assumed that neither the in-degree nor the out-degree could be larger than the node size, i.e. the number of animals in the farm.

Once we assigned to each node an in-degree and an out-degree, we used a heuristic algorithm to exactly match the number of outgoing connections from farms in the network to that of ingoing connections to farms in the same network (Supplementary materials S2). Then, we completed the network by adding 20 additional nodes representing the 20 ITF and assigned to each of them the observed in- and out- degrees.

## 2.3. Within-farm model

We described the within-farm bTB dynamics through a compartmental stochastic Susceptible–Exposed–Infected (SEI) model with homogeneous frequency dependent transmission (Agusto et al., 2011; Brooks-Pollock et al., 2014). The compartment of the susceptible individuals ( $S$ ) represents cattle that have not been infected yet. Following successful infection, each individual is classified as exposed ( $E$ ) but not infectious yet. The incubation period ends when the infected individual becomes also infectious ( $I$ ). Then, the infection dynamics for farm  $i$  can be represented by the following system of ordinary differential equations:

$$\begin{cases} \dot{E}_i = \frac{\beta_i S_i I_i}{N_i} - (\sigma + \mu) E_i - \sum_{j \neq i} \gamma_{ij} E_i + \sum_{j \neq i} \gamma_{ji} E_j \\ \dot{I}_i = \sigma E_i - \mu I_i - \sum_{j \neq i} \gamma_{ij} I_i + \sum_{j \neq i} \gamma_{ji} I_j \end{cases} \quad (1)$$

where farm size  $N_i$ , i.e. the number of cattle in farm  $i$ , was assumed constant in time, and the number of susceptible animals in farm  $i$  was computed as  $S_i = N_i - E_i - I_i$ ;  $\beta_i$  represents the within-farm transmission rate;  $\sigma$  the rate at which exposed individuals become infectious;  $\gamma_{ij}$  the movement rate of individuals from farm  $i$  to farm  $j$ , which is proportional to farm  $i$  out-degree; and  $\mu$  the rate at which individuals leave the farm system, either because they are sent to

**Table 2**

The list and rates of the possible events for the stochastic model.

Event in farm $i$	Transition	Rate at which event occurs
Infection	$E_i \rightarrow E_i + 1$	$\beta S_i I_i / N_i$
Exposed individual become Infectious	$E_i \rightarrow E_i - 1, I_i \rightarrow I_i + 1$	$\sigma E_i$
Exposed individual is sent to farm $j$	$E_i \rightarrow E_i - 1, E_j \rightarrow E_j + 1$	$\gamma_i E_i$
Exposed individual leaves the system	$E_i \rightarrow E_i - 1$	$\mu E_i$
Infectious individual sent to farm $j$	$I_i \rightarrow I_i - 1, I_j \rightarrow I_j + 1$	$\gamma_i I_i$
Infectious individual leaves the system	$I_i \rightarrow I_i - 1$	$\mu I_i$

slaughterhouse, to farms outside the ER system, or because they die.

To explicitly account for the stochastic nature of the contact and transmission processes in a large network of farms, we ran stochastic simulations through an event-driven approach in which time steps between two consecutive events were described through a Poisson process with exponentially distributed means (Gillespie, 1977; Rohani et al., 2002). All the events simulated by the stochastic infection model are reported in Table 2.

#### 2.4. Parameter estimation

The basic reproduction number represents the mean number of secondary infections caused by a single infected individual introduced into a completely susceptible population (Diekmann et al., 1990). As ER is an officially bTB-free region since 7 years, there are no available outbreaks data to estimate a within-farm basic reproduction number,  $R_0$ . Thus, we set  $R_0$  value in our simulations using estimates for bTB found in the literature (Brooks-Pollock and Keeling, 2009; Agosto et al., 2011; Conlan et al., 2012; O'Hare et al., 2014). In particular, we described the uncertainty in  $R_0$  by assuming a triangular distribution with mode 2.40 (which corresponds to the mean value of literature estimates), lower limit 0.83, and upper limit 4.9 (which correspond to the extreme values found), see Supplementary materials S3.1 for details. In further simulations we tested the effect of  $R_0$  variability, comparing the obtained results against those of simulations ran using a fixed  $R_0$  value (see Supplementary materials S3.2).

Moreover, in order to test the robustness of our results against possible variations in the within-farm bTB basic reproduction number, we run further simulations using as fixed value the highest ( $R_{0,i} \equiv 4.9$ ) and the lowest ( $R_{0,i} \equiv 0.83$ ) of the literature estimates (see Supplementary materials S3.3).

The  $i$ th farm transmission rate,  $\beta_i$ , was indirectly derived from the expression for the within-farm basic reproduction number of model (1), i.e. assuming infection in  $i$ th farm only, by using Next Generation Matrix techniques (Diekmann et al., 1990):

$$\beta_i = R_0 \frac{(\sum_{j \neq i} \gamma_{ij} + \mu)(\sum_{j \neq i} \gamma_{ij} + \mu + \sigma)}{\sigma} \quad (2)$$

Following Barlow et al. (1997), we set the mean time  $\tau (=1/\sigma)$  spent in the exposed class  $E$  to 202 days. Likewise, parameters  $\mu$  and  $\text{mean}[\gamma_{ij}]$  were estimated from movement data as the inverse of the mean time that animals spent inside the farm before being moved out of the system and towards other ER dairy farms, respectively.

ITFs are characterized by substantial different behaviours with respect to dairy farms. As we assumed that there is no bTB transmission inside these farms, we set  $\beta_{ITF} = 0$  and we estimated ITF specific movement ( $\gamma_{ITF}$ ) and exit ( $\mu_{ITF}$ ) rates from available data.

#### 2.5. Assessment of the surveillance system

We used the stochastic model described in Table 2 to assess the effectiveness of the three surveillance components of the current surveillance system implemented in ER Region. Specifically: (i) a systematic control on every farm based on a tuberculin skin-tests (RS). This is performed on every individual in the farm older than 24 months, which represents about 60% of the total farm population. Following current legislation for bTB-free areas in ER all cattle herds are tested with a turnaround period of three years; (ii) a skin-test performed at the destination farm on moved cattle within 45 days after the arrival (ECT); (iii) a visual inspection for bTB characteristic lesions on cattle slaughtered (SI).

To simulate the RS we assumed that, within a turnaround period, farms are tested in a random order (with a frequency of about 4 farms a day). To simulate the other surveillance components, we assumed to test all individuals moved between dairy farms and to all individuals sent to slaughterhouses. When an animal tests positive to the tuberculin skin-test, both for RS and ECT cases, the procedures to verify whether the animal is truly infected by *M. bovis* last usually 2 months. These procedures consist in a carcass inspection for bTB typical lesions and in a bacteriological examination. During this confirmation period, cattle from the same farm cannot be transferred to other farms. This protocol was simulated in the model by assuming that, when a positive individual is detected by the skin-test, the farm cannot have any contact with other farms, but the simulation of disease dynamics lasts for other 2 months.

The skin-test currently in use in Italy is the cervical Single Intra-dermal Test (SIT). In their review, de la Rua-Domenech et al. (2006) showed that the SIT sensitivity estimates fall between 0.7 and 1. However, on-farm test sensitivity can be substantially smaller than in controlled laboratory experiment trials as other factors than the imperfect nature of the test may affect test outcome, such as the training level, care and experience of the veterinarian and the actual protocol used. Therefore, following Welby et al. (2012), we simulated the uncertainty in test sensitivities by randomly drawing sensitivity values from a beta distribution with mean 0.60 and coefficient of variation 0.10. Analogously to Barlow et al. (1997), we assumed a reduction of test sensitivity in infective but not infectious animals (mean value 0.54). Sensitivity of *post-mortem* inspection at the slaughterhouses can also be very variable (Asseged et al., 2004; Fischer et al., 2005; Smith et al., 2013; van Asseldonk et al., 2005; Welby et al., 2012). Therefore, similarly to Welby et al. (2012), we simulated the uncertainty in *post-mortem* inspection as a beta distribution with mean 0.60 and coefficient of variation 0.10 (with a reduction of sensitivity for exposed animals as in tuberculin skin-test).

In addition, with the intent to simulate different levels of accuracy and awareness in the testing procedures, we ran a sensitivity analysis to assess the effect of *post-mortem* inspection and tuberculin skin-test sensitivity values on surveillance system performance (Hadorn and Stärk, 2008; Humblet et al., 2011). The results are shown in Supplementary materials S4.

Disease dynamics following the introduction of an infected individual in the network of dairy farms of ER were assessed under five scenarios. Firstly, we simulated a baseline scenario of bTB epidemics spreading without surveillance so as to understand the potential impacts of uncontrolled bTB epidemics on the system. Secondly, we ran simulations on the integrated surveillance system currently in place, which includes all the three surveillance components (Scenario 1). Then, in order to assess the performances of each component of the surveillance system, we analyzed three alternative scenarios in which we removed one of the three components at a time and simulated epidemic dynamics with the other two systems in place. In Scenario 2a, Scenario 2b and Scenario 2c we removed RS, ECT and SI components, respectively (Fig. 2).

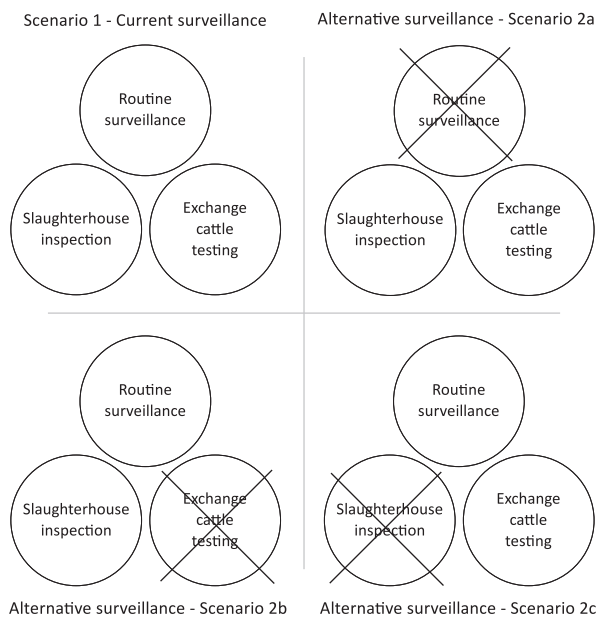


Fig. 2. Different surveillance system scenarios simulated.

For each scenario we ran 10 thousand stochastic Monte Carlo simulations of disease dynamics until infection detection or up to 10 years at most. For each simulation we generated a network of 4535 dairy farms as described above and assumed that an infected but not infective individual was randomly introduced in the network. To simulate variable test sensitivity, the values of skin test and *post-mortem* inspection sensitivity were drawn from the respective beta distributions each time a test was performed. Then, the 10 thousand replicates were used to derive a number of statistics on disease dynamics and on the performance of the specific surveillance system under assessment. In particular, for each scenario we derived: (i) the mean and 95th percentile of the time for an epidemic to be detected (when surveillance is in place); (ii) the mean and 95th percentile of the number of infected farms; (iii) the number of epidemics that involved more than one farm (i.e. multi-farms epidemics); (iv) the number of undetected epidemics after 10 years; and (v) the number of epidemics that went naturally extinct in less than 10 years.

### 3. Results

#### 3.1. Farm size, in- and out-degree distributions, and parameters estimations

The size of the 4353 ER cattle farms was quite variable and ranged from just few individuals to almost two thousands: farm size distribution was highly skewed with mean equal to 102 and median 63 (Fig. 1).

The average number of outgoing [ingoing] links in the 837 sampled farms was 1.67 [1.91], the median 1 [1] and the maximum number 23 [29]. The in-degree and out-degree distributions were not significantly different (Kolmogorov-Smirnov test,  $D=0.044$ ,  $p=0.387$ ) and were best fitted by a discrete log-normal distribution (Fig. 3 and Table 3). In-degree and out-degree were weakly correlated with farm size (Kendall's  $\tau = -0.028$  and  $0.20$ , respectively). The correlation between in- and out-degrees was also very weak (Kendall's  $\tau = -0.064$ ). Therefore, for each of the 10 thousand runs we generated a network of 4353 farms by independently drawing farms' in-degree and out-degree from their corresponding distributions, assuming no correlation between

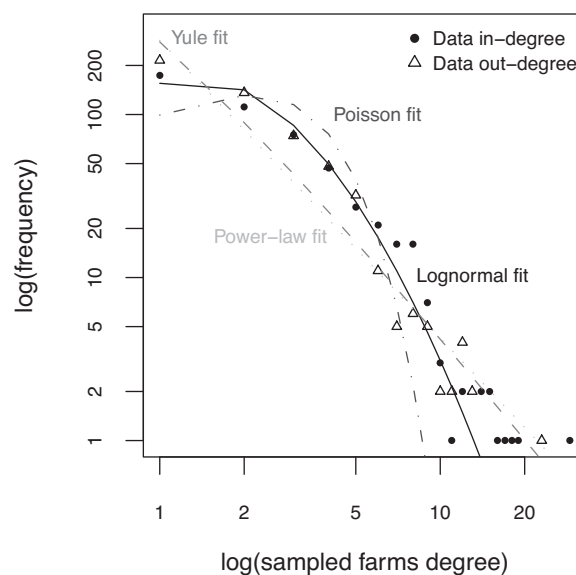


Fig. 3. Points represents the observed in- (circles) and out-degree (triangles) distributions of the sampled dairy farms. Lines represent the fitting for different distributions to the empirical data: discrete log-normal (solid line), Yule (dashed line), discrete power-law (dotted line) and Poisson (dashed-dotted line).

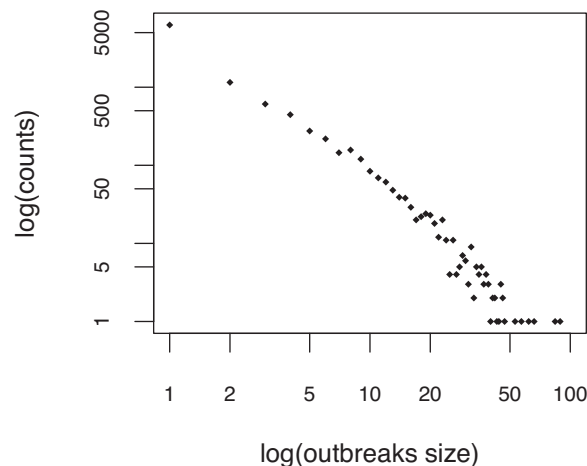


Fig. 4. The distribution (in log–log scale) of maximum number of infected farms (outbreak size) in each simulated outbreak.

them. The resulting networks were weakly connected, with average density of  $5.2 \times 10^{-4}$  ( $SD \pm 8.7 \times 10^{-6}$ ). The value of parameters  $\mu$  and  $\text{mean}[\gamma_{ij}]$  estimated from movement data was  $0.240 \text{ y}^{-1}$  (S.E.  $\pm 0.044$ ) and  $0.043 \text{ y}^{-1}$  (S.E.  $\pm 0.008$ ), respectively, for dairy farms and,  $19.981 \text{ y}^{-1}$  (S.E.  $\pm 1.499$ ) and  $15.901 \text{ y}^{-1}$  (S.E.  $\pm 1.192$ ) for ITFs.

#### 3.2. The baseline scenario: no surveillance

In the absence of any surveillance system, about half of the epidemics lasted for 10 years or more (56.05%), while the others (43.95%) naturally faded out in a median time of 14.92 months (lower [upper] quartile 5.95 [32.89] months). Epidemic size was highly skewed (Fig. 4): the mean number of infected farms was 2.91 (S.E.  $\pm 0.05$ ), but 62.66% of the epidemics involved only a single farm. In the worst 5% of the cases more than 11 farms got infected, with a maximum of 89.

**Table 3**

The result of the Vuong test on the degree data for discrete log-normal distribution vs. discrete power-law, Poisson and Yule distributions.

Discrete log-normal distribution	loglike.ratio	mean.LLR	sd.LLR	Vuong	p-Value
vs. Power law	158.903	0.151	0.647	7.57	3.6e–14
vs. Poisson	314.182	0.299	1.735	5.58	2.4e–08
vs. Yule	107.584	0.102	0.583	5.69	1.3e–08

**Table 4**

The main indicator for the surveillance system performances. Results for 5 different surveillance scenarios: no surveillance, 1: current surveillance, 2a: RS removed, 2b: ECT, 2c: SI removed.

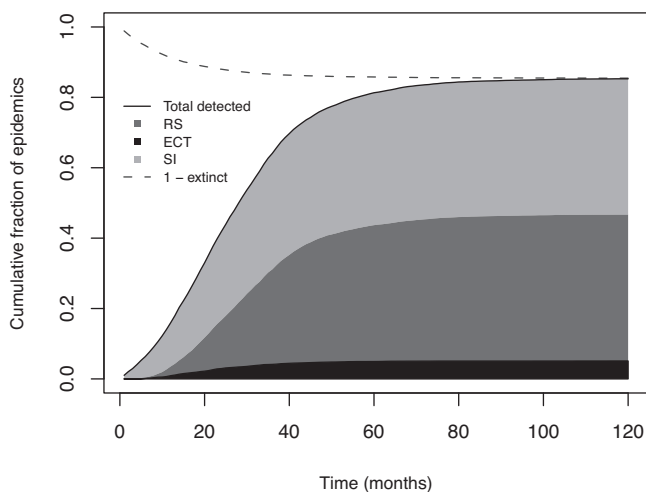
Scenario	Mean (and 95p) time to detection (months)	Mean (and 95p) number of infected farms	% of multi-farm epidemics	% of epidemic over 10 years	% of epidemic extinct
No surveillance	–	2.91 (11)	37.34%	56.05%	43.95%
Scenario 1	27.04 (59.20)	1.12 (2)	10.15%	0.10%	14.55%
Scenario 2a	33.77 (76.91)	1.20 (2)	16.80%	0.70%	16.23%
Scenario 2b	27.52 (60.09)	1.11 (2)	9.61%	0.14%	14.80%
Scenario 2c	35.45 (71.34)	1.15 (2)	12.01%	0.18%	33.57%

### 3.3. Performance of the current surveillance system

Fig. 5 shows the cumulated distribution of the time of epidemic detection computed as the fraction of epidemics monthly detected by the current surveillance system. The mean detection time was 27.04 months (S.E.  $\pm 0.19$ ). Epidemics were identified more frequently by routine surveillance, RS, and by *post-mortem* inspection at the slaughterhouse, SI. In 10 years, RS identified 41.66% of the epidemics and SI the 38.59%. Only 5.10% of the epidemics were first detected by ECT, i.e. intra-dermal testing of exchanged cattle; 14.55% of the epidemics faded out unreported while only 0.1% of the epidemics lasted 10 years or more. The average number of infected farms during the epidemics was 1.12 (S.E.  $\pm 0.003$ ); the worst 5% of the epidemics lasted more than 59.20 months affecting from 2 to 5 farms at most. Multi-farm epidemics occurred in 10.15% of the replicates. The performances of the current surveillance and the alternative scenarios described hereafter are summarized in Table 4.

### 3.4. Performance of alternative surveillance systems

Fig. 6 shows the cumulative fraction of monthly detected epidemics registered for a surveillance system implementing only two

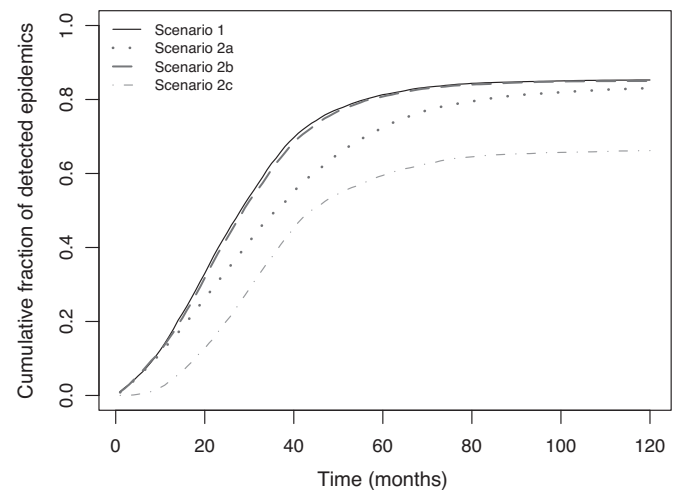


**Fig. 5.** The cumulated fraction of simulated epidemics monthly detected by the current surveillance system. Different colours correspond to the fraction of epidemics detected by each surveillance strategy: in light grey by slaughterhouse inspection (SI), in dark grey by routine surveillance (RS) and in black by exchanged cattle testing (ECT). The solid line represents the fraction of total of detected epidemics while the dashed line represents the fraction of epidemics not naturally faded out, or extinct, at any given time.

of the three surveillance methods currently in place. Our analysis showed that removing RS testing from the integrated surveillance system (Scenario 2a) led to an almost 7-month delay in the detection time driven by a significant reduction in the number of epidemics detected starting from the second year (Fig. 6). Compared with the current integrated surveillance system, this scenario was characterized by a small increase in the mean number of infected farms, in the total number of unreported epidemics lasting 10 years or more (from 0.10% to 0.70%), and in the number of unreported epidemics naturally fading out before the end of the simulation time (from 14.55% to 16.23%). In the worst 5% of the cases, the epidemics remained undetected for about 6 and a half years (76.91 months) and involved 2–5 farms.

Removing the ECT (Scenario 2b) did not cause significant changes in any of the performance indicators. In the worst 5% of the cases the time to detection was about 60 months and the number of infected farms between 2 and 7.

The removal of SI (Scenario 2c) led to a more than 8 months increase in the mean detection time mostly driven by a significant reduction in the detection rate since the first months. The number of undetected epidemics still ongoing after 10 years did not significantly change, while the fraction of multi-farm epidemics increased from 10.15% in Scenario 1 to 12.01%. The largest change in scenario 2c was represented by the number of unreported epidemics that naturally faded out, increased from 14.55% in the Scenario 1



**Fig. 6.** The cumulated fraction of simulated epidemics monthly detected by the surveillance system in Scenario 1 (solid line); Scenario 2a (only ECT and SI components, dotted line); Scenario 2b (only RS and SI components, dashed-dotted line); and Scenario 2c (only RS and ECT components, dashed line).

to the 33.57% in Scenario 2c, that explains the lower number of totally detected epidemics (Fig. 6). In the worst 5% of the cases, the epidemics remained undetected for 71 months and involved 2–7 farms.

#### 4. Discussion

The goal of this study was to assess the effectiveness of the current bTB surveillance system in Emilia-Romagna (ER) and the specific role played by its three components: on-farm routine testing, exchanged animal testing, and slaughterhouse inspection. To assess the performance of the bTB surveillance system we computed two main indicators: the time needed to detect a prospective newly introduced bTB epidemic in the dairy farms of ER; and the magnitude of the epidemic, in terms of number of farms infected before the detection of the epidemic. The time to epidemic detection is a very important measure of the surveillance performance (Hadorn and Stärk, 2008); firstly, because an early detection of the epidemic limits the number of both animals and farms infected; secondly, because according to Italian and European legislations at least 6 months without bTB cases are required for farms to regain their disease-free status. Indeed, the trade restrictions following an epidemic represent one of the worst consequences for the cattle industry (Gordon, 2008). The magnitude of the epidemic allows us to assess the damages caused by a bTB incursion quantifying the number of infected farms and, consequently, the total economic burden (i.e. loss of earnings, costs for animal culling and re-stocking).

Our analysis showed that the integrated surveillance system currently in place in ER can effectively reduce the number of farms involved in a potential epidemic of bTB with respect to a baseline scenario with no surveillance (see Table 4). The model predicts that about the 15% of the epidemics cannot be detected by the system. However, the undetected epidemics usually faded out during the first nine months after the introduction of the infection and generally involved one or few individuals in a single farm.

Numerical simulations also showed that *post-mortem* inspection at the slaughterhouse (SI) and on-farm routine testing (RS) were the most effective surveillance methods. These methods were significantly more effective in detecting bTB in the ER network of dairy farms than testing cattle upon moving to a new farm (ECT). Considering that the cattle exchanges were the only hypothesized route of between-farm transmission in the model, this result seems, at first sight, unexpected. However, it can be explained by the low bTB transmission rate and some specific proprieties of the ER cattle system (such as the low network density and the low number of cattle traded).

Slaughterhouse inspection turned out to be particularly effective as an early detection tool of the epidemics. This seemed to be due to the fairly regular flow of cattle sent out to slaughterhouses at the end of their productive cycle, on average at 5 years of age. Therefore, when an outbreak occurred in a farm, SI was likely the earliest diagnostic intervention able to detect it compared to ECT and RS. However, the large number of epidemics that naturally faded out when SI was absent (Scenario 2c) points out that most of the outbreaks that remained undetected at the end of the first year were likely to get extinct afterwards without developing into significant epidemics.

On-farm routine surveillance was the most effective in preventing major, or multi-farm, outbreaks. This was probably due to the low value of within-farm bTB basic reproduction number ( $R_0$ ). Indeed, a low within-farm  $R_0$  is followed by a low number of infected individuals inside farms, that means a low number of infected individuals exchanged or sent to slaughterhouses. In these epidemiological conditions, RS was the most effective method to

detect outbreaks before bTB spreads to other farms. Moreover, this method was also the most effective in detecting the small portion of minor epidemics that can persist unnoticed for many years.

The performances of SI and RS, both with regard to time to bTB detection and to fraction of multi-farm epidemics, were comparable and which one performed better depended on the value of the basic reproduction number ( $R_0$ ), see Supplementary Materials S3.3, and on the values of skin-test and SI sensitivity, see Supplementary materials S4.2.

As the  $R_0$  value increased, the number of detected epidemics by the SI tended to increase compared to the number of epidemics detected by RS (see Supplementary materials S3.3). This result can be explained considering that a larger within-farm disease prevalence, as a consequence of a larger within-farm  $R_0$ , implies a higher probability of sending infected individuals to the slaughterhouse in the early stages of epidemics, speeding up bTB detection, while the timing of RS is not affected by farm prevalence.

The values of skin-test and carcass inspection sensitivity played an important role as well. This was particularly significant in the case of slaughterhouse inspection, since a very large range of values of inspection sensitivity has been estimated in different contexts, from 0.1 to 0.65 (Asseged et al., 2004; Fischer et al., 2005; Smith et al., 2013; van Asseldonk et al., 2005; Welby et al., 2012).

The RS turnaround period, i.e. the time frame in which all farms are tested once for bTB, was set to 3 years, as currently is in ER region. The regional administration decided to move this period from 2 to 3 years in 2010. Our results suggested that this change had a negligible impact on the overall surveillance system performance and, moreover, that moving it to 4 years would have marginal impact as well (Supplementary materials S5).

The limited performance improvement provided by ECT raised questions about its usefulness and whether it could be safely dropped out from ER integrated surveillance system without significantly weakening it. Of course, this kind of decision should also be based on cost-benefit analysis. On the other hand, the role of ECT on animals entering a bTB-free region is not negligible, especially for cattle originating from regions where bTB is endemic and if pre-movement testing – in contrast to post-movement testing – is adopted to prevent the risk of disease introduction (Clegg et al., 2008; Schiller et al., 2011).

In agreement with our results, Shittu et al. (2013) showed that SI plays an important role in bTB detection in the UK, both in low incidence and endemic areas, but is highly influenced by inspection sensitivity. Another study conducted in Belgium by Welby et al. (2012) showed that SI is one of the most effective surveillance strategy for bTB. However, further analyses performed with our model showed that the use of the SI component only determined a significant reduction in the surveillance system performance compared to a surveillance based on SI coupled with routine skin-testing (see Supplementary materials S6). This result is in agreement with findings by Fischer et al. (2005) and van Asseldonk et al. (2005), who showed that SI surveillance alone is ineffective in detecting bTB in The Netherlands. This was confirmed by Schöning et al. (2013) on US cattle herds, who showed how SI needed to go along with the skin-test component in order to provide an effective surveillance system.

In this study, cattle movement data were available for a subset of the network of dairy farms in ER. These data were used to infer the fundamental topological properties of the whole system in terms of connectivity, so as to generate synthetic networks of the same size of the ER one. While we are confident that our approach provides a solid preliminary understanding of bTB dynamics on the network of dairy farms in ER, we did not have the possibility to derive more sophisticated metrics, such as the clustering coefficient and the Disease Flow Centrality, that would help to have more detailed prediction on how diseases spread through the network,

as shown by Bajardi et al. (2011) and Natale et al. (2011). We simulated disease dynamics on a static network, ignoring seasonality in cattle movement and the dynamical nature of cattle trade. Dynamical networks can effectively represent the time-varying structure of the network – which is crucial to simulate the dynamics of acute and highly contagious diseases, such as Food-and-Mouth Disease (Bajardi et al., 2011, 2012; Vernon and Keeling, 2009). However, since bTB is characterized by slow infection dynamics and it is able to remain unnoticed for a long period of time, we believe that it is not essential to track the small structural changes occurring on a short time scale for suitably describe bTB dynamics.

Other studies were previously conducted on cattle movements in Italy by Natale et al. (2009, 2011). In particular, they found that the degree distribution of cattle movement was best approximated by a *fat-tailed* power-law probability distribution. Our degree distributions best fitting was obtained through a discrete log-normal distribution, characterized by lower right-tails than the power-law (Fig. 3). This could be a consequence of isolating the dairy system, i.e. by not considering the movements towards fattening farms and slaughterhouses.

This study was specifically performed on the dairy cattle system, ignoring the beef sector. The main reason was that the bTB surveillance system in ER is in place on the dairy sector only. Moreover, further reasons supported this choice: (i) the higher economic value of the dairy sector in the Region; (ii) the fact that generally beef farms do not exchange animals with other farms, they only receive male calves within 100 days of age from dairy farms and send animals to slaughterhouses at the end of the fattening process; (iii) the two systems are almost fully separated, so there is no possibility of spill-over from the beef to the dairy system; and (iv) dairy cattle live substantially longer than beef cattle, i.e. up to 5 years vs. 2 respectively, thus epidemics have more possibility to develop in the dairy system because of bTB long incubation period.

Our analyses showed that the farms in-degree and the out-degree were not coupled. In other words, farms having a higher in-degree, i.e. that import relatively more cattle from other farms in the Region, do not necessarily have a high out-degree, and vice versa. A similar result is outlined in Volkova et al. (2010) on Scottish farms, suggesting that this could be a recurrent pattern for cattle herds in different management contexts.

In the UK and in other countries where bTB is endemic, the high cost of the surveillance and eradication programme, namely £74–99 million a year for UK (Smith and Clifton-Hadley, 2008; Torgerson and Torgerson, 2008) has been put under scrutiny. Our results indicate that a proposal for simplification or strengthening of an integrated surveillance system should be always based on a rigorous, quantitative understanding of the role played by each of its components. In fact understanding the actual effectiveness of a specific control strategy, is not always straightforward, and can be affected by factors like network topology, the trading system, rearing methods, test frequency and test sensitivity. Moreover, the increasing density of ungulates and other potential wildlife reservoir species occurring in several European countries poses new challenges for the existing surveillance systems even in areas that are currently bTB-free (Schöning et al., 2013).

*A priori* information on the network structure of cattle exchanges during non-emergency periods can help orienting control strategies to prevent epidemics in areas characterized by a high number of industrial farms (Bajardi et al., 2012; Gilbert et al., 2005). Our framework, based on a mathematical modelling approach, provided decision-makers with a powerful cost-effective tool to assess the effectiveness of the current bTB surveillance system in ER, by highlighting strengths and weaknesses its different components.

Moreover, the methodological approach proposed here will allow the health authorities to assess the effectiveness of future alternative strategies for bTB detection that are not currently

implemented in ER, such as antigen detecting tests (ELISA) on milk and blood sample (van Asseldonk et al., 2005). Furthermore, by taking into consideration the cost of different testing strategies, it will be possible to use our modelling approach to run cost-effectiveness analyses of different options of surveillance (Anderson et al., 2013; Cameron, 2012).

## Acknowledgements

We would like to thank Marco Tamba for the constructive discussions about bovine tuberculosis surveillance and the herd system of Emilia-Romagna.

This study was funded by IZSLER within the research project AUTIFIN-TBC-EMILIA-2011 'Development of an Epidemiological Model for Bovine Tuberculosis in Emilia-Romagna'.

## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:10.1016/j.epidem.2015.02.007.

## References

- Abernethy, D.A., Upton, P., Higgins, I.M., McGrath, G., Goodchild, A.V., Rolfe, S.J., Broughan, J.M., Downs, S.H., Clifton-Hadley, R., Menzies, F.D., de la Rúa-Domenech, R., Blissitt, M.J., Duignan, A., More, S.J., 2013. Bovine tuberculosis trends in the UK and the Republic of Ireland, 1995–2010. *Vet. Rec.* 172, 312.
- Agosto, F.B., Lenhart, S., Gumel, A.B., Odoi, A., 2011. Mathematical analysis of a model for the transmission dynamics of bovine tuberculosis. *Math. Methods Appl. Sci.* 34, 1873–1887.
- Anderson, D.P., Ramsey, D.S.L., Nugent, G., Bosson, M., Livingstone, P., Martin, P.A.J., Sergeant, E., Gormley, A.M., Warburton, B., 2013. A novel approach to assess the probability of disease eradication from a wild-animal reservoir host. *Epidemiol. Infect.* 141, 1509–1521.
- Anonymous, 2008. Bovine tuberculosis. In: *Manual of Diagnostic Tests and Vaccines for Terrestrial Animals*. World Organization for Animal Health (OIE), Paris, France, pp. 683–697.
- Asseged, B., Woldeesenbet, Z., Yimer, E., Lemma, E., 2004. Evaluation of abattoir inspection for the diagnosis of *Mycobacterium bovis* infection in cattle at Addis Ababa abattoir. *Trop. Anim. Health Prod.* 36, 537–546.
- Bajardi, P., Barrat, A., Natale, F., Savini, L., Colizza, V., 2011. Dynamical patterns of cattle trade movements. *PLoS ONE* 6, e19869.
- Bajardi, P., Barrat, A., Savini, L., Colizza, V., 2012. Optimizing surveillance for livestock disease spreading through animal movements. *J. R. Soc. Interface* 9, 2814–2825.
- Barlow, N.D., Kean, J.M., Hickling, G., Livingstone, P.G., Robson, A.B., 1997. A simulation model for the spread of bovine tuberculosis within New Zealand cattle herds. *Prev. Vet. Med.* 32, 57–75.
- Brooks-Pollock, E., Keeling, M.J., 2009. Herd size and bovine tuberculosis persistence in cattle farms in Great Britain. *Prev. Vet. Med.* 92, 360–365.
- 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.
- 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.
- Cheeseman, C.L., Wilesmith, J.W., Stuart, F.A., 1989. Tuberculosis: the disease and its epidemiology in the badger, a review. *Epidemiol. Infect.* 103, 113–125.
- Clauset, A., Shalizi, C., Newman, M., 2009. Power-law distributions in empirical data. *SIAM Rev.* 51, 661–703.
- Clegg, T.A., More, S.J., Higgins, I.M., Good, M., Blake, M., Williams, D.H., 2008. Potential infection-control benefit for Ireland from pre-movement testing of cattle for tuberculosis. *Prev. Vet. Med.* 84, 94–111.
- Conlan, A.J.K., McKinley, T.J., Karolemeas, K., Pollock, E.B., Goodchild, A.V., Mitchell, A.P., Birch, C.P.D., Clifton-Hadley, R.S., Wood, J.L.N., 2012. Estimating the hidden burden of bovine tuberculosis in Great Britain. *PLoS Comput. Biol.* 8, e1002730.
- Cousins, D.V., 2001. *Mycobacterium bovis* infection and control in domestic livestock. *Rev. Sci. Tech.* 20, 71–85.
- de la Rúa-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, gamma-interferon assay and other ancillary diagnostic techniques. *Res. Vet. Sci.* 81, 190–210.
- Diekmann, O., Heesterbeek, J., Metz, J., 1990. On the definition and the computation of the basic reproduction ratio  $R_0$  in models for infectious diseases in heterogeneous populations. *J. Math. Biol.* 28, 365–382.
- Fischer, E.A.J., 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.
- Fitzgerald, S.D., Kaneene, J.B., 2013. Wildlife reservoirs of bovine tuberculosis worldwide: hosts, pathology, surveillance, and control. *Vet. Pathol.* 50, 488–499.



- Gilbert, M., Mitchell, A., Bourn, D., Mawdsley, J., Clifton-Hadley, R., Wint, W., 2005. Cattle movements and bovine tuberculosis in Great Britain. *Nature* 435, 491–496.
- Gillespie, D., 1977. Exact stochastic simulation of coupled chemical reactions. *J. Phys. Chem.* 93555, 2340–2361.
- Gordon, S., 2008. Bovine TB: stopping disease control would block all live exports. *Nature* 456, 700.
- Griffin, J.M., Williams, D.H., Kelly, G.E., Clegg, T.A., O'Boyle, I., Collins, J.D., More, S.J., 2005. The impact of badger removal on the control of tuberculosis in cattle herds in Ireland. *Prev. Vet. Med.* 67, 237–266.
- Hadorn, D., Stärk, K., 2008. Evaluation and optimization of surveillance systems for rare and emerging infectious diseases. *Vet. Res.* 39, 57–68.
- Huang, Z.Y.X., de Boer, W.F., van Langevelde, F., Xu, C., Jebara, K.B., Berlingieri, F., Prins, H.H.T., 2013. Dilution effect in bovine tuberculosis: risk factors for regional disease occurrence in Africa. *Proc. R. Soc. B* 280, 20130624.
- Humblet, M.-F., Moyon, J.-L., Bardoux, P., Boschioli, M.L., Saegerman, C., 2011. The importance of awareness for veterinarians involved in cattle tuberculosis skin testing. *Transbound. Emerg. Dis.* 58, 531–536.
- Italian National Statistics Institute (ISTAT), 2010. 6° Censimento Generale dell'Agricoltura. <http://censimentoagricoltura.istat.it/>
- Johnston, W.T., Vial, F., Gettinby, G., Bourne, F.J., Clifton-Hadley, R.S., Cox, D.R., Crea, P., Donnelly, C.A., McInerney, J.P., Mitchell, A.P., Morrison, W.I., Woodroffe, R., 2011. Herd-level risk factors of bovine tuberculosis in England and Wales after the 2001 foot-and-mouth disease epidemic. *Int. J. Infect. Dis.* 15, e833–e840.
- Independent Scientific Group, 2007. Bovine Tuberculosis: The Scientific Evidence. DEFRA Publications, London.
- Marangon, S., Martini, M., Dalla Pozza, M., Neto, F., 1998. A case-control study on bovine tuberculosis in the Veneto Region (Italy). *Prev. Vet. Med.* 34, 87–95.
- Morris, R.S., Pfeiffer, D.U., Jackson, R., 1994. The epidemiology of *Mycobacterium bovis* infections. *Vet. Microbiol.* 40, 153–177.
- Natale, F., Giovannini, A., Savini, L., Palma, D., Possenti, L., Fiore, G., Calistri, P., 2009. Network analysis of Italian cattle trade patterns and evaluation of risks for potential disease spread. *Prev. Vet. Med.* 92, 341–350.
- Natale, F., Savini, L., Giovannini, A., Calistri, P., Candeloro, L., Fiore, G., 2011. Evaluation of risk and vulnerability using a Disease Flow Centrality measure in dynamic cattle trade networks. *Prev. Vet. Med.* 98, 111–118.
- O'Hare, A., Orton, R., Bessell, P.R., Kao, R.R., 2014. Estimating epidemiological parameters for bovine tuberculosis in British cattle using a Bayesian partial-likelihood approach. *Proc. R. Soc. B* 281, 1783.
- Phillips, C.J.C., Foster, C.R.W., Morris, P.A., Teverson, R., 2003. The transmission of *Mycobacterium bovis* infection to cattle. *Res. Vet. Sci.* 74, 1–15.
- Reilly, L.A., Courtenay, O., 2007. Husbandry practices, badger sett density and habitat composition as risk factors for transient and persistent bovine tuberculosis on UK cattle farms. *Prev. Vet. Med.* 80, 129–142.
- Reynolds, D., 2006. A review of tuberculosis science and policy in Great Britain. *Vet. Microbiol.* 112, 119–126.
- Rohani, P., Keeling, M.J., Grenfell, B.T., 2002. The interplay between determinism and stochasticity in childhood diseases. *Am. Nat.* 159, 469–481.
- Schiller, I., Waters, W.R., Vordermeier, H.M., Jemmi, T., Welsh, M., Keck, N., Whelan, A., Gormley, E., Boschioli, M.L., Moyon, J.L., Vela, C., Cagiola, M., Buddle, B.M., Palmer, M., Thacker, T., Oesch, B., 2011. Bovine tuberculosis in Europe from the perspective of an officially tuberculosis free country: trade, surveillance and diagnostics. *Vet. Microbiol.* 151, 153–159.
- 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.
- Shittu, A., Clifton-Hadley, R.S., Ely, E.R., Upton, P.U., Downs, S.H., 2013. Factors associated with bovine tuberculosis confirmation rates in suspect lesions found in cattle at routine slaughter in Great Britain, 2003–2008. *Prev. Vet. Med.* 110, 395–404.
- Smith, N.H., Clifton-Hadley, R., 2008. Bovine TB: don't get rid of the cat because the mice have gone. *Nature* 456, 700.
- Smith, R.L., Schukken, Y.H., Lu, Z., Mitchell, R.M., Grohn, Y.T., 2013. Development of a model to simulate infection dynamics of *Mycobacterium bovis* in cattle herds in the United States. *J. Am. Vet. Med. Assoc.* 243, 411–423.
- Skuce, R.A., Allen, A.R., McDowell, S.W.J., 2012. Herd-level risk factors for bovine tuberculosis: a literature review. *Vet. Med. Int.* 2012, 621210.
- Torgerson, P., Torgerson, D., 2008. Does risk to humans justify high cost of fighting bovine TB? *Nature* 455, 1029.
- 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.
- Vernon, M., Keeling, M.J., 2009. Representing the UK's cattle herd as static and dynamic networks. *Proc. R. Soc. B: Biol. Sci.* 276, 469–476.
- Volkova, V.V., Howey, R., Savill, N.J., Woolhouse, M.E.J., 2010. Potential for transmission of infections in networks of cattle farms. *Epidemics* 2, 116–122.
- Vuong, Q., 1989. Likelihood ratio tests for model selection and non-nested hypotheses. *Econom. J. Econom. Soc.* 57, 307–333.
- 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.