Resilience of French cattle farms to bovine tuberculosis detection between 2004 and 2017

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Abstract

France was recognized officially bovine tuberculosis (bTB) free by the European Union in 2001, however an increase of bTB detections has been reported since 2004. Even though the recommended method for bTB control is whole herd depopulation, test-and-cull protocols have been authorized in pilot areas since 2008 and in the rest of France since 2014. BTB impact at the state level and on trade has been thoroughly studied, however the consequences of these control measures at a farm level are poorly understood.

We used bovine movement data from the French cattle tracing system and surveillance data from the National reference laboratory to compare time to closure between case farms with a bTB detection and matched control farms between 2004 and 2017 in France. For this purpose, we considered two modes of closure: (i) long-lasting (more than 12 months) depopulation and (ii) change of farm owner. Using a competing risk analysis, we showed that bTB detection significantly increased the odds of long-lasting depopulation (particularly during the first three months after bTB detection) indicating that farmers renounced restocking after the depopulation, whereas it decreased the odds of a change of owner. Larger farms, characterized by an increased average weekly number of cattle, had a lesser risk of long-lasting depopulation. Farms owned by a natural person had an increased risk of closure. We also showed that the possibility to control bTB by test-and-cull protocol decreased the long-lasting depopulation risk.

Overall, bTB control measures contribute to reshaping the agricultural landscape by increasing the probability of closure for small vulnerable farms and by favoring large, professionalized and specialized agricultural holdings. Our results also suggest an improvement in control management with the introduction of test-and-cull protocols instead of systematic whole herd depopulation.

Keywords: Bovine tuberculosis, Farm resilience

Introduction

Bovine tuberculosis (bTB) is a chronic disease caused mainly by *Mycobacterium bovis*. It can affect cattle and other domestic and wild ruminants, but also many other mammalian species including humans. The zoonotic nature of this pathogen justified the design and implementation of control programs, in line with the European Union (EU) Directive 64/432/EEC. In France, such an eradication program started in 1954, and became compulsory 11 years later, in 1965. This was followed by a quick decrease of herd incidence, from about 13% in 1965 to 1.5% in 1980 and <0.1% in 2000 (Bekara et al., 2014). The EU recognized France as officially free of bTB in 2001 (Decision 2001/26/EC), after a 6-year period with a herd prevalence <0.1%. This bTB-free status is a condition for trading livestock and animal products with other countries and is therefore crucial to maintain French cattle farming competitiveness. However, since 2004, an upsurge of bTB detections is reported in specific areas located in the South-Western (Dordogne, Charentes and Pyrénées Atlantiques administrative divisions called *départements*) and Eastern parts of the country (Côte-d'Or) (Cavalerie et al., 2015).

The surveillance of bTB in cattle in France relies on three complementary approaches: systematic meat inspection at the slaughterhouse, systematic periodic screening in herds, and targeted screening of animals before movements or in at-risk herds, identified by epidemiological investigations performed in bTB-infected farms. At the slaughterhouse, each carcass is visually inspected by incision of selected tissue (lungs, retropharyngeal lymph nodes…) and, when suspect lesions are observed, samples are collected and sent to certified laboratories for the detection of *M. bovis* by polymerase chain reaction (PCR) and bacteriology. The systematic periodic screening in herds differs according to the epidemiological situation of the *département*: the screening rhythm can vary between a yearly testing of all animals older than 6 weeks to no testing. At risk herds can be subject to reinforced surveillance protocols. Finally, all cattle in transit for more than 6 days or coming from an at-risk herd or transiting through a high risk herd with high turn-over or coming from a *département* with a 5-year cumulated incidence higher than the national average incidence are tested. All live animals are tested by single intradermal comparative tuberculin tests (SICTT) or by single intradermal tuberculin tests (SITT). Both tests are performed in the cervical region and read 72h post-injection (Cavalerie et al., 2015; Ministère de l'agriculture, de l'alimentation, de la pêche et des affaires rurales, 2003).

In France, each bTB detection is officially notified and leads to control measures at the herd level, which vary according to the local epidemiological situation. After bTB detection, two control protocols are available: either all animals are culled and the farm is subsequently disinfected (whole herd depopulation protocol), or only positive animals are culled and movements are restricted until recovering bTB-free status after three negative tests (test-and-cull protocol). The recommended method is whole depopulation within a month after bTB detection, a reinforced meat inspection in slaughtered animals at the slaughterhouse, and a disinfection of the farm buildings (Delavenne et al., 2019). However, the majority of culled animals are bTB free because of the low within-herd prevalence. In 2014, among 7669 culled bovines as part of a whole herd depopulation, 175 (2.28%) showed bTB-consistent lesions (Cavalerie et al., 2015; Ladreyt et al., 2018). In addition, bTB detections have been observed in farms after restocking, questioning the efficacy of whole herd depopulation which makes this control measure less and less acceptable to farmers (Good et al., 2011). For this reason, a test-and-cull protocol has been progressively authorized (since 2008 for two *départements* -Dordogne and Côte-d'Or; since 2014 for the rest of France) and improvements have been suggested (Ladreyt et al., 2018). The protocol is chosen on a case-by-case basis, and, if the farmer chooses the test-and-cull protocol, animal health authorities must first approve it. All animals from the herd are then tested by SICTT and interferon gamma, and positive animals are culled. A herd regains the bTB-free status after three negative herd-level tests, carried out two months apart (Ladreyt et al., 2018). In 2014, bTB was controlled by whole herd depopulation in 61 out of 105 farms with a confirmed infected animal (Cavalerie et al., 2015).

At the EU level in 2012, out of the 193 million euros allocated to surveillance and eradication plans, one third was used for bTB detection and control (Delmotte and Lecomte, 2013). The burden and cost of bTB surveillance and control have been studied across different jurisdictions and vary greatly according to the epidemiological situation. In the Republic of Ireland, the annual cost of bTB surveillance and control was estimated at 84 million € in 2017 (funded by the Exchequer (42 million €), farmers (32 million €) and the EU (10 million €)) (Department of Agriculture Food and the Marine, 2018), 40 million £ in Northern Ireland, and 38 million $ in the USA (Smith et al., 2013). In Morocco, depending on the control strategies, it was simulated that the cumulated cost to reach bTB elimination would vary between 1.47 and 1.99 billion euros (Abakar et al., 2017). In France, in 2014, the annual cost of bTB surveillance and control was estimated at more than 17 million euros (for the screening cost, farmers compensation and veterinary fines, mainly) and at 107 000 € per breakdown (Cavalerie et al., 2015).

In France, the screening cost is shared between farmers but the way in which it is shared can differ between *départements*. For instance, in Dordogne (Aquitaine-North) and Pyrénées Atlantiques (Aquitaine-South), all farmers belonging to the animal health protection group (*groupement de défense sanitaire*) participate to the screening cost at the *département* level, whereas in Côte-d'Or only owners of infected farms participate (Gibon and Parle, 2015).

At the farmers' level, the monthly cost of bTB detection has been evaluated between £500 and > £3000 in South West of England (Butler, 2010). Besides this high economic impact, control measures, especially depopulation, have a strong psychologic impact on the farmers (Delmotte and Lecomte, 2013). Both economic and psychologic impacts may induce longer-term effects (Turner et al., 2008), as they may lead farmers to abandon cattle farming and diversify their production, or to sell their cattle production unit to another farmer, or even to close the whole agricultural holding.

Our goal was to quantify the impact of bTB detection on the risk of farm closure. Based on data from the French cattle tracing system, bTB surveillance and the National Reference Laboratory (NRL), we used survival analysis methods to study the time to farm closure with and without bTB detection, in

France between 2004 and 2017, considering two competing causes of farm closure: long-lasting depopulation and sale of the cattle-breeding unit.

Material and methods

Data

Case farms identification

All bTB detections between 2000 and 2017 which were declared to the Directorate General on Food Safety (*Direction Générale de l'Alimentation – DGAl*), included the herd identification number and date of bTB detection. The National Reference Laboratory (NRL) (Anses, Maisons-Alfort) checked this dataset for consistency with the samples they analyzed. This list was completed for herds that were confirmed by typing but not included in the *DGAl* list. These added case farms corresponded to herds connected with previously identified case farms or to large herds with two herd identification numbers. We selected the bTB detections for which typing results (spoligotyping and/or VNTR) and animal identification number were available.

Suspect animals had been identified either by skin tests (in the cervical region, using SITT or SICTT) provided by different surveillance protocols (periodic screening, epidemiological investigations, pre-movement of cattle (Delavenne et al., 2019)), or following the detection of lesions at slaughterhouse. For each detection, the presence of *M. bovis* was confirmed by PCR and/or bacterial culture.

Cattle tracing system

The French cattle tracing system (*Base de Données Nationale d'Identification* or BDNI) records data regarding cattle and cattle herds (Ministère de l'agriculture, de l'agroalimentaire et de la forêt, 2014). It allows reconstruction of the life history of each cow in France, from birth (or importation) to death (or export), through the entry and exit dates for each herd the animal has been residing in. For any given day, it is therefore possible to define the list of animals present in a herd. Besides, herd ownership data are also recorded (i.e. the owner of each herd), the dates at which the herd-owner relationship change, and the owner's legal status: natural person (i.e. an individual person) or legal person (i.e. a producer group or a company). Herd types at the time of bTB detection were defined according to the classification proposed by Sala et al. (2019): dairy breeder herds, dairy breeder-fattener herds, beef (-suckler) breeder herds, beef (-suckler) breeder-fattener herds, mixed breeder herds, mixed breeder-fattener herds, fattener herds, very small herds and other herds (Sala et al., 2019).

Study design

The objective of this study was to analyze the longer-term impact of bTB detection on agricultural holdings. Although a bTB detection affects the cattle herd, its longer-term impacts result from decisions taken by the owner to deal with this event. For this reason, the association between a herd and an owner defined the unit of interest, termed below “farm”, and we named the longer-term impact we analyzed “farm closure”. We defined farm closure as (i) a change of owner identification number (which represents the sale or inheritance of the whole cattle breeding unit or a change of the owner’s legal status), or (ii) the sale, slaughter or death of each cattle until farm emptiness for more than 12 months called “long-lasting depopulation”.

To define depopulation, we computed the number of cattle present each day during the follow-up (i.e. between bTB detection and December 31 2017). When this number was zero, we considered that the farm was depopulated. We computed the duration of depopulation as the number of consecutive days where the farm was depopulated. A depopulation of at least 12 months is the duration used by the authorities to characterize a cessation of livestock farming activity (Ministère de l’agriculture, de l’alimentation, de la pêche et des affaires rurales and Institut de l’élevage, 2004).

Farm closure date was defined as the date at which the owner changed as notified in the BDNI, or as the first day of a long-lasting depopulation. Both types of farm closures may correspond to the closure of a whole agricultural holding, its diversification away from cattle breeding and/or production or a change of legal status with the owner joining a producer group for instance.

Restocking was defined as the entry of cattle in the farm and the time of restocking as the first day when at least one animal was present in the farm.

The impact of a bTB detection on both types of farm closure was analyzed using a case/control design and survival analysis methods. Cases were farms with a bTB detection between July 2004 and December 2017. We decided to exclude bTB detections that occurred before July 2004 since herd type was not available. We also excluded the farms breeding bullfighting animals and the farms from Corsica, which correspond to very specific breeding systems. When several detections had been reported for the same farm, the last bTB detection date was used. Control farms were bTB-free farms (i.e. farms without bTB detection).

It has been well documented that bTB incidence has a heterogeneous geographical distribution and is associated with the production type (Karolemeas et al., 2011; Ramírez-Villaescusa et al., 2010). Furthermore, the most obvious cause of farm closure is farmer retirement. To control these factors, we matched the control farms to case farms on the *département* (the level 3 of the Nomenclature of Territorial Units for Statistics), on the farm production types proposed by Sala (Sala et al., 2019), and on the ownership (of the herd by the owner) start date ± 5 years, considering the latter variable as a proxy for owners' age. To control the impact of the local epidemiological context, we excluded control farms that were closed at the time of bTB detection in the matched case farm. Finally, we excluded control farms that had been populated less than 6 months during that period. Based on the preceding criteria, we chose to match one control farm for each case farm randomly.

Statistical analysis

Covariates definition

We studied the resulting dataset using competing risk analysis methods. The event of interest was the occurrence of a farm closure event during the follow-up between a bTB detection (for a case and its associated time controls) and December 2017. The two causes of farm closures (change of owner, and long-lasting depopulation) were analyzed jointly. For both causes, case and control farms were compared for the (right-censored) survival duration (in days). Besides the owner's age and the herd type at time of bTB detection (for which case-control matching criteria were defined), the risk of farm closure was expected to vary according to the cattle breeding unit's economic performance. To control for this presumably major factor of farm closure, we computed the average weekly number of cattle during the year preceding bTB detection. For each week, we counted the number of cattle present in the farm using the entry and exit dates. This covariate described the size of the farm and was therefore used as a proxy for the owner's overall income. The owner legal status (natural person *vs.* other forms of agricultural holdings) was considered as a proxy for the owner's ability to diversify their farming activity. The type of control measures (i.e. whole herd depopulation or test-and-cull) may influence the risk of farm closure although the nature of this influence is difficult to predict: whole herd depopulation has a stronger psychologic impact than test-and-cull, however the latter may induce a longer period of movement restriction and have a higher economic impact on the farmer. As the information on the type of control measure was not available for the whole study period (it was only available starting 2013), we defined a tag-variable (0/1) for the possibility of test-and-cull control program. Since the situation was different according to the *département*, we set this variable to 1 for all *département* starting 2014 and for Dordogne (in Aquitaine-North) and Côte-d'Or starting 2008.

Competing risk analysis

To account for the mutually exclusive causes of closure (cause 1: change of owner, and cause 2: long-lasting depopulation), we used a competing risk model to describe the cumulative incidence curve. The standard approach to analyze competing risk data is to model and estimate the cause-specific hazards. We used the model proposed by Scheike et al. (Scheike et al., 2008) with a logit link function, according to which the cumulative incidence function (CIF) for cause 1 is modeled as:

$$logit\ P_1(t \mid x_1, \dots, x_n, z_1, \dots, z_m) = \alpha_0(t) + \sum_{i=1}^{n} \alpha_i(t)\, x_i + \sum_{j=1}^{m} \gamma_j\, z_j$$

where:

- $\alpha_0(t)$ is the baseline time-varying risk,
- $x_{i=1,\dots,n}$ are the *n* covariates having a time-varying effect, and $\alpha_i(t)$ the associated time-varying effect, estimated in a non-parametric way,
- the $z_{j=1,\dots,m}$ are the *m* covariates having a time-constant effect, and γ_j the associated parameters.

The CIF $P_1(t \mid x_1, \dots, x_n, z_1, \dots, z_m)$ then represents the probability, for a farm with the covariates x_i and z_j, to close from cause 1 by time t, whilst also at risk of closing from the other competing cause of closure.

To use this model it is first necessary to determine if the covariate effect is time-varying or constant. For this purpose, we fitted a model where all covariate effects are time-varying (i.e. a fully non-parametric model). We then successively tested whether the effect of a specific covariate, x_i, was constant over time (with $H_0: \alpha_i(t) \equiv \alpha$) using a Cramer-von Mises test. Four covariates were considered:

- occurrence of a bTB detection in the farm: Yes/No, i.e. case *vs.* control (reference),
- legal status of the owner: natural person/other (reference),
- possibility of test-and-cull control program: Yes/No (reference),
- average weekly number of cattle (x100),

For the covariates z_j having a time-constant effect, the significance of the effect was investigated by testing $H_0: \gamma_j = 0$ with the test statistic $\widehat{\gamma_j}/\widehat{\sigma_\gamma^j}$ which is asymptotically normally distributed and where $\widehat{\sigma_\gamma^j}$ is the j^{th} diagonal element of the variance matrix $\widehat{\Sigma_\gamma}(t)$. We computed the sub-distribution hazard ratio (SHR) for the variables that were not varying with time. SHR for covariate z_j is computed as $exp(\gamma_j)$. If the probability of events is low (<20%) over the entire follow-up period and when a logistic link function is used, then the SHR can be interpreted as an odds ratios of CIF (Austin and Fine, 2017).

For the covariates x_i that had a time-varying effect, the significance of the effect was assessed using a supremum test ($H_0\colon \alpha_i(t) = 0, t \in [0, \tau]$) with the test statistic: $T = \sup_{t[0,\tau]} \left| \frac{\widehat{\alpha_i}(t)}{\sqrt{\widehat{\Sigma_\alpha^i}(t)}} \right|$, where $\sqrt{\widehat{\Sigma_\alpha^i}(t)}$ is the i^th^ diagonal element of the variance matrix $\widehat{\Sigma_\alpha}(t)$. Ten thousand resampling processes were used to compute the p-value. For each covariate having a time-varying effect, we additionally plotted the estimated $\hat{\alpha}_i(t)$ with its confidence band since it represents the time-varying effect of the variable x_i (i.e. a non-flat curve), and the time-varying significance of this effect (i.e. whether, at a given time, the confidence interval contains zero or not).

We considered that the matching pairs were independent and modeled it with a cluster variable, which uniquely identified each pair.

We estimated the regression parameters by direct binomial regression approach as implemented in the *comp.risk()* function from the *timereg* package in R3.6.0 (Scheike and Zhang, 2011). Figures were drawn using the *ggplot2* package (Wickham, 2009). To plot the maps we used in addition the packages *rgdal* (Keitt, 2010) and *broom* (Robinson, 2014).

Results

French farming landscape between 2004 and 2017

Herd distribution is heterogeneous in France, with two main areas of farming: one in the North-West mainly with dairy breeder and dairy fattener herds and one in the Center/South-West with mainly suckler fattener and suckler breeder herds (**Figure S1A**).

Herd type census campaigns are held between July 1st of year x and June 30th of year x+1. The number of herds decreased from 263,284 to 173,941 between the 2004-2005 and the 2017-2018 campaigns, which corresponds to a 33.9% herd loss (**Figure S1B**). All production types were affected with the biggest loss observed for fattener (-58.5%), dairy-breeder (-42.7%) and very small farms (-42,2%),

Case farms description

Between 2000 and 2017, bTB was detected 1532 times in 1364 herds. Among these, we excluded 52 herds from Corsica, 179 herds breeding bullfighting animals and 237 herds where bTB was detected before July 2004. In total, 1064 bTB detections in 952 herds were considered, corresponding to 962 farms (associated herd and owner) (**Figure 1A**).

According to the data available between 2013 and 2017, for the 504 farms with bTB detection, bTB was mainly detected during periodic screening (N=257, 51.0%), during meat inspection (N=115, 22.8%) and after epidemiological investigations (N=78, 15.5%). The other circumstances of detection were: reinforced screening in at-risk farms (N=47, 9.3%), interferon gamma screening (N=4, 0.8%), animal screening before farm introduction (N=2, 0.4%) and screening after clinical suspicion (N=1, 0.2%).

Eight-hundred and fifty-three herds had one bTB detection, 84 had two bTB detections, 13 herds had three bTB detections and one herd had four bTB detections. In these 98 herds with at least two bTB detections, the average time interval between two successive detections was 4.2 years (min-max: 97 days – 10.7 years). Finally, in 11 farms the owner changed between two detections.

Although bTB detection occurred in 62/94 *départements*, three geographical areas were more affected: Côte d'Or *département*, Aquitaine-North (Dordogne, Charente and Haute-Vienne *départements*) and Aquitaine-South (Pyrénées-Atlantiques and Landes *départements*) (**Figure 2A**).

The production type of case farms was suckler-fattener (N=430, 44.7%), suckler-breeder (N=134, 13.9%), dairy-fattener (N=97, 10.1%), fattener (N=91, 9.5%), other (N=63, 6.5%), very-small (N=57, 5.9%), dairy-breeder (N=40, 4.2%), mixed-fattener (N=40, 4.2%) and mixed-breeder (N=10, 1%). Most herds (685/962, 71%) belonged to the same owner since 01-01-2000 or before.

Between 2013 and 2017, after bTB detection (N=504 farms), the disease was controlled by test-and-cull protocol (N=242, 48.0%) and whole herd depopulation (N=211, 41.9%). The information was missing for 10.1% (N=51) of farms.

Control farms selection

From the 1 317 402 farms identified in the French cattle tracing system, after matching on *département*, herd type and ownership start date and after removing farms that had been inactive during the follow-up period, 54 523 farms remained for selection as control farms. For each case farm, from 1 to 1762 potential control farms were available.

Activity before bTB detection

Before bTB detection, case farms were owned less frequently by natural persons than control farms (52.1% (N=501) vs. 58.4% (N=562), p=0.002, McNemar's test) and had a higher average weekly number of cattle (median: 88.5 [2.5th – 97.5th percentile: 11.2 ; 308.3] *vs.* 62.0 [7.7 ; 268.7], p<0.001, paired Wilcoxon test) (**Table 1**).

Farm closure

A similar proportion (67.5% vs. 67.9%) of farms remained open during the follow-up period (653/962 and 650/962 for control and case farms, respectively). Among those which closed, the cause of closure was long-lasting depopulation for 42% of control farms (130/309) and 54% of case farms (169/312). According to the Cochran's Q test, bTB detection and cause of closure were not significantly associated (p=0.626) (**Table 1 & Figure 1B**). However, among the case farms, the cause of closure was significantly associated with the multiplicity of bTB detections (p<0.001, exact Fisher's test). Surprisingly 67.1% (580/864) vs. 70.9% (69/98) of farms remained open, 13.7% (118/864) vs. 23.1% (23/98) changed owner, and 19.2% (166/864) vs. 6.0% (6/98) closed due to long-lasting depopulation in farms with one or several bTB detections, respectively.

The cause of closure was also significantly ($p<0.001$, exact Fisher's test) associated with the type of control measure between 2013 and 2017, with 88.8% (215/242) vs. 79.1% (167/211) of farms remaining open, 8.3% (20/242) vs. 3.8% (8/211) changing owner, and 2.9% (7/242) vs. 17.1% (36/211) closing due to long-lasting depopulation in farms controlled by test-and-cull protocols or by whole herd depopulation, respectively.

The timing of long-lasting depopulation significantly differed between case and control farms: 10% (99/962) of case farms were depopulated within the 3 months following bTB detection *vs.* 2.1% (20/962) in the control group ($p<0.001$, McNemar's chi-squared test) (**Figure 3**). This also corresponds to 59% (99/169) and 15% (20/130) of the closures caused by long-lasting depopulation in case and control farms, respectively (**Figure 1B**). However, the type of control measure was not significantly associated ($p=0.090$, Wilcoxon test) with the timing of long-lasting depopulation (between 2013 and 2017). Before a long-lasting depopulation, some farms were subjected to short depopulation periods. Such patterns appeared more rarely in control farms (10% of farms finally closed by a long-lasting depopulation) than in case farms: after a first depopulation period (which was due to the control measures), 28% of case farms were repopulated, before permanently closing afterwards.

Besides long-lasting depopulation, 639/962 (66.4%) and 209/962 (21.7%) of case and control farms respectively have been depopulated for short period during the follow-up. The first depopulation was on average longer in case farms than in control farms ($p<0.001$).

Concerning the change of owner, 143 (14.9% of closures) events occurred in case farms *vs.* 179 (18.6% of closures) in control farms (**Table 1 & Figure 1B**).

Animals' fate after long-lasting depopulation

Before long-lasting depopulation, 10 666 animals were present in the 299 farms: 3066 animals in the 130 control farms and 7600 animals in the 169 case farms, with a range of 1 to 287 animals in each farm. Six exit causes were found: butchering, self-consumption, sale, heritage/loan, death (rendering) and unknown (**Figure 4**). The exit cause significantly differed between the control and case farms (p<0.001) with 32.8% *vs.* 64.6% of animals being butchered or used for self-consumption and 62.0% *vs.* 28.3% of animals being sold, lent or given as heritage, respectively. We also observed a greater proportion of rendered animals (3%) in case farms than in control farms (0.6%).

Cause-specific cumulative incidence of closure events

<u>Long-lasting depopulation</u>

From the Cramer-von Mises tests, we found that bTB detection and the average weekly numbers of cattle x100 had time-varying effects on long-lasting depopulation (p<0.001 for each covariate), and that the remaining variables, i.e. legal status and the possibility of test-and-cull control program had time-constant effects.

For the closures caused by long-lasting depopulation, **Figure 5** shows the cumulative coefficient for the time-varying variables, i.e. the baseline (panel A), and the effects of covariates: bTB detection (panel B) and average weekly number of cattle (panel C). At time t, the value of a cumulative coefficient can be interpreted as the cumulative hazard difference induced by a 1-unit increase of the covariate, compared to its reference level. Therefore, a value of zero indicates an absence of effect of the covariate, whereas a positive value indicates a higher risk (and a negative value, a lower risk) induced by the change of the covariate, this effect being significant if 0 is not included in the 95% confidence interval. BTB detection had a strong time-varying effect and was therefore an important predictor of closure, mainly during the first 3 months (**Figure 5B**). Indeed during this time-period, cumulative coefficient increased from 0 to 2.78 (95% CI: [2.1;3.45]), before decreasing back to baseline by 9.1 years (cumulative coefficient: 0.28 (95% CI: [-0.03; 0.60])). This suggests that the effect of bTB detection is to increase the risk of closure by ~3-fold during the first 3 months before progressively vanishing, as shown by the peak of cumulative coefficient. The average weekly number of cattle also had a time varying effect. The negative values of CRF during the follow-up (**Figure 5C**) indicates that larger farms had a lower risk of being closed. These results are confirmed by the significance test assessing whether the covariates effects was different from zero (**Table 2**).

Concerning the time-constant effects, the SHR was estimated as 1.66 [95%CI: 1.13 ; 2.44] (p=0.010) for natural person vs. other legal status. The estimated SHR was 0.414 [0.301 ; 0.569] (p<0.001) for the possibility of test-and-cull program (**Table 2**). Since the probability of events is low (<20%) over the 13 years of follow-up and considering that we used a logistic link function (Austin and Fine, 2017), we therefore meet the criteria to interpret the SHR as odds ratios. Hence, we can conclude that the odds of long-lasting depopulation is 1.66-fold higher if the owner is a natural person, and if bTB notification occurred when test-and-cull program was possible the odds of long-lasting depopulation is 0.414 times the odds of bTB notification occurred when whole-herd-depopulation was mandatory.

<u>Change of owner</u>

From the Cramer-von Mises tests, we considered that only the possibility of test-and-cull control program had a time-varying effect (p<0.001), and that the remaining variables, i.e. bTB detection, legal status and the average weekly numbers of cattle had time-constant effects.

Figure 6 suggests that after 2.5 years post bTB detection the risk of change of owner decreased for farms with bTB-detection occurring when test-and-cull program was possible comparatively to bTB detection occurring when whole-herd depopulation was mandatory. This was confirmed by the significance test (**Table 2**).

Unlike long-lasting depopulation, bTB detection decreased the odds of a change of owner (P=0.011) which in case farms was 0.704 [0.538 ; 0.922] times the odd of that in control farms, whereas the average weekly number of cattle increased the odds of a change of owner (P=0.009, SHR=1.19 [1.04 ; 1.36] for an increase of 100 heads). The legal status was not significantly associated with the change of owner (**Table 2**).

Discussion

Unlike the economic impact of bTB, which has been extensively studied at the state level (Chambers et al., 2018; Kao et al., 2018; Reviriego Gordejo and Vermeersch, 2006; Smith et al., 2013), as well as its impact on animal trade (Adkin et al., 2016; Gates et al., 2013; Little et al., 2017), the individual burden of bTB detection on farms remains largely unexplored. In a report from the Centre for Rural Policy Research, eight farmers from the South West of England were interviewed to identify the costs induced by bTB detection. In these case study farms, the monthly cost of bTB detection ranged from £500 to more than £3000, depending on the number of animals involved and on the management of the farm and of the breakdown (type of farm, number of holdings, restocking policy, marketing of livestock and livestock products) (Butler, 2010). Several types of costs or of reduction in farmers' income induced by bTB were identified. These costs may explain a higher risk of farm long-lasting depopulation after a bTB detection (Butler, 2010). Movement restriction induces additional costs due to the bedding, feeding and labor to keep the stock as well as an increased workload. Longer-term costs include paperwork, financing biosecurity measures, or postponing investment for farm development. Years of genetic selection can be lost (Skuce et al., 2012) and high-value stocks are under-compensated, inducing a restocking cost. Moreover, beside animal welfare issues during whole herd depopulation (Schiller et al., 2011), the loss of an entire herd can be traumatic for the farmer and represent a personal cost (Butler, 2010; Delmotte and Lecomte, 2013).

In this work, we assessed for the first time the effect of bTB detection on farm survival in France between 2004 and 2017. We found that bTB detection had a different effect depending on the cause of closure. Whereas it increased the long-lasting depopulation risk, bTB detection decreased the risk of a change of owner. More specifically, the long-lasting depopulation risk dramatically increased during the first three months following bTB detection. This suggests that after the culling and disinfection of the farm, the owner did not restock.

The case farms included in this study were on average larger than control farms, which is consistent with previous findings showing that farms of larger size are more at risk of bTB detection (Brooks-Pollock and Keeling, 2009; Carrique-Mas et al., 2008; Green and Cornell, 2005; Ramírez-Villaescusa et al., 2010). However, the increased odds of long-lasting depopulation for smaller case farms suggest that bTB control measures may induce, as a side effect, the closure of the most vulnerable cattle farms in the affected areas. The increased risk of long-lasting depopulation for farms owned by natural persons is also consistent with a lower ability to address risks and to build resilience conferred by local, horizontal social networks extending beyond the family circle (Naylor and Courtney, 2014). This is also in line with previous work on bTB history in France, showing how control measures induced the closure of many small farms owned by natural persons, at the beginning of the bTB eradication program, which started in 1954 and became compulsory in France in 1965. Thus, bTB eradication programs while inducing a decrease of bTB incidence in France, participated to the reshaping of the French agricultural landscape (Berdah, 2008) with an advantage for more professionalized and specialized agricultural holdings (Bekara et al., 2014).

Interestingly, we found that farms with bTB detection occurring when test-and-cull control program was possible had lower odds of long lasting depopulation, supporting the lesser burden of the test-and-cull protocols. The possibility to control bTB by test-and-cull protocol was also associated with decreasing odds of changing owner. The underlying reasons of this effect are unknown, but we can speculate that farmers buying a herd could fear starting their farming activity with undetected infected animals. We also identified that bTB detection decreased the chance of changing owner, suggesting that bad reputation due to bTB detection could limit the possibility of selling a herd.

The main limitation of our study is related to the identification of farms and their owner. Indeed, when two farms merge, the identification number of one of the two farms is preserved. All the animals from the second farm appears then as transferred to the first one and would be identified as depopulated, according to our definition. We cannot therefore differentiate a long-lasting depopulation from a fusion of two farms. Nevertheless, this reflects a major change in the farm management. Similarly, a change of the owner identification number may correspond to a sale, an inheritance or to a change of legal status, all of which cannot be distinguished (Ministère de l'agriculture, de l'agroalimentaire et de la forêt, 2014).

Here we used legal status and farm size related variables as proxies for financial health. However, other activities such as animal product processing, sale or tourist activities that can increase a farm's income could be considered. Forage (hay, straw, silage or bales) and crop production can also enhance a farm's finances by reducing the animal feeding costs (Veysset et al., 2005). Conversely, climatic risks such as drought or flooding could undermine the farm capital.

Conclusion

To conclude, bTB detection has a significant impact on farms resilience and increases long-lasting depopulation risk, while decreasing the probability for the affected farm to be sold, and change owner. The risk of long-lasting depopulation was decreased when test-and-cull control program was possible suggesting an improvement in control management with the introduction of these protocols instead of systematic whole herd depopulation and a habituation to the epidemic situation.

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Tables' legend

Table 1. Comparison of baseline characteristics of case farms (with bTB detection) and control farm (without bTB detection). P-values were computed as paired Wilcoxon test for continuous variables and McNemar's chi-squared test for 2-categories covariates, Cochran q test for >2-categories covariates.

Table 2. Semi-parametric additive competing risk models estimates for change of owner and long-lasting depopulation (> 12 months). 95% CI stands for 95% confidence interval; SHR stands for subdistribution hazard ratio and is computed only for covariates with non-significant constant effect test. When the test for constant effect is significant (Cramer-von Mises test), the non-parametric effect of the covariate is tested for significance but not estimated as noted by "-". Ref stands for reference level. * average weekly numbers: mean of weekly count of every cattle of the studied category during the year preceding the bTB detection (or corresponding time for the matched control farm).

Figures' legend

Figure 1. Flow diagram for farms inclusion (A) and flow diagram of the farms' fate according to group (case vs. control) (B).

Figure 2. Number of bTB detection (A), average weekly number of cattle in case (B) and control (C) farms and percentage of case farms (D) and control farms (E) owned by a natural person, at the département level. For all panels, in grey: départements not included in the analysis due to the lack of bTB detection. Thick line: six départements with the highest prevalence (North East: Côte-d'Or (yellow), Center West: Aquitaine-North (purple) and South West: Aquitaine-South (magenta)).

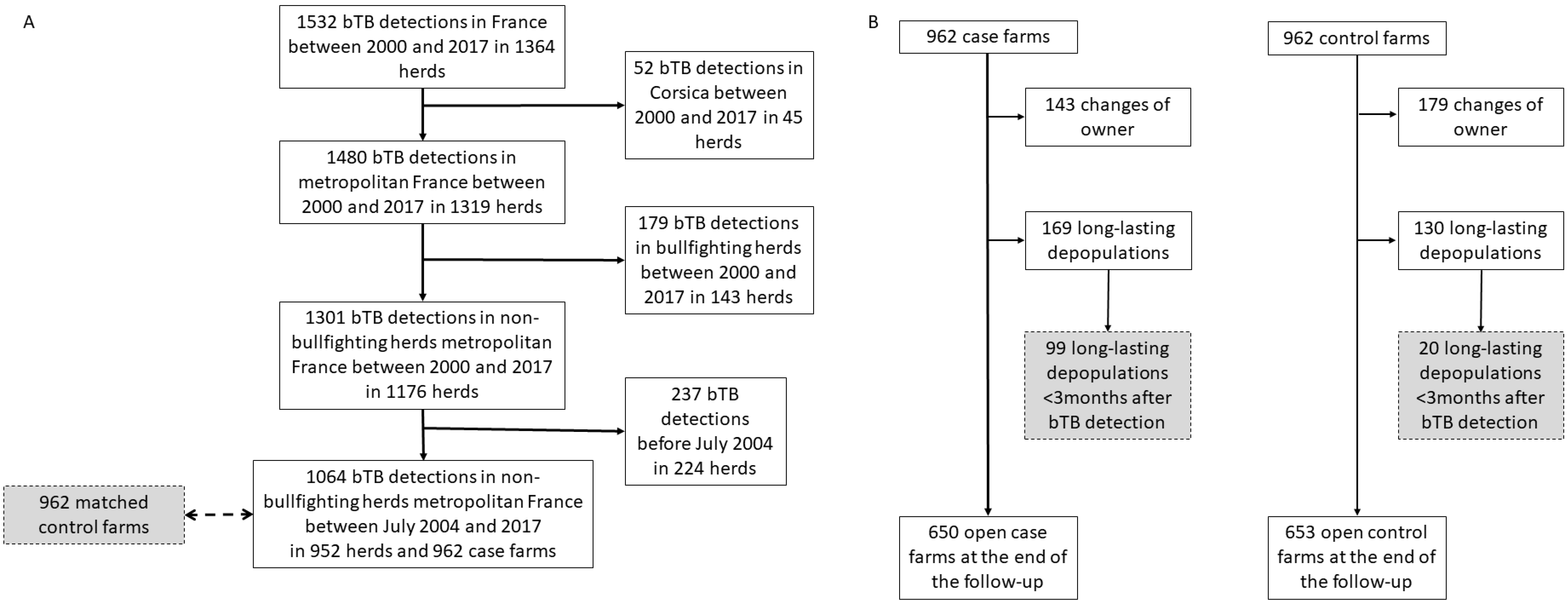
Figure 3. Closure cause-specific cumulative incidence functions for case farms (blue) and control farms (yellow) for competing causes of closure: Change of owner (A) and long-lasting depopulation

(B). The blue and yellow intervals show the 95% confidence interval for the two causes of closure. The grey vertical line is set at 3 months.

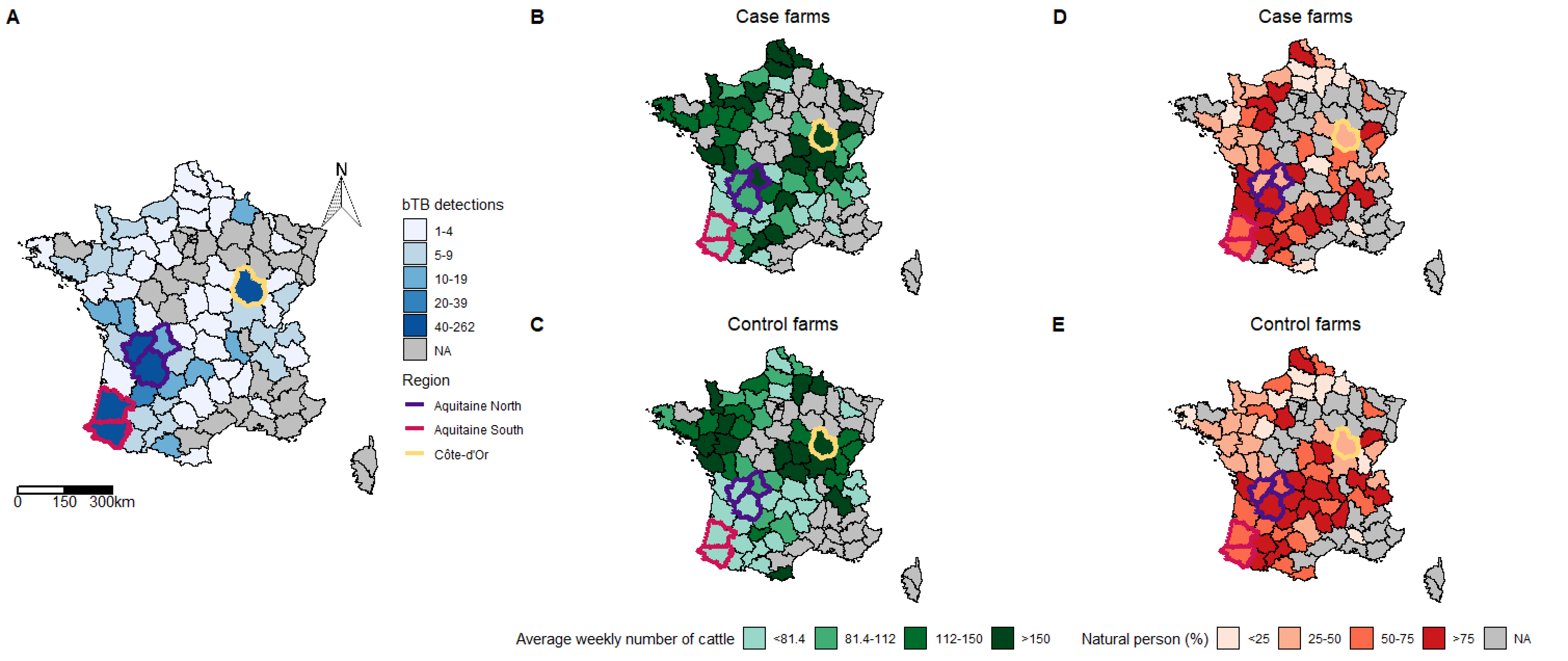
Figure 4. Exit cause of animals at time of closure when cause is long-lasting depopulation in case farms (blue) and in control farms (yellow). The number above the bar shows the corresponding percentage.

Figure 5. Cumulative additive effect for closure by long-lasting depopulation, based on semi-parametric model (or additive-multiplicative**;** additive part: bTB detection, average weekly number of cattle; multiplicative part: region and legal status). Solid black line: cumulative regression curve; dashed lines: 95% confidence interval; horizontal solid grey line: cumulative coefficient = 0. Vertical grey line: 90 days

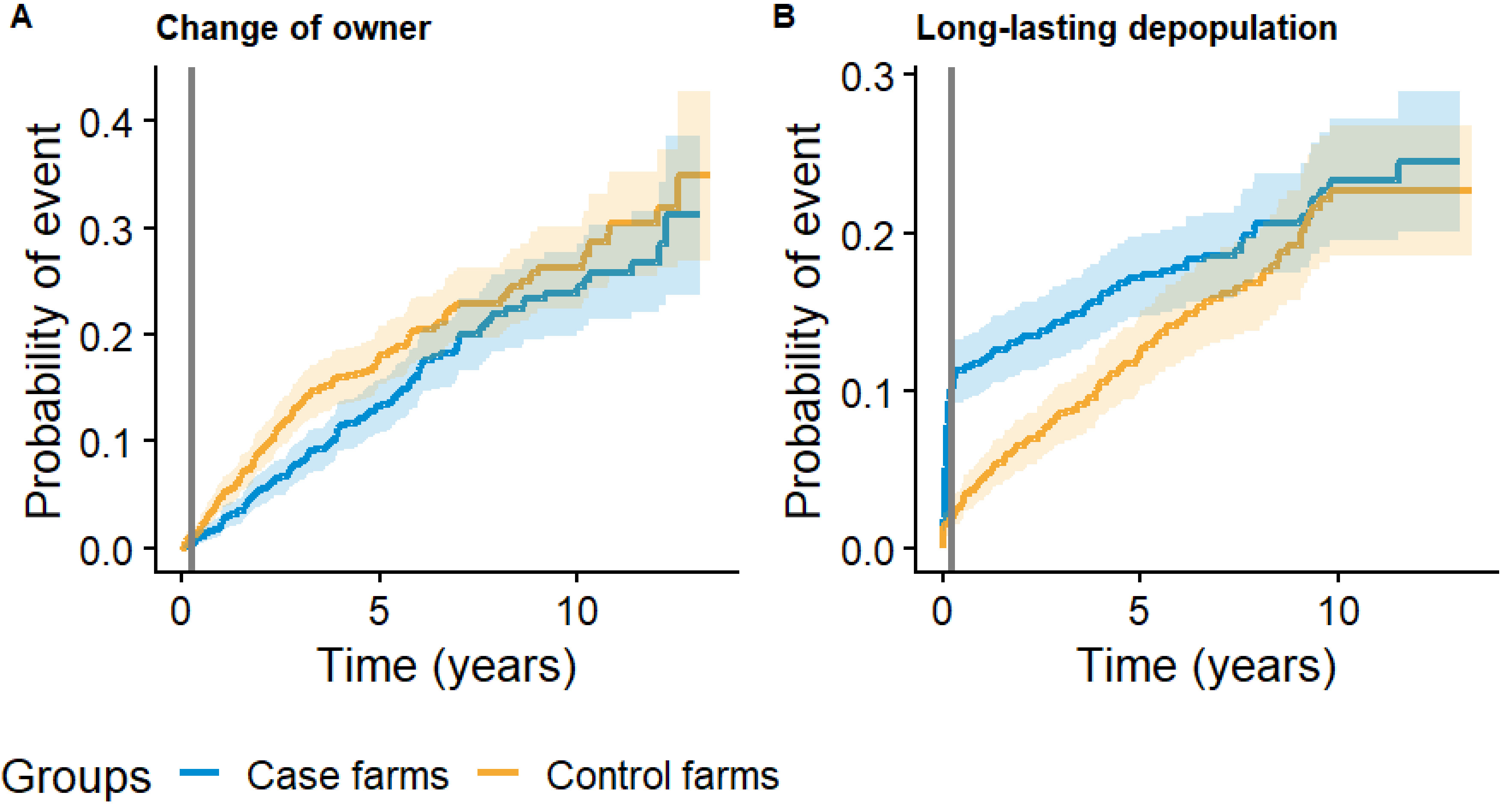
Figure 6. Cumulative additive effect for closure by change of owner based on semi-parametric model (or additive-multiplicative**;** additive part: region; multiplicative part: bTB detection, legal status, average weekly number of cattle). Solid black line: cumulative regression curve; dashed lines: 95% confidence interval; horizontal solid grey line: cumulative coefficient=0. Vertical grey line: 90 days.



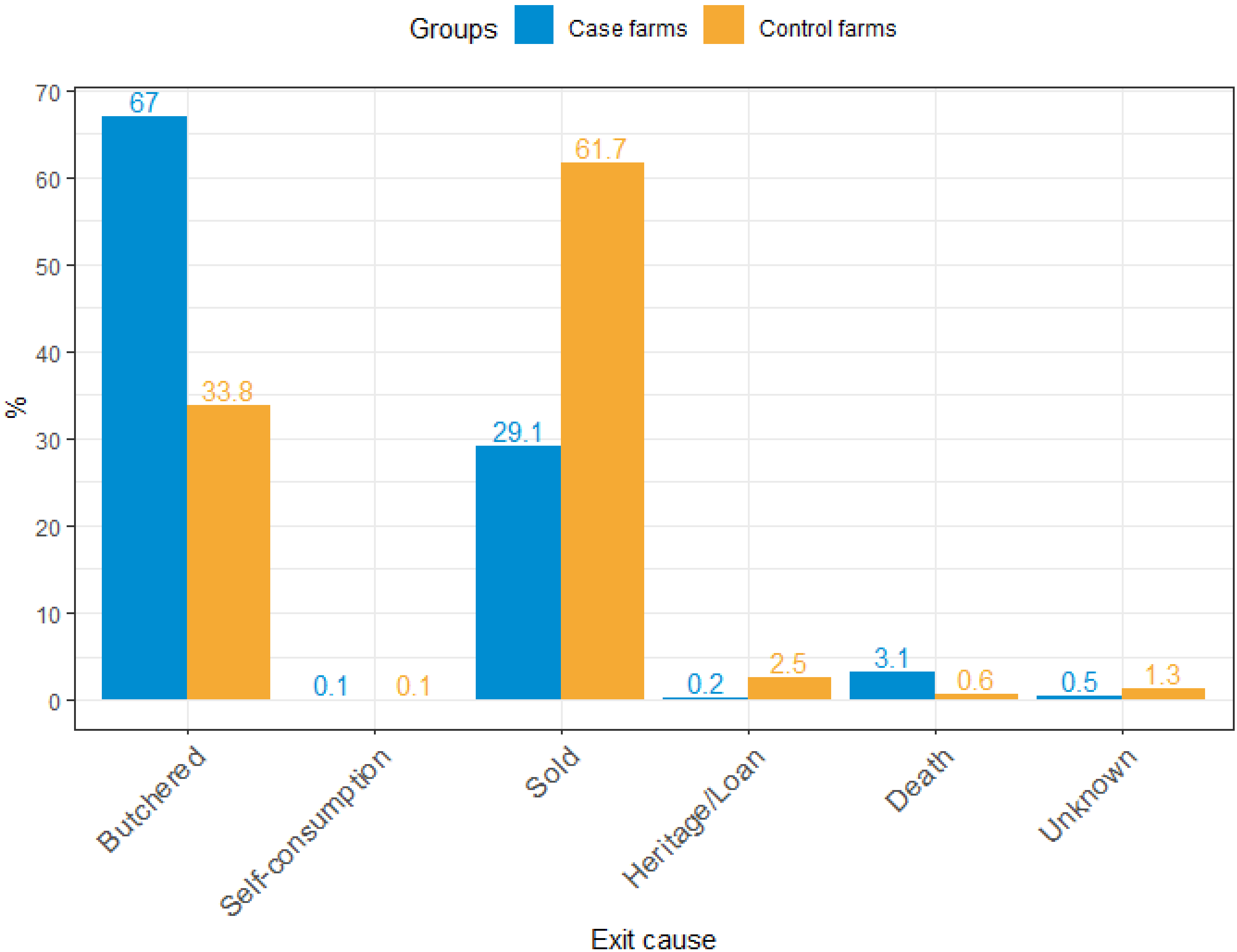
A
1532 bTB detections in France between 2000 and 2017 in 1364 herds
52 bTB detections in Corsica between 2000 and 2017 in 45 herds
1480 bTB detections in metropolitan France between 2000 and 2017 in 1319 herds
179 bTB detections in bullfighting herds between 2000 and 2017 in 143 herds
1301 bTB detections in non-bullfighting herds metropolitan France between 2000 and 2017 in 1176 herds
237 bTB detections before July 2004 in 224 herds
1064 bTB detections in non-bullfighting herds metropolitan France between July 2004 and 2017 in 952 herds and 962 case farms
962 matched control farms
B
962 case farms
143 changes of owner
169 long-lasting depopulations
99 long-lasting depopulations <3months after bTB detection
650 open case farms at the end of the follow-up
962 control farms
179 changes of owner
130 long-lasting depopulations
20 long-lasting depopulations <3months after bTB detection
653 open control farms at the end of the follow-up

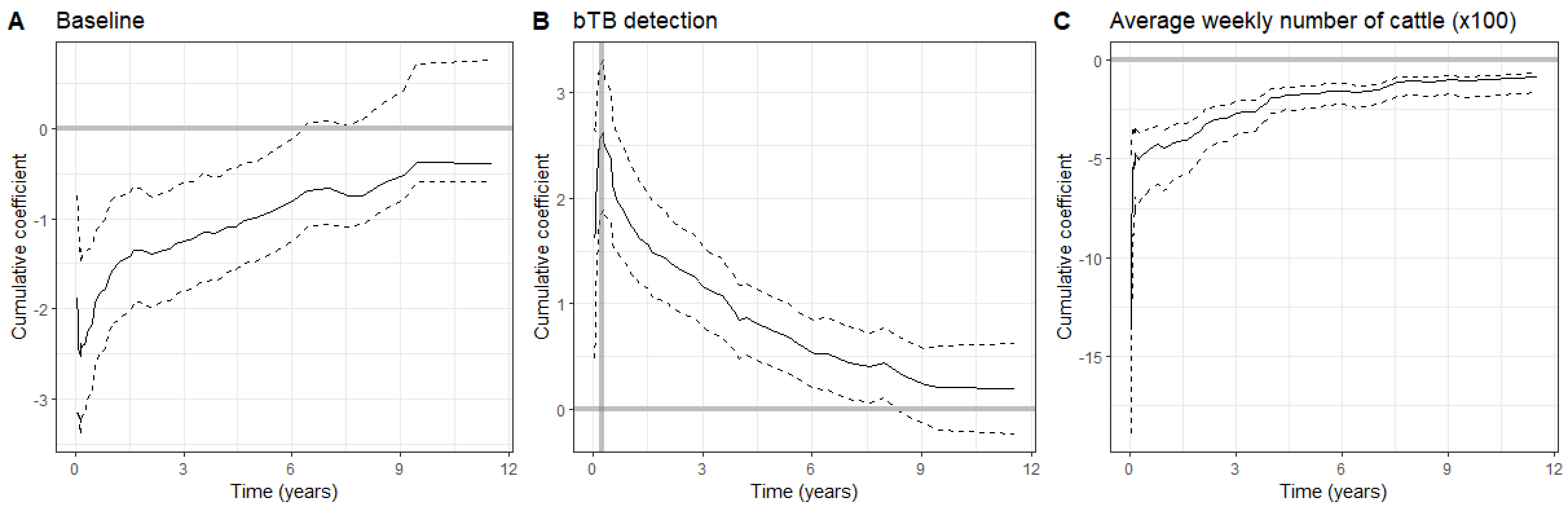


A
bTB detections
1-4
5-9
10-19
20-39
40-262
NA
Region
Aquitaine North
Aquitaine South
Côte-d'Or
N
0
150
300km
B
Case farms
C
Control farms
D
Case farms
E
Control farms
Average weekly number of cattle
<81.4
81.4-112
112-150
>150
Natural person (%)
<25
25-50
50-75
>75
NA



A
Change of owner
Probability of event
0.0
0.1
0.2
0.3
0.4
0
5
10
Time (years)
B
Long-lasting depopulation
Probability of event
0.0
0.1
0.2
0.3
0
5
10
Time (years)
Groups
Case farms
Control farms


Groups
Case farms
Control farms
70
60
50
40
30
20
10
0
%
67
33.8
0.1
0.1
29.1
61.7
0.2
2.5
3.1
0.6
0.5
1.3
Butchered
Self-consumption
Sold
Heritage/Loan
Death
Unknown
Exit cause



A
Baseline
B
bTB detection
C
Average weekly number of cattle (x100)
Cumulative coefficient
Time (years)
0
3
6
9
12
-3
-2
-1
0
1
2
3
-5
-10
-15

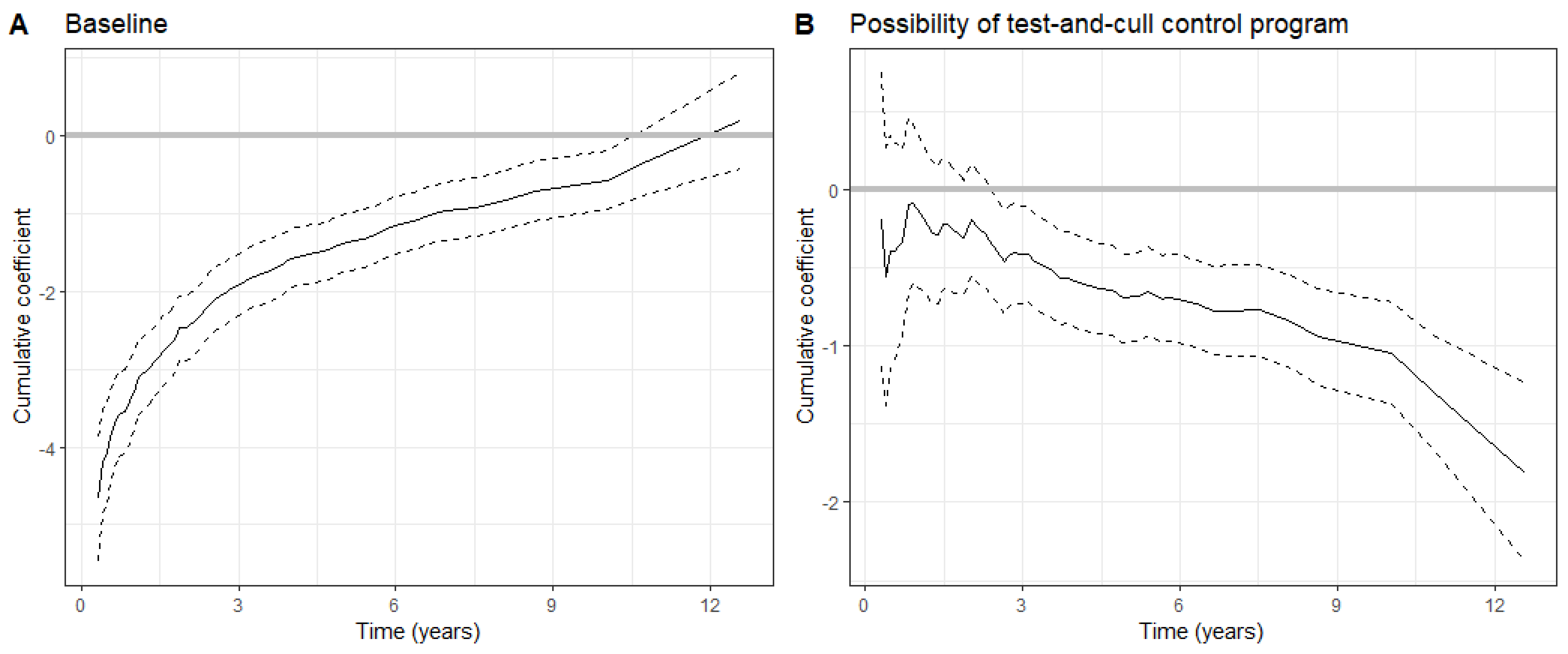

A
Baseline
Cumulative coefficient
0
-2
-4
0
3
6
9
12
Time (years)
B
Possibility of test-and-cull control program
Cumulative coefficient
0
-1
-2
0
3
6
9
12
Time (years)

Table 1. Comparison of baseline characteristics of case farms (with bTB detection) and control farm (without bTB detection). P-values were computed using paired Wilcoxon test for continuous variables, McNemar's chi-squared test for 2-categories covariates, Cochran's Q test for >2-categories covariates.

variable		**Case farms N=962**	**Control farms N=962**	**p-value**
Owner's legal status - Natural person: N (%)		501 (52.1%)	562 (58.4%)	0.002
Average number of cattle /week: median [2.5^{th} ; 97.5^{th} percentile]		88.5 [11.2;308.3]	62.0 [7.7;268.7]	<0.001
First closure event: N (%)	Long-lasting depopulation (> 12 months)	169 (17.6%)	130 (13.5%)	0.626
	Owner change	143 (14.9%)	179 (18.6%)	
	No change	650 (67.5%)	653 (67.9%)	

Table 2. Semi-parametric additive competing risk models estimates for the risk of farm closure caused by a change of owner and by a long-lasting depopulation (> 12 months). 95% CI stands for 95% confidence interval; SHR stands for subdistribution hazard ratio and is computed only for covariates with non-significant constant effect test. When the test for constant effect is significant (Cramer von Mises test), the non-parametric effect of the covariate is tested for significance but not estimated as noted by "-". Ref stands for reference level. * average weekly number of cattle: mean of weekly count of every cattle during the year preceding the bTB detection (or corresponding time for the matched control farm). Use of a test-and-cull control program became possible in 2014 or in 2008 in *départements* Dordogne (in Aquitaine North) and Côte-d'Or

Covariate	**Semi-parametric model SHR [95% CI] (p)**	
	Long-lasting depopulation (>12 months)	**Owner change**
Intercept	- (0.002)	- (<0.001)
bTB detection (ref : No)	- (<0.001)	0.704 [0.538 ; 0.922] (0.011)
Legal status: natural person (ref: legal person)	1.66[1.13 ; 2.44] (0.010)	1.07 [0.785 ; 1. 45] (0.677)
Average weekly number of cattle (x100)*	- (0.002)	1.19 [1.04 ; 1.36] (0.009)
Possibility of test-and-cull control program (ref: No)	0.414 [0.301 ; 0.569] (<0.001)	- (<0.001)