

ORIGINAL ARTICLE

Detection of a local *Mycobacterium bovis* reservoir using cattle surveillance data

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Abstract

The incidence of bovine tuberculosis (TB, caused by *Mycobacterium bovis*) in cattle has been associated with TB in badgers (*Meles meles*) in parts of England. The aim was to identify badger-associated *M. bovis* reservoirs in the Edge Area, between the High- and Low-Risk Areas for cattle TB. Data from badger TB surveys were sparse. Therefore, a definition for a local *M. bovis* reservoir potentially shared by cattle and badgers was developed using cattle TB surveillance data. The performance of the definition was estimated through Latent Class Analysis using badger TB survey data. Spatial units (25 km²) in the Edge Area were classified as having a reservoir if they had (i) at least one TB incident in at least three of the previous 7 years, (ii) at least one TB incident in a cattle herd confirmed by post-mortem tests as due to *M. bovis* infection and not attributable to cattle movements in the previous 2 years and (iii) more confirmed TB incidents than un-confirmed in the previous 2 years. Approximately 20% of the Edge Area was classified as having a local *M. bovis* reservoir using the cattle-based definition. Assuming 15% TB prevalence in Edge Area badgers, sensitivity for the local *M. bovis* reservoir definition varied from 25.7% [95% credible interval (CrI): 10.7%–85.1%] to 64.8% (95% CrI: 48.1%–88.0%). Specificity was 91.9% (CrI: 83.6%–97.4%). Over 90% of the local reservoir was in stable endemic TB areas identified through previous work and its spatial distribution was largely consistent with local veterinary knowledge. Uncertainty in the reservoir spatial distribution was explored through its recalculation in spatial units shifted in different directions. We recommend that the definition is re-evaluated as further data on badger infection with *M. bovis* become available.

KEYWORDS

cattle, disease reservoirs, latent class analysis, Mustelidae, *Mycobacterium bovis*

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1 | INTRODUCTION

Bovine tuberculosis (TB) caused by *Mycobacterium bovis* is a persistent insidious disease of cattle to which many other animals including man are susceptible (O'Reilly & Daborn, 1995). The costs for the control and eradication of TB to the farming industry and society are considerable (Bennett & Cooke, 2006; Defra, 2020; Godfray et al., 2018; More et al., 2015). Once endemic within a cattle population, TB is difficult to eradicate. This can be due to limitations in diagnostic tests and cattle surveillance. However, the presence of a local wildlife host can make a disease particularly intractable. Important wildlife hosts for *M. bovis* include the European badger (*Meles meles*) in the United Kingdom, Ireland and France, wild boar in Spain, white-tailed deer (*Odocoileus virginianus*) in Michigan USA, the brushtail possum (*Trichosurus vulpecula*) in New Zealand and prior to 1997, feral pigs (*Sus scrofa*) in Australia (Aranaz et al., 2004; Bourne et al. 2007; Goodchild et al., 2012; More et al., 2015; Nugent et al., 2015; Ní Bhuachalla et al., 2015; VerCauteren et al., 2018). Cattle are an acknowledged reservoir for *M. bovis*. The extent to which infection control in wildlife can affect TB in cattle varies according to factors affecting between-species transmission and the propensity for the wildlife to maintain a *M. bovis* reservoir. In Australia, feral pigs were found to be a spillover or dead-end host but not a reservoir (More et al., 2015). By contrast, the brush-tailed possum and white-tailed deer have been shown to be self-sustaining reservoirs for *M. bovis* and sources for TB incidents in cattle (Nugent et al., 2015; VerCauteren et al., 2018).

In England, the majority of evidence that the badger is a wildlife host for *M. bovis* comes from the south-west, although infected badgers have also been detected in the north (Bourne et al. 2007; Delahay et al., 2000, 2001; Rossi et al., 2021). In Woodchester Park in south-west England, the prevalence of TB in badgers monitored within a 15 km² area increased from 5% to over 30% between 1982 and 2005 (Delahay et al., 2013). Studies of this population and others show persistence of TB in badger social groups and evidence for infection transmission between badgers and cattle (Benton et al., 2016; Goodchild et al., 2012; McDonald et al., 2018; Weber et al., 2013; Woodroffe et al., 2005). In these situations, cattle and badgers meet the criteria for epidemiologically connected populations maintaining a joint reservoir for *M. bovis* (Haydon et al., 2002). A recent genetic study confirmed transmission of TB between cattle and badgers in Woodchester Park and also showed that the majority of infected badgers in the population examined had acquired infection from other badgers (Crispell et al., 2019). This suggests that there are situations where badgers act as a reservoir, transmitting TB between themselves and spreading the disease to cattle.

England is divided into three risk areas for TB (Figure S1): the High-Risk Area (HRA) characterized by high TB incidence, frequent testing of cattle and extensive wildlife controls (mainly badger culling but also localized badger vaccination); the Low-Risk Area (LRA) with low TB incidence, less frequent testing of cattle and fewer wildlife TB controls; and the Edge Area characterized by highly variable levels of TB in cattle and local variations in disease controls. Cattle TB incidence is generally much higher along the Edge Area's western border with the HRA than along its eastern border with the LRA. For example county-level

TB incidence rates in 2019 were more than six times higher in Oxfordshire [23.8 TB incidents per 100 Herd Years at Risk (HYR)], which borders the HRA than in Nottinghamshire (3.4 TB incidents per 100 HYR), which borders the LRA (APHA, 2020a). UK Government policy in the Edge Area has focused on enhanced cattle controls to prevent the establishment of new areas of infection and spread of TB into the LRA (Defra, 2014). For example routine field surveillance of cattle for TB using the comparative tuberculin skin test has increased from annually to 6 monthly in counties with higher TB incidence rates (APHA, 2019a).

There are also increased controls for TB in the Edge Area where a positive TB test result is confirmed by an additional post-mortem test, for example where a positive tuberculin skin test has been confirmed by observation of lesions typical of *M. bovis* infection during slaughterhouse inspection and/or the bacterium has been isolated. Confirmed incidents are referred to as Officially Tuberculosis Freedom Withdrawn (OTF-W) incidents (ANON, 1964). Unconfirmed incidents, referred to as Officially Tuberculosis Freedom Suspended (OTF-S) incidents, occur where at least one animal in a cattle herd is positive to a TB test but there is no confirmatory post-mortem test result. An example of increased controls in OTF-W incidents is the application of the interferon gamma blood test in addition (in parallel) with tuberculin tests to remove infection.

In 2015, the Animal and Plant Health Agency (APHA) developed a model to measure the spread and retraction of endemic TB in cattle across the Edge Area (Ashton et al., 2015; Brunton et al., 2015). This has shown retraction in some areas of the Edge Area and spread in others but no generalized retraction over time. The overall incidence rate for TB in cattle in the Edge Area was 9.9 TB incidents per 100 HYR in 2019 and 9.1 in 2018 (APHA 2020a).

Surveys of badger populations within England suggest that the density of badgers in the Edge Area is highly variable. Based on broad land class types, badger density is estimated to range from 1 to 6 km² (Judge et al., 2014; 2017) (Figure 1). In some areas, badger densities are comparable with densities in south-west England (HRA) and are considered likely to be sufficient for between-badger infection transmission (G. Smith and A. Robertson personal communication, 2 July 2020). Although data from badgers are relatively sparse, TB confirmed by post-mortem tests has been detected in badgers from the Edge Area (Bennett, 2018; Palgrave & Chambers 2018; Sandoval Barron et al., 2018).

The independent review of the UK Government's strategy for eradicating TB and achieving OTF status for England concluded that it was unclear what drives the spread of TB in the Edge Area (Godfray et al 2018). The review recommended research leading to a better understanding of the prevalence of TB in badgers. The aim of this study was to develop criteria, using currently available data, for defining areas with a *M. bovis* reservoir associated with badgers within the Edge Area for TB in England.

2 | MATERIALS AND METHODS

A Working Group was established, which included three veterinary epidemiologists (two of which worked in the field), two analytical

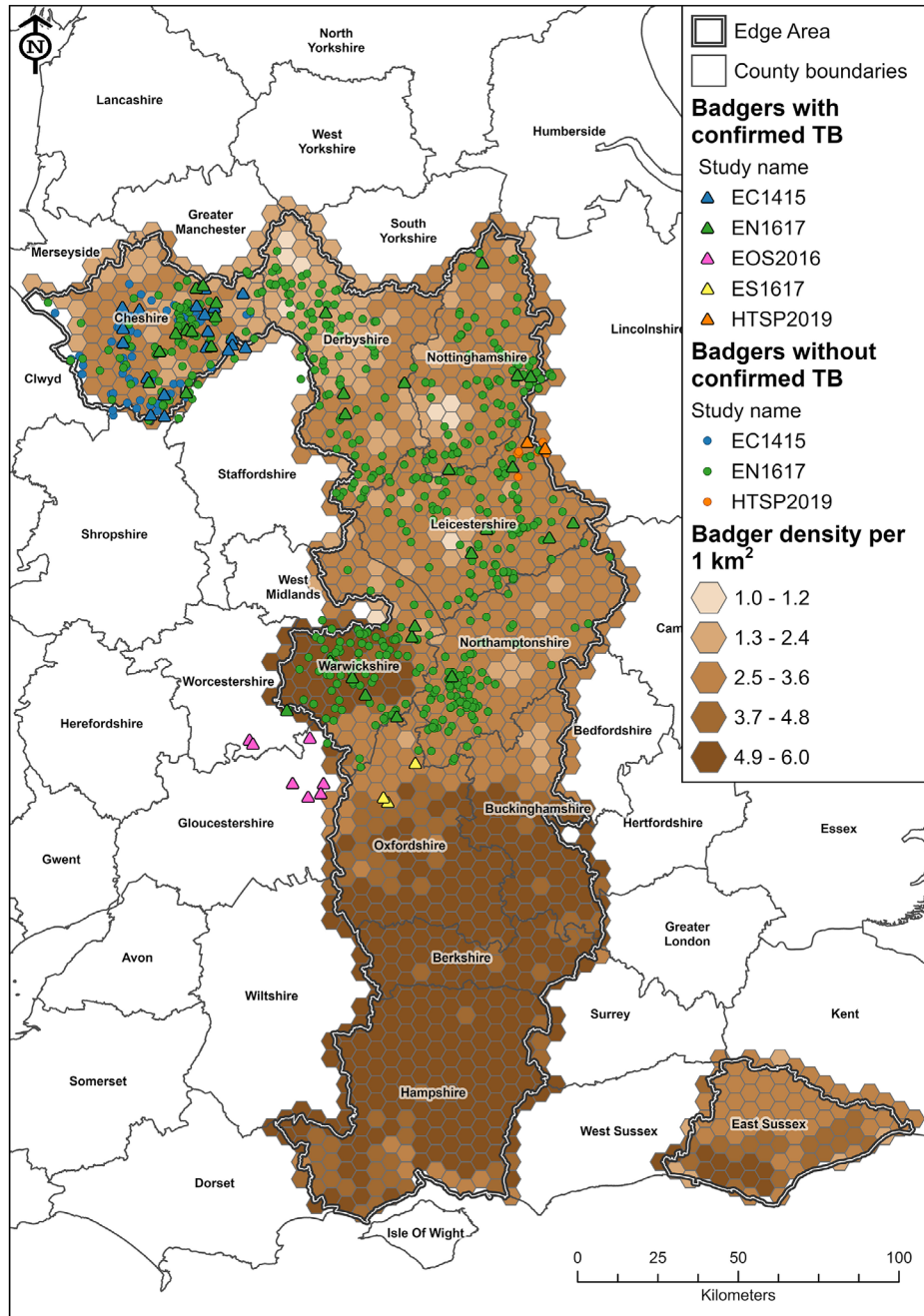


FIGURE 1 Badger density in the Edge Area and locations of samples from badgers with TB confirmed by post-mortem tests or no confirmed TB detected in different surveys. Badger samples from the border area in England are also shown. The border area extends up to 14 km beyond the Edge Area boundary. Its precise width is dependent upon where hexagonal spatial units crossing the Edge Area boundary are bisected.

epidemiologists, a TB database analyst, a GIS analyst, two statistical modellers and a wildlife ecologist. An iterative discursive approach was taken in the development of the definition of a *M. bovis* reservoir associated with badgers in the Edge Area starting with a review of existing data sources with potentially relevant information.

During the development of the reservoir definition, data were mapped as points and/or summarized and mapped on grids of 25-, 50- or 100-km² hexagonal spatial units to enable between-area comparisons. We also explored how to represent uncertainty in the reservoir definition.

2.1 | Data

Potentially relevant data sources identified included:

- Ad hoc surveys for *M. bovis* infection in badgers such as badgers found dead after road traffic accidents;
- *M. bovis* genotype data from infected cattle and badgers in the Edge Area;
- Test results from surveillance for TB in cattle recorded on the APHA TB management system;

TABLE 1 Samples from badger TB surveys within and bordering the Edge Area

Survey	Year	Negative for TB	Confirmed positive for TB
North (EN1617) Bennett, 2018	2016/2017	569	33
South (ES1617) Palgrave & Chambers, 2018	2016/2017	0 ^a	3
Cheshire (EC1415) Sandoval Barron et al., 2018	2014/2015	74	20
HRA border (EOS2016) ^b	2016	0 ^c	8
Hotspot Leicester (HTSP 2019)	2019	9	2

Note: All the included surveys used culture to grow colonies of MTBC (*Mycobacterium tuberculosis* complex), and confirmation of *M. bovis* was achieved through spoligotyping (genotyping by spacer oligonucleotide patterns).

^bSamples from badgers obtained from licensed culling.

^a90 and ^c84 samples were excluded because of reported degradation of the samples.

All samples were from within the Edge Area and border areas within England (Figure 1). The border area extended up to 14 km beyond the Edge Area boundary. Its precise width was dependent upon where hexagonal spatial units crossing the Edge Area boundary are bisected.

- Information recorded on Disease Report Forms (DRFs) by APHA veterinarians during investigation and management of TB incidents in cattle herds.

2.1.1 | Ad hoc surveys for *M. bovis* infection in badgers

Six surveys of infected badgers conducted between 2014 and 2019 were identified with potentially relevant data from the Edge Area or land in England bordering the Edge Area (Table 1). The sampling methodology in the surveys was primarily opportunist collection of badgers, for example, found dead due to road traffic accidents. None of the surveys covered the entire Edge Area. Procedures for handling collected badgers and sample processing varied between studies. To improve accuracy, the following data were excluded from our analysis:

1. Studies where detection of *M. bovis* had not been confirmed by isolation of the bacterium and genotyping or spoligotyping;
2. Samples found to be negative for *M. bovis* where the survey methodology had led to sample degradation, which reduces sensitivity.

2.1.2 | *Mycobacterium bovis* genotype data from infected cattle and badgers

We reviewed maps of the Edge Area with *M. bovis* genotypes from cattle with TB grouped by inferred whole genome sequence (WGS) clade. Where WGS data existed, the spatial distributions of *M. bovis* isolates

from cattle were also viewed at different scales of genetic relatedness based on single-nucleotide polymorphisms (SNPs). Genetic data from *M. bovis* isolates from badgers could be classified into WGS clades inferred from their spoligotype and variable number tandem repeat type and mapped. However, the badger data could not be analyzed using SNP data because these data did not exist. WGS of *M. bovis* isolates was not routinely conducted at APHA prior to 2017 and virtually all the badger data were from earlier studies.

2.1.3 | Test results from surveillance for TB in cattle

Characteristics that could be derived from cattle TB surveillance data and were likely to be indicative of a *M. bovis* reservoir were investigated. Discussions focussed on the following:

- Evidence for persistent and/or recurrent TB in cattle herds in an area over several years;
- Evidence that TB incidents in cattle herds in an area were unlikely to be due to infection brought in by cattle movement;
- Evidence for a predominance of TB incidents in cattle herds in an area that had been confirmed by post-mortem tests such as detection of macroscopic lesions typical of TB during slaughterhouse inspection or isolation of the *M. bovis* bacterium, that is more OTF-W incidents than OTF-S.

Cattle TB data were summarized to hexagonal spatial units within and bordering the Edge Area (Figure 2). We recognized that differences in the numbers of cattle and herds within a spatial unit would be associated with differences in definition accuracy. However, we wanted to ensure that the level of aggregation did not obscure clusters of infection that could indicate discrete reservoirs (Blangiardo et al., 2020). The 100-km² spatial unit was considered too large and we focused on the resolution provided by 25- and 50-km² hexagonal spatial units. Badger dispersal distances were also considered and these supported the selection of the smaller spatial unit in our analyses (Table S1).

Evidence for persistence of TB in cattle in an area

Evidence for persistence of TB in an area was measured from 2013, which was when annual TB testing for TB in cattle herds was introduced into all counties in the Edge Area. The influence of testing frequency, herd size and incident duration on incident detection in an area was considered. The sum of years when at least one TB incident (OTF-W or OTF-S) had occurred was counted in each 25-km² spatial unit over a 7-year period (2013–2019). The count was limited to one TB incident per spatial unit per year to reduce possible bias due to differences in TB testing frequency, for example the introduction of 6-monthly routine surveillance testing in six Edge Area counties between 2015 and 2018.

Evidence that cattle TB incidents were not due to cattle movement

DRFs are completed by APHA veterinarians during TB incidents in the Edge Area for case management and to gather epidemiological information (APHA, 2019a). DRFs include an assessment of the level of

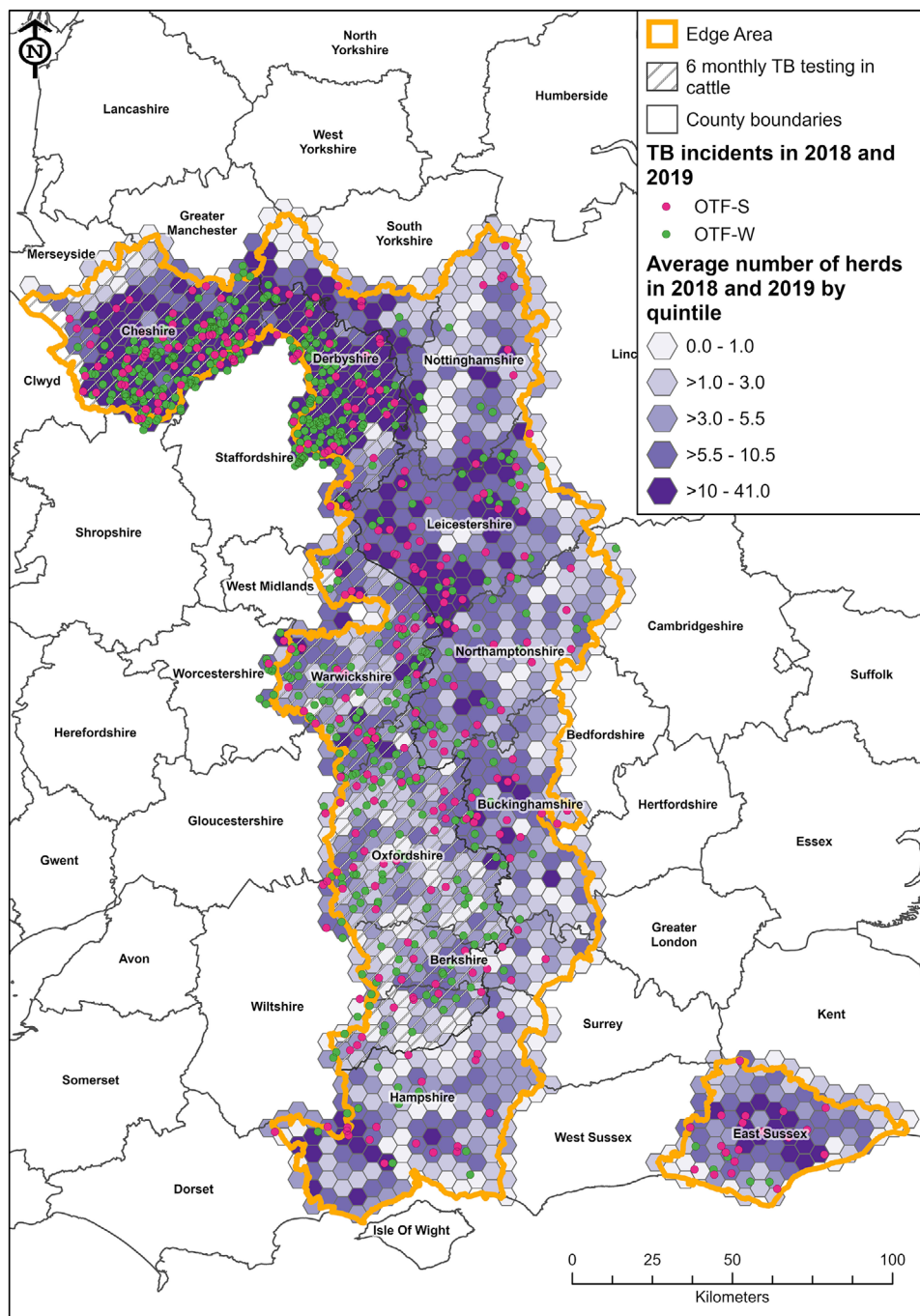


FIGURE 2 Herd density in 25-km² hexagonal spatial units in the Edge Area and TB (OTF-W and OTF-S) incidents in cattle in 2018 and 2019

evidence for different infection sources and transmission (risk) pathways. Evidence that the risk pathway is via cattle movement relies on surveillance records of cattle movements. Genetic evidence of the *M. bovis* genotype in the source and receiving herd is also incorporated where available. The information goes through an auditing procedure annually and the proportion of an incident attributable to different risk pathways is calculated and reported in annual reports (APHA, 2020a). TB incidents in the Edge Area where the DRF data showed that the risk attributed to cattle movement was $\geq 75\%$ were classified as not attributable to a local reservoir for this analysis.

Evidence for a predominance of confirmed TB incidents in cattle

The field veterinary epidemiologists reported that seeding of new infection into cattle herds in an area was often initially characterized by detection of cattle with inconclusive tuberculin skin test results and OTF-S incidents (T. Roberts and S. Frost, personal communication, 15 January 2020). These were followed in time by increased detection of OTF-W incidents, suggestive of an emerging reservoir with wildlife involvement, rather than cattle-mediated pathways. It was also noted that culling in the Randomized Badger Culling Trial (RBCT) was associated with a reduction in OTF-W incidents but not OTF-S

(Donnelly et al., 2007). This evidence together suggested that OTF-W incidents were more closely associated with the presence of infected wildlife than OTF-S. We concluded that evidence for recent predominance of OTF-W over OTF-S incidents would be supportive of a contemporary *M. bovis* reservoir.

2.2 | Evaluation of a *M. bovis* reservoir based on cattle TB data (the cattle-based definition)

The cattle-based definition for a *M. bovis* reservoir was evaluated in three ways:

1. The sensitivity and specificity of the definition were calculated through Latent Class Analysis (LCA) comparing the spatial distribution of the reservoir in the Edge Area to data from badger TB surveys.
2. The spatial distribution of the reservoir in the Edge Area was compared to the distribution of areas classified as having endemic TB using the APHA TB Spread Model (Ashton et al., 2015; Brunton et al., 2015).
3. The spatial distribution of the reservoir in the Edge Area was evaluated using local veterinary knowledge.

2.2.1 | LCA to calculate the performance of the cattle-based definition

Using a Bayesian approach, areas classified as positive or negative for a reservoir according to the cattle-based definition were compared to areas classified as positive or negative according to the *ad hoc* surveys of infection in dead badgers. An area was positive if it had at least one infected badger recorded and negative if all badgers surveyed within it were negative. The approach depended on priors specified for unknown parameters (sensitivities/specificities and prevalence of cells with a reservoir of infection). However, for the present study there was no strong view on the expected value of the unknown parameters, and so uninformative priors were used—uniform distributions represented by beta distributions with both parameters equal to 1 (more detail is provided in the Supporting Information).

The assessment of the sensitivity of the cattle-based definition took account of the sensitivity of post-mortem detection of *M. bovis* infection in badgers and the number of badger samples (Figure 3). Evaluation of the specificity was more problematic because of an absence of empirical data showing the relationship between detecting a negative badger and all badgers in an area being negative for TB. There was agreement that the detection of an infected badger was strong evidence for TB within the local badger population, but not necessarily that TB was endemic in that population. The precise estimate for specificity for a local reservoir was therefore model determined. LCA was conducted for scenarios for high (30%), medium (15%) and low (7.5%) *M. bovis* prevalence in badgers. These were based on published estimates of TB prevalence in badgers anticipated in the Edge Area (Bourne et al. 2007; Delahay et al., 2013; Sandoval Barron et al., 2018).

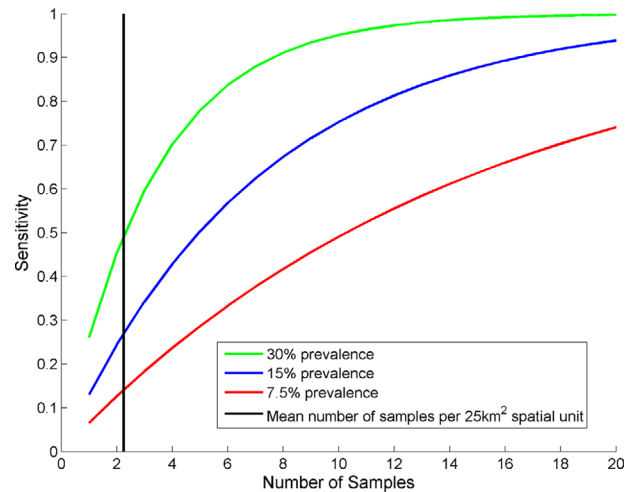


FIGURE 3 The estimated sensitivity for the detection of a local *M. bovis* reservoir in 25-km² hexagonal spatial units by number of samples for three levels of badger infection prevalence, assuming random mixing and random sampling

The Edge Area was partitioned into six areas that we estimated as having different risks for a *M. bovis* reservoir (Table 2). The performance of the cattle-based definition was estimated separately for these areas and for different TB prevalence to accommodate heterogeneity.

2.2.2 | Comparison of areas classified as having a reservoir using the cattle-based definition to areas classified as having endemic TB using the TB spread algorithm

A previously developed method for measuring spatial spread and retraction of TB classifies a cattle farm with TB, as being in an area with endemic TB if it is located within 7 km of the third nearest OTF-W incident within a 2-year time period (Ashton et al., 2015; Brunton et al., 2015). To improve specificity, we modified this algorithm for the current study by excluding TB incidents where the incident had been predominantly attributed to cattle movement based on DRF information. Edge Area classified as endemic using the spatial spread definition was compared to areas classified as having a *M. bovis* reservoir using the cattle-based definition.

2.2.3 | Evaluation of the cattle-based definition using local veterinary knowledge

Working group veterinary field epidemiologists (S. Frost and T. Roberts) with detailed knowledge of the disease situation in the Edge Area were asked to make a qualitative assessment of the validity of the local reservoir location using large-scale (1:100,000) maps.

APHA veterinarians have developed a detailed picture of the location of reservoirs of infection in the Edge Area (APHA, 2020b). A range of data sources including DRFs have been used to inform local knowledge. For example since mid-2017, the WGS data have provided more

TABLE 2 Edge Area and border categories for a *M. bovis* infection reservoir in badgers

Area category	Description	Rationale
1	Cheshire	Higher prevalence of <i>M. bovis</i> infection in badgers anticipated. Cattle in most of the county were subject to 6-monthly TB surveillance testing since 2015. The county has had more surveys for <i>M. bovis</i> infection in found dead badgers than any other county in the Edge.
2	Six monthly TB testing areas minus Cheshire (Warwickshire, Oxfordshire, part of Berkshire, part of Hampshire and part of Derbyshire).	Higher prevalence of <i>M. bovis</i> infection in badgers anticipated. Cattle in these areas were subject to 6-monthly TB surveillance testing since 2018.
3	HRA border abutting the western boundary of the Edge Area. This area starts from the south-coast and ends with a northern boundary to Clwyd.	Higher prevalence of <i>M. bovis</i> infection in badgers anticipated. Endemic infection in cattle and badgers probable. Cattle in these areas were subject to annual TB surveillance testing up to September 2020.
4	East Sussex and north east Edge Area counties including part of Derbyshire, Nottinghamshire, Leicestershire and Northamptonshire.	The distribution of a <i>M. bovis</i> infection reservoir is thought to be heterogeneous in these counties. All cattle herds were subject to annual TB surveillance testing.
5	Edge Area counties of Buckinghamshire, part of Berkshire and part of Hampshire.	The prevalence of <i>M. bovis</i> infection in badgers is thought likely to be similar and low in these counties. Cattle herds were subject to annual TB surveillance testing.
6	LRA border to the east and north of the Edge Area from the south coast ending at the northern border with Clwyd in Wales.	Lower levels of <i>M. bovis</i> infection in cattle and anticipated in badgers. Cattle in these areas were subject to 4 yearly testing.

Note: Data for spatial units were assigned to the area category that contained the greatest proportion of their land, for example data for a spatial unit with 51% of land in Area Category 1 and 49% of land in the Area Category 2 would be assigned to Area Category 1. Areas are within the Edge Area and border areas within England. The border area extends up to 14 km beyond the Edge Area boundary. Its precise width is dependent upon where hexagonal spatial units crossing the Edge Area boundary are bisected.

robust evidence for local wildlife reservoirs where there has been high genetic relatedness between isolates in local geographical areas, and cattle movements and contiguous contact between herds have been ruled out as methods of local infection spread. Confirmation of TB in small numbers of isolates from camelids, pigs, goats and zoo collections as well as wild deer and badger isolates has complemented and supported the local picture over time. For example in the Edge Area during 2019, there were three cases in cats, all in different counties, one case in alpacas and one wild fallow deer (APHA, 2020b). Except for two of the cat isolates, genetic information for the rest matched local cattle isolates suggesting local sources for infection.

2.2.4 | Uncertainty

To account for possible wildlife spread from the identified reservoir, the addition of a buffer around areas defined as having a *M. bovis* reservoir was considered.

Possible bias due to spatial heterogeneity was explored with the presence or absence of a reservoir recalculated for spatial units shifted in cardinal and inter-cardinal directions. A slight shift in position of an individual spatial unit could change the herds within a spatial unit's boundaries and therefore the outcome of the reservoir definition for that locality. The shape of the unit was also considered with both hexagons and circles evaluated.

A final map showing the location of the reservoir was generated that provided an indication of levels of uncertainty due to spatial unit location. The presence or absence of a local reservoir using the cattle-based

definition was calculated for circular 25-km² spatial units on a regular grid with the centroids 2 km apart. This was then re-calculated for the spatial unit shifted 2 km in four directions.

3 | RESULTS

There were insufficient TB data from badgers and/or WGS data from badgers to develop a definition for a reservoir based on badger data. Therefore, a definition for a *M. bovis* reservoir was developed using cattle TB surveillance data. This definition is hereafter referred to as a 'local reservoir' and identifies areas where there is a potential localized reservoir in cattle and/or badgers.

Genetic data from TB infected cattle, although considerably more abundant than for badgers, were insufficient to develop a model that would identify incidents due to local reservoirs in the Edge Area, potentially shared by badgers, as opposed to common sources from cattle that had moved into the area. Infected badgers and cattle shared the same inferred WGS clades in some areas of the Edge Area but not all. However, a clade can include isolates that differ by as much as 50 SNPs and clades could not be used to define localized areas of transmission.

3.1 | A cattle-based definition for a local reservoir of *M. bovis* infection

An area was classified as having a local *M. bovis* reservoir if it met all of the following criteria:

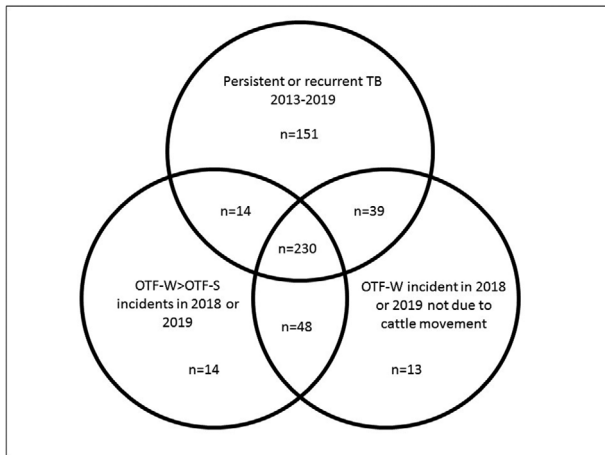


FIGURE 4 Venn diagram of 25-km² hexagonal spatial units within the Edge Area that fulfilled at least one criterion for a local *M. bovis* reservoir. TB = OTF-W and/or OTF-S incidents. Counts include hexagonal spatial units entirely within the Edge Area or touching the border of the Edge Area and in England. The spatial distribution of the 230 hexagons that fulfilled the three criteria for a reservoir within the Edge Area are shown in Figure 5.

1. At least one TB incident (OTF-S or OTF-W) in a cattle herd in at least three of the previous 7 years (2013–2019);
2. At least one confirmed (OTF-W) incident in a cattle herd not attributed to cattle movements in the previous 2 years (2018 or 2019).
3. More confirmed (OTF-W) incidents than unconfirmed (OTF-S) incidents in cattle herds in the previous 2 years (2018 or 2019).

Approximately 20% (230/1177) of the 25-km² hexagonal spatial units in the Edge Area were classified as having a local *M. bovis* reservoir using the cattle-based definition (Figures 4 and 5; APHA, 2021). More spatial units were classified as having a local reservoir in the western part of the Edge Area than in the east. A small number of spatial units were classified as having a local reservoir in Leicestershire and East Sussex and isolated locations elsewhere. Applying the same definition to 50-km² spatial units showed a similar spatial distribution of putative local reservoirs for *M. bovis* infection (Figure S2).

Spatial units with more cattle herds were statistically significantly more likely to be classified as having a local *M. bovis* reservoir. For example 25-km² hexagonal spatial units classified as having a local reservoir had a median of nine [interquartile range (IQR) = 5–18] cattle herds in 2018 and 2019, whereas spatial units without a reservoir had a median of four (IQR = 2–8). The median number of cattle herds per 25- and 50-km² hexagons for 2018 and 2019 were seven (IQR = 4–12) and 12 (IQR = 8–20), respectively (detail provided in Tables S3a and S3b).

A buffer of one hexagonal spatial unit was added to the putative boundary of local reservoirs to account for uncertainty in the boundary and potential additional TB spread due to ranging by badgers (Figure 5). This increased the percentage of Edge Area associated with a local reservoir (324/1177 25-km² spatial units).

3.2 | Results from assessments of the performance of the cattle-based definition

3.2.1 | LCA comparing the cattle-based definition to the badger TB survey data

The sensitivity of the cattle-based definition generally increased with the estimated badger TB prevalence. The sensitivity estimates were most often highest for Cheshire (area category 1) and the 6-monthly testing areas other than Cheshire (area category 2), slightly lower for the HRA border (area category 3) and lowest for north-east counties and East Sussex (area category 4) (Table 2). The definition could not be evaluated in the group of similar southern Edge Area counties (area category 5) and the LRA because there were none or too few badger TB data available.

The specificity estimate for the cattle-based definition in the LCA was highest for a 15% badger TB prevalence, but lower than the specificity of the badger data (Table 3). Specificity was lowest for badger TB prevalence of 7.5%. Similar trends were observed in an LCA applied to 50-km² spatial units (results not shown).

3.2.2 | Comparison of the reservoir defined by the cattle-based definition to areas with endemic TB defined using the TB spread algorithm

There was extensive overlap between areas defined as having a local *M. bovis* reservoir using the cattle-based definition, and areas defined as having endemic TB using the algorithm for calculating TB spread (Figure S3). Ninety-one per cent (209/230) of spatial units in the Edge Area that were classified as having a local reservoir were located within areas defined as having endemic TB using the spread model.

Table 4 shows the percentage of spatial units classified as positive within and bordering the Edge area using the cattle-based definition, the badger TB survey data and the TB spread model. Overall, the TB spread model classified a higher proportion of spatial units as positive according to its definition than the other methods according to theirs, with the badger TB survey data classifying the lowest proportion. The proportion of positive badger TB survey spatial units was greatest in areas 1 and 3, whereas it classified far fewer positive spatial units than the cattle-based definition in area 2.

3.2.3 | Evaluation of the cattle-based definition using local veterinary knowledge

The working group field veterinary epidemiologists found that there was overall a good match between areas classified as having a local *M. bovis* reservoir based on the cattle definition and the areas currently assessed locally by APHA veterinarians as having endemic infection in badgers (detail provided in the Supporting Information). In Cheshire, for example, the map of the local reservoir agreed very well with local expert knowledge. Additionally, the map showed two areas of reservoir (in the north-east and north-west), which had been highlighted by

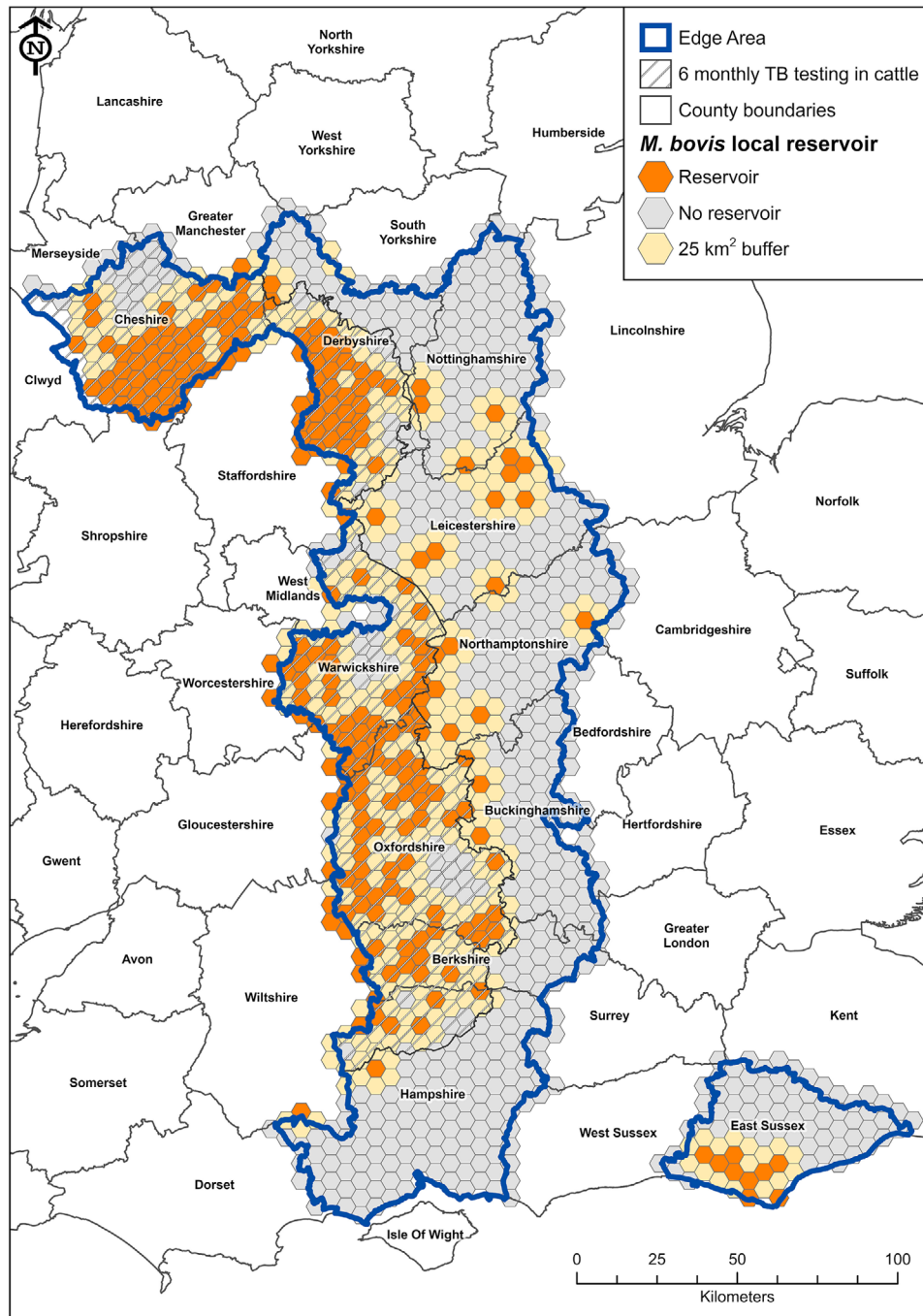


FIGURE 5 Original map of local reservoir of *Mycobacterium bovis* with buffer across 25-km² hexagonal spatial units in the Edge Area

veterinary field epidemiologists as likely areas of emerging endemicity and of increased risk of infection spread to the neighbouring LRA. There were some inconsistencies. The map of a local associated reservoir of infection in Derbyshire agreed in part with local knowledge. There were areas, for example, from Buxton in the north to Swadlincote in the south considered to have emerging endemicity not covered by the local reservoir defined using the cattle-based definition. There was a spatial unit that contains a large water body (Carsington Water), which was not classified as having a reservoir of infection but where local knowledge indicates a strong suspicion of established endemicity.

3.3 | Uncertainty

The final map shows the presence or absence of a local reservoir for circular 25-km² spatial units 2 km apart (Figure 6). Each grid point was overlapped by five circular 25-km² spatial units. The highest certainty for a local reservoir at a grid point was when all five of its circular spatial units were classified as having a reservoir. The lowest level was when only one spatial unit at a grid point was classified as having a reservoir. A buffer 2.8 km in width was also applied to the new boundary of the reservoir to incorporate potential additional TB spread by badgers.

TABLE 3 Latent Class Analysis estimates for the performance of the cattle-based definition for a local *Mycobacterium bovis* reservoir in 25-km² hexagonal spatial units

Parameter	Area category	Assumed mean badger infection prevalence		
		7.5%	15%	30%
Se_c	1. Cheshire	73.6 (50.2, 98)	64.8 (48.1, 88)	71.3 (55.5, 89.4)
Se_c	2. Six-monthly testing areas minus Cheshire	42.9 (36.2, 57.1)	63.0 (42.5, 94.4)	74.8 (56.6, 94.5)
Se_c	3. HRA border	76.6 (50.8, 98.7)	54.9 (41.6, 94.5)	51.7 (41.2, 76.9)
Se_c	4. Edge northeast & East Sussex	7.8 (5.1, 11.2)	25.7 (10.7, 85.1)	30.7 (14.3, 84.6)
Sp_c	All	60.2 (33.3, 86.9)	91.9 (83.6, 97.4)	88.9 (81.7, 94.7)
Sp_b	All	64.5 (36.3, 85.6)	94.1 (87.6, 99.5)	96.5 (90.6, 99.8)
π_1	1. Cheshire	55.8 (33.6, 87.2)	78.3 (54.5, 97.7)	67.4 (50.1, 85.4)
π_2	2. Six-monthly testing areas minus Cheshire	90.5 (65.8, 99.5)	61.4 (39.8, 91.5)	50.4 (38, 66.6)
π_3	3. HRA border	55.7 (40.6, 82.9)	80.1 (45.7, 99.1)	85.0 (56.7, 99.2)
π_4	4. Edge northeast & East Sussex	95.4 (73.4, 99.8)	23 (6.7, 49.6)	17.3 (6.1, 31.1)

Note: Se_c = Sensitivity of the cattle-based definition. Sp_c = Specificity of the cattle-based definition. Sp_b = Specificity of the badger TB data. π = TB prevalence. 95% credible intervals are reported beneath central estimates. From a two-test LCA model including the cattle-based definition and badger TB test data. Sensitivity is the percentage of spatial units classified as having a reservoir using the badger TB survey data that were classified as having a local reservoir. Specificity is the percentage of spatial units classified as not having a reservoir using badger TB survey data that were negative for a local reservoir using the cattle-based definition. Data for hexagonal spatial units were assigned to the area that contained the greatest proportion of their land. Further detail is in the Supporting Information.

The width (2.8 km) was narrower than the buffer on the original map (5.6–6.2 km) (Figure 5). This was because some of the uncertainty in the boundary to the reservoir had been addressed in the final map. The area of the local reservoir had been extended through its recalculation across shifted spatial units.

Comparison of the spatial distribution of the local *M. bovis* reservoir in the original map to the reservoir regenerated by the different shifts in the final map showed small differences in its spatial distribution and a very high degree of overlap (Figure S4). The new reservoir boundaries were for the most part within the external boundary to the buffer to the reservoir on the original map. However, some isolated spatial units were classified as having a local reservoir in the final map that was not detected in the original map. Generally, the fit between local knowledge and the spatial distribution of the reservoir was improved with the final map (Figure 6) compared to the original map (Figure 5) (see Supporting Information). However, none of the new areas classified as having a reservoir incorporated a grid point with five levels of evidence.

4 | DISCUSSION

A definition for a local *M. bovis* reservoir has been developed using cattle TB surveillance data. It identified areas likely to have a reservoir associated with cattle that may be shared with other epidemiologically

connected populations. Eradication of disease is challenging where there is evidence for substantial infection in wildlife and transmission between wildlife and domesticated animals (Livingstone et al., 2015). A robust definition requires comprehensive and accurate test data from susceptible populations and environmental sources with transmission supported by molecular genetic evidence from pathogen isolates. However, obtaining such data over large areas, particularly from wildlife, can be extremely difficult and expensive. This work shows that a definition can be developed that may have practical value in absence of comprehensive data from wildlife.

The findings indicate that local reservoirs for *M. bovis* are found in some parts of the Edge Area for TB in England but not throughout the entire area. Haydon and colleagues proposed that a disease reservoir can exist in one or more epidemiologically connected populations or environments where a pathogen can be permanently maintained and transmitted to other populations (Haydon et al., 2002). Our definition is dependent on cattle TB surveillance data being a reliable sentinel for infection in badgers. We assumed that locations with higher levels of TB in cattle are more likely to have infection present in badgers than areas with little or no TB in cattle. There is considerable evidence of transmission between cattle and badgers (Woodroffe et al., 2005; Goodchild et al., 2012; Weber et al., 2013; Benton et al., 2016; McDonald et al., 2018; Crispell et al. 2019; Rossi et al. 2021) and cattle have

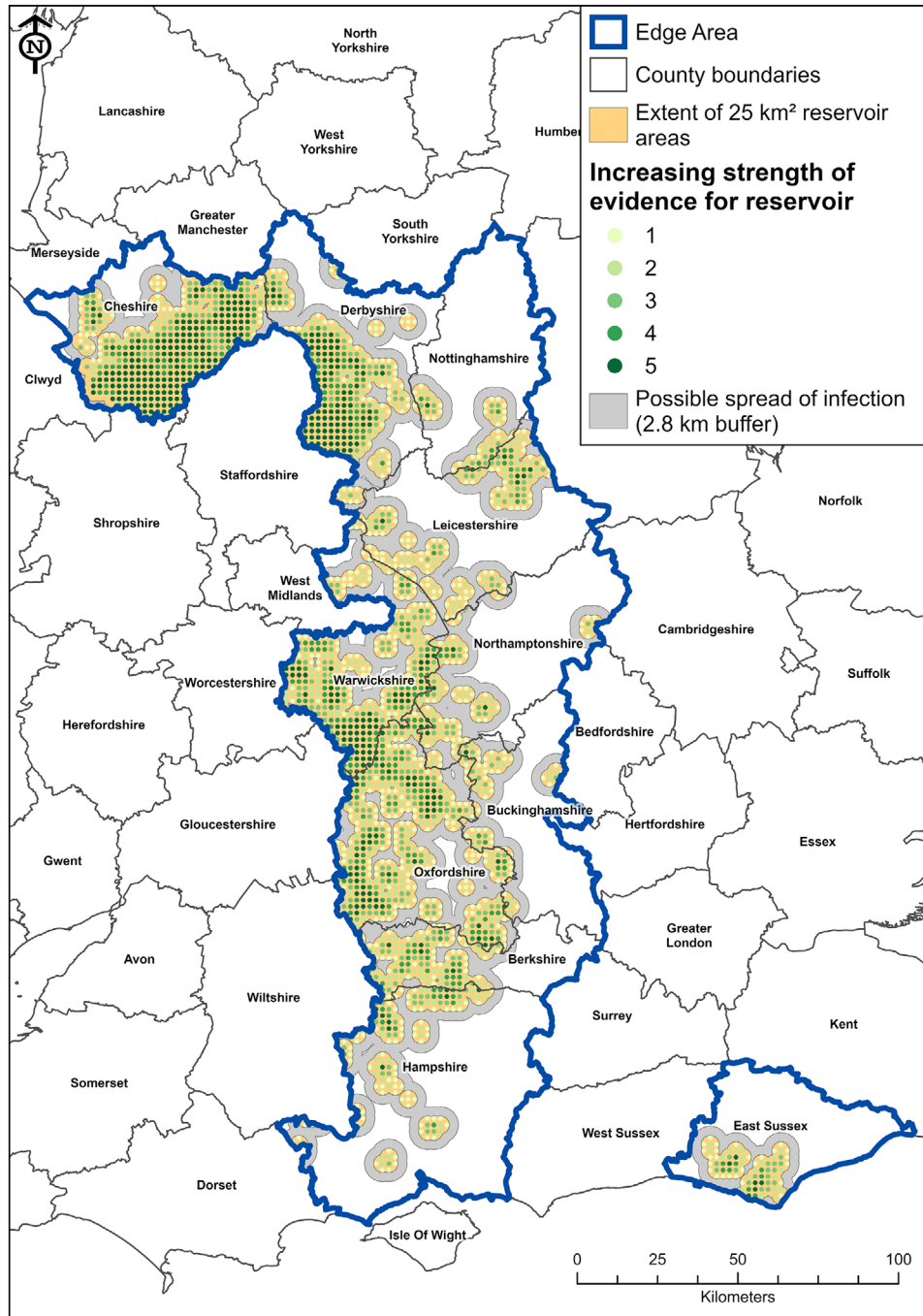


FIGURE 6 Final map showing a local reservoir of *Mycobacterium bovis* infection in the Edge Area using the cattle-based definition with buffer. The depth of colour indicates the number of times (up to a maximum of five) a grid point was within 25-km² circular spatial units defined as having a local reservoir using the cattle-based definition. Spatial units have centroids 2 km apart

been proposed as reliable sentinels for TB in badgers elsewhere (Murphy et al., 2011). A study in New Zealand used TB surveillance data from cattle to estimate the probability of freedom from *M. bovis* infection in the brushtail possum (Anderson et al., 2017).

The first criterion for a local reservoir was evidence for repeated TB incidents in local cattle in an area over a period of 7 years indicating persistent infection. The threshold of 'a TB incident in at least three of the 7 years' was applied to reduce bias due to differences in testing

frequency. Assuming the median duration of TB incidents in the Edge Area in 2019 [197 days (IQR = 168–278)], there would be on average at least four field testing occasions in different years when a new incident could be detected through annual surveillance. Controlling for the influence of herd size was considered. However, this could operate by both increasing the frequency of new incidents because TB is more likely to be detected in larger herds and also decreasing the frequency of the detection of new incidents because persistent incidents

TABLE 4 Number of 25-km² spatial units with a local *Mycobacterium bovis* reservoir, at least one badger with confirmed TB and with endemic TB in the Edge Area and border

Area category	Number of hexagonal spatial units positive in an area (% of spatial units positive in an area)		
	Cattle-based definition	Badger TB survey	TB spread model
1. Cheshire	51 (52.3)	19 (32.8)	74 (76.3)
2. Six-monthly testing areas minus Cheshire	122 (39.7)	12 (13.5)	240 (78.2)
3. West Border (HRA)	109 (46.4)	8 (42.1)	179 (76.5)
4. North-eastern counties and East Sussex	31 (7.8)	12 (7.8)	69 (17.4)
5. Other Southern counties/part counties	4 (1.8)	0 (0)	23 (10.3)
6. North and East Border (LRA)	3 (0.8)	0 (0)	7 (1.8)

Note: Positive indicates a 25-km² hexagonal spatial unit classified as having a local *M. bovis* reservoir, with at least one badger with confirmed TB or classified as having endemic TB according to the cattle-based definition, badger TB survey data or the TB spread model, respectively. Denominators differ. Both the cattle-based definition and the TB spread model were calculated using cattle TB surveillance data throughout the Edge Area and border (extending up to 14 km from the boundary of the Edge Area) in England and including a total of 1645 hexagonal spatial units. Badger TB survey data were from five surveys conducted in different parts of the Edge Area and data from badgers were available for a total of 323 hexagonal spatial units (Table 1 and Figure 1).

(lasting 18 months or more) are more common in larger herds (APHA, 2020a).

The second criterion required evidence of recent TB incidents in an area that were unlikely to be due to cattle moving into the area. This relied on data collected by veterinary field epidemiologists during DRF risk pathway assessments. These assessments incorporate information from farm surveys, cattle movement records and *M. bovis* genotype data, where available. Pathways are given a score reflecting the level of evidence and certainty in the pathway. In this study, we only used audited DRF data produced for annual TB Epidemiology reports. However, at the time of the audit some TB incidents were still ongoing and provisional risk pathways can be revised by the end of an incident. This will have introduced a misclassification bias, which is difficult to eliminate where DRF data from recent TB incidents are required and some incidents will be ongoing.

The third criterion was a predominance of OTF-W (confirmed by post-mortem TB tests) incidents over OTF-S (unconfirmed). Seventy-five per cent of spatial units in the Edge Area with more OTF-W incidents than OTF-S were classified as having a reservoir. The positive predictive value of TB tests will increase as background TB prevalence increases. Anecdotal evidence from veterinarians working in TB control suggested an increase in the OTF-W/OTF-S ratio as infection becomes established in the local wildlife. However, the criterion could also relate solely to increased transmission and residual infection within local cattle herds, particularly large herds.

The performance of the local *M. bovis* reservoir definition was assessed using LCA. The LCA methodology was adapted from previously published models (Branscum et al., 2005) to allow for the sensitivity of the badger TB data to detect infection in badgers to vary between 25-km² spatial units according to the number of badgers sampled. The disadvantage of this approach was that it requires an estimate of the infection prevalence in spatial units where there were limited data. The model itself could be used to infer the sensitivity of the badger TB data and the mean infection prevalence in badgers by including them as unknown parameters, but this would result in too many unknown parameters.

Local reservoir specificity of the cattle-based definition was estimated in the LCA to be over 90%, but sensitivity estimates varied widely. The lack of contemporary badger TB data may have reduced the reliability. Assuming 15% TB prevalence within badgers in the Edge Area, sensitivity for the local *M. bovis* reservoir varied from 25.7% [95% credible interval (CrI): 10.7%–85.1%] to 64.1% (95% CrI: 48.1%–88.0%). Specificity was 91.9% (CrI: 83.6%–97.4%). Sensitivity estimates from Cheshire were probably most reliable because more badger surveys had been conducted in this county than any other and cattle herds are found in most parts of the county. Central estimates for the sensitivity of the cattle-based definition in Cheshire ranged from 64.8% to 73.6%.

The power of the badger data was limited by the low number of samples obtained through opportunist surveys, especially in some areas. This meant that we were unable to infer infection prevalence from the data but rather had to look at scenarios with assumed badger infection prevalence. The low prevalence scenario may be inappropriate for some areas. For example the mean sensitivity of badger data (assuming an infection prevalence of 7.5%) in badgers is around 14% (Table 3), whereas for area 1 (Cheshire) 33% of the badger samples were positive (Table 4). The model reconciles this by assuming many of the badger-positive 25-km² spatial units in Cheshire are false positives, which also results in a low specificity estimate for the cattle definition in this scenario (Table 3). Given that Cheshire is an area with high cattle density, it might be expected to be one of the better performing areas for the cattle definition, suggesting that the low prevalence assumption is not appropriate for this area.

The distribution of areas defined as having a local reservoir in this analysis and areas defined as having stable endemic TB using a model for TB spread algorithm overlapped. This was unsurprising because both models used cattle TB data (Brunton et al., 2015; Ashton et al., 2015). However, the distribution of the local reservoir showed more spatial heterogeneity than the distribution of the endemic areas and covered less of the Edge Area. The TB spread model took account of distance between incidents, whereas distance was not explicitly included in the cattle-based definition for a local reservoir, although incidents were summarized to a spatial unit.

The distribution of the local reservoir was reviewed by veterinary epidemiologists with local knowledge. Although developed over a long period of time, local knowledge is still essentially cattle based. As with the cattle-based definition, where cattle density is low, uncertainties in local knowledge are higher. The certainty associated with emerging

areas of local reservoir is generally lower than for older established areas. However, experience indicates that such areas generally continue to develop and expand with time and as more data are collected, this has supported earlier indications of local reservoirs.

Our aim was to select as small a spatial unit as reasonably possible to increase our ability to detect local variations (Malleon et al., 2019; Blangiardo et al., 2020). If the spatial unit had been too large and within-area variability substantial, our results could suffer from false-negative observations as areas with a reservoir are aggregated with areas without a reservoir. However, a spatial unit that is too small increases uncertainty where data are sparse and more liable to misclassification biases, for example the geo-coordinates of farms may be imprecise indicators for the location of cattle herds. By shifting the centroids to the spatial unit and recalculating the definition for presence or absence of a reservoir, we increased the geographical area (and therefore the information) associated with any grid point whilst also showing where the data were most consistent. Areas defined as having a local reservoir were shown in five levels relating to the consistency of evidence (the number of times) that an area was classified as having a local reservoir. A 2.8-km-wide buffer was also added around the local reservoir border to indicate the range of possible TB spread from the reservoir. A straight-line distance of 2.8 km encompasses approximately two badger social group territories in the LRA (G.C. Smith, personal communication, 11 March 2021).

The cattle-based definition is likely to be a less precise predictor for local *M. bovis* reservoirs where there are few or no cattle herds, despite the addition of a buffer to take account of infection transmission in the absence of cattle. The definition is likely to be more sensitive to local reservoirs maintained jointly between cattle and badgers and less sensitive to reservoirs maintained independently of cattle. However, there are contradicting views regarding whether badgers can be an independent *M. bovis* reservoir (Godfray et al., 2018; Ni Bhauchalla et al., 2015).

Our cattle-based definition may also indicate joint local reservoirs between cattle, other livestock and wildlife other than badgers. Both wild deer and boar infected with TB have been detected in England and Wales (Delahey et al., 2007; Foyle et al., 2010). Boars are rarely sighted and research suggests that deer are less important than badgers for TB in cattle, and are more likely to be reservoir hosts in areas of high deer density (Ward et al., 2009; Ward & Smith 2012). Related strains of TB have been reported in pigs and local badgers in the Edge Area (Bailey et al., 2013). Residual infection (e.g. undisclosed infected cattle and *M. bovis* in the environment) may also contribute to the local reservoir (Broughan et al., 2016). Anderson et al.'s (2017) work found that the probability of eradication was greatest with approaches based on both wildlife and cattle TB monitoring data.

In the longer term, robust evidence should be sought from analysis of transmission pathways in areas of low and high cattle and wildlife densities. Genetic analyses of *M. bovis* isolates from badgers and cattle show that the level and the predominant direction of transmission between cattle and badgers vary between areas (Crispell et al., 2019; Rossi et al., 2021). Incorporation of data from other wildlife and domesticated species could provide a clearer ecological picture.

This work increases the information available for locally focused TB controls. A novel approach was taken to define the areas on the basis of cattle TB surveillance data because of the scarcity of direct evidence for the presence or absence of TB in badgers. This approach has been rarely used with TB and may have useful applications for other geographical regions. The evidence produced here suggested that local *M. bovis* reservoirs predominate on the western border of the Edge Area for TB in England. However, reservoirs were also detected in other areas including to the east near the LRA border in Leicestershire and Northamptonshire. We suggest this definition is re-evaluated when further data on badger infection become available. Even within a given species or country, the role that wildlife plays in TB transmission is likely to vary with variations in population density, disease prevalence as well as other ecological factors that change over time.

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AUTHOR CONTRIBUTIONS

All authors contributed to discussions that led to the development of the cattle-based definition. MA conducted the Latent Class Analysis. AP extracted cattle surveillance data from the APHA management system and in conjunction with SD and SA conducted the descriptive data analyses. SA undertook the GIS analyses and produced all maps during the development phase and also produced the final maps. KH helped with presentation of maps. TR and SF reviewed the distribution of the local reservoir against their local field knowledge of TB in the Edge Area. KH undertook the literature review of badger dispersion distances with help from AR. All authors reviewed and commented on the final manuscript. SD was the project leader and wrote the first draft of the manuscript.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ETHICS

The authors confirm that the ethical policies of the journal, as noted on the journal's author guidelines page, have been adhered to. The work used pre-existing data.

DATA AVAILABILITY STATEMENT

The underlying individual data are not publicly available due to privacy restrictions. An excel workbook with the reservoir classification for the centroids to each 25-km² circular spatial unit in the final map (Figure 6) and their grid reference has been supplied.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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