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BOVINE TUBERCULOSIS IN CATTLE AND BADGERS IN LOCALIZED CULLING AREAS

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ABSTRACT: Bovine tuberculosis (TB) is a zoonotic disease that can have serious consequences for cattle farming and, potentially, for public health. In Britain, failure to control bovine TB has been linked to persistent infection of European badger (*Meles meles*) populations. However, culling of badgers in the vicinity of recent TB outbreaks in cattle has failed to reduce the overall incidence of cattle TB. Using data from a large-scale study conducted in 1998–2005, we show that badgers collected on such localized culls had elevated prevalence of *Mycobacterium bovis*, the causative agent of bovine TB, suggesting that infections in cattle and badgers were indeed associated. Moreover, there was a high degree of similarity in the *M. bovis* strain types isolated from cattle and associated badgers. This similarity between strain types appeared to be unaffected by time lags between the detection of infection in cattle and culling of badgers, or by the presence of purchased cattle that might have acquired infection elsewhere. However, localized culling appeared to prompt an increase in the prevalence of *M. bovis* infection in badgers, probably by disrupting ranging and territorial behavior and hence increasing intraspecific transmission rates. This elevated prevalence among badgers could offset the benefits, for cattle, of reduced badger densities and may help to explain the failure of localized culling to reduce cattle TB incidence.

Key words: Badger, *Meles meles*, *Mycobacterium bovis*, perturbation, proactive culling, randomized badger culling trial, reactive culling, tuberculosis.

INTRODUCTION

Bovine tuberculosis (TB) is a zoonotic disease that can have serious consequences for cattle farming and, potentially, for public health. In Britain, a nationwide eradication program reduced the incidence of cattle TB to very low levels by the 1970s; however, infection rates among cattle have been rising since the mid-1980s (Krebs et al., 1997), and the first case of human-to-human transmission was reported recently (Evans et al., 2007).

European badgers (*Meles meles*) are implicated in transmitting *Mycobacterium bovis*, the causative agent of bovine TB, to cattle. Studies have shown that *M. bovis* infections in badgers and cattle are associated in space (Woodroffe et al., 2005c; Jenkins et al., 2007), and experimental reduction of badger density by culling over large ($\geq$100 km^2) tracts of land has been found to lower the incidence of cattle TB inside culled areas (Griffin et al., 2005; Donnelly et al., 2006). However, such widespread badger culling

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is labor-intensive, costly, and unpopular with the general public (Dunnet et al., 1986; White and Whiting, 2000; Woodroffe et al., 2008). For these reasons, past TB control policies restricted badger culling to localized areas centered on farms that had recently experienced TB incidents in cattle (termed "herd breakdowns"). These past culling policies, which operated in various forms between 1973 and 1998 (Zuckerman, 1980; Dunnet et al., 1986), aimed to remove badgers associated in time and space with cattle herd breakdowns, on the basis that such badgers might have been the source of cattle infection and could spread disease to additional cattle if left unmanaged. Unfortunately, these past policies were not accompanied by marked reductions in the incidence of cattle TB (Krebs et al., 1997). Recent experimental evidence suggests that localized badger culling failed to reduce, and may even have increased, the local incidence of cattle TB (Donnelly et al., 2003).

There are several potential explanations for the apparent failure of localized badger culling to reduce the overall incidence of cattle TB:

1) Localized culling might have failed to capture the badgers that were the source of the cattle infection, allowing them to continue transmitting *M. bovis* to additional cattle. Such a scenario might occur if culling was targeted in the wrong areas, if trapping failed to capture infectious badgers, or if substantial delays occurred between detecting infection in cattle and culling badgers.
2) Localized culling might elevate the prevalence of *M. bovis* infection in badgers, offsetting any benefits, for cattle, of reduced badger density. Widespread badger culling is known to be associated with such increases in prevalence in badgers (Woodroffe et al., 2006b), so it is reasonable to expect similar effects of localized culling. Badgers range more widely when their territorial organization has been disrupted by culling (Woodroffe et al., 2006a; Pope et al., 2007); this behavioral change could increase transmission among badgers, thus elevating local *M. bovis* prevalence. This increased ranging behavior could also increase contact between infectious badgers and susceptible cattle herds, even if *M. bovis* prevalence were unaffected.
3) Finally, localized badger culling might fail to reduce TB risks for cattle where herd breakdowns originate from a source other than badgers, such as cattle purchased from other farms (Gilbert et al., 2005).

In this paper, we use available data to explore the association between *M. bovis* infections in badgers and cattle in areas subjected to localized badger culling. We investigate whether localized culling successfully removed badgers that might have caused recent infections in cattle by asking whether badgers taken on localized culls were more likely to: 1) be infected with *M. bovis*; 2) show TB lesions that might indicate infectiousness; and 3) share *M. bovis* strain types with associated cattle, than were badgers culled in similar landscapes but in a less targeted manner. We also investigate whether delays between detecting cattle infection and culling badgers influenced the patterns of infection observed in the two species. We evaluate the potential role of purchased cattle by asking whether *M. bovis* strain types in cattle and badgers were less similar where such cattle were implicated in herd breakdowns. Finally, we evaluate whether localized culling prompted increased *M. bovis* prevalence in badgers. We use this information to explore possible reasons for the past failure of localized culling and to determine whether a more effective localized culling strategy could be devised.

MATERIALS AND METHODS

Badger culling

All data presented here were collected during the course of the Randomized Badger Culling Trial (RBCT), a large-scale field trial of the effectiveness of badger culling as a control

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measure for cattle TB in Britain (Donnelly et al., 2003, 2006). Thirty 100-km^2 trial areas were situated in areas of high cattle TB risk and recruited sequentially as 10 "triplets" (designated A–J) between 1998 and 2002. Trial areas were all located in southern and western England (Donnelly et al., 2006) as follows: triplet A (51°58′N, 2°39′W); triplet B (50°54′N, 4°26′W); triplet C (50°22′N, 4°32′W); triplet D (52°4′N, 2°27′W); triplet E (51°20′N, 2°3′W); triplet F (50°8′N, 5°34′W); triplet G (53°0′N, 1°38′W); triplet H (51°7′N, 3°29′W); triplet I (52°0′N, 2°0′W); and triplet J (50°44′N, 4°22′W). Within each triplet, trial areas were randomly assigned to receive either reactive (localized), proactive (widespread), or no badger culling.

The reactive treatment involved a series of localized culls in response to specific cattle herd breakdowns. When TB was confirmed in a cattle herd within a reactive trial area, field staff mapped the land used by the affected herd. Survey data were then used to estimate the likely home ranges of badgers using this land (Woodroffe et al., 1999) and to identify setts (dens) used by these badgers (sometimes on neighboring properties). Areas targeted for culling in this way often coalesced where multiple cattle herds in the same vicinity were affected by TB (breakdown clusters); hence, the number of herd breakdowns that prompted reactive culling operations exceeded the number of operations. The average reactive culling operation targeted an area of 8.8 km^2 and involved eight nights of badger trapping. In contrast, the proactive culling treatment involved a single initial cull across all accessible land, with follow-up culls repeated approximately annually thereafter.

Badgers were captured in cage traps and killed by shooting. The majority of badgers received no injuries from confinement in the trap (Woodroffe et al., 2005b), and independent audit deemed dispatch methods "humane" (Kirkwood, 2000). No culling occurred during February–April each year to avoid killing females with dependent cubs confined to the sett (Woodroffe et al., 2005a). Culling was also suspended in May 2001–January 2002 due to a nationwide epidemic of foot and mouth disease (FMD). Reactive culling was discontinued in November 2003 (Donnelly et al., 2003); hence, no reactive culls were conducted in triplet J. Proactive culling continued until October 2005 (Donnelly et al., 2006).

Diagnosis and severity of *M. bovis* infection in badgers

Each badger carcass was chilled after death and necropsied (at one of nine laboratories), usually within 72 hr of dispatch. A proportion of carcasses (9.2% of the total) was stored (almost always frozen) for >7 days before necropsy. Veterinarians conducting necropsies first recorded sex and tooth wear (a measure of age; Neal and Cheeseman, 1996). Eighteen prespecified tissue sites, in five body compartments (head, lungs, chest, abdomen, peripheral), were then incised and examined for lesions suggestive of TB (Jenkins et al., 2008). If a lesion was visible at any of these sites, the badger was considered "lesioned." Each site was scored for lesion severity as: 1=a single lesion; 2=2–3 lesions; 3=multiple (>3) lesions affecting parts of tissue; 4=diffuse lesions throughout the tissue. A sample was collected from every lesion, along with one half of each retropharyngeal, both bronchial, and the mediastinal lymph nodes. Badgers were considered infected if *M. bovis* was detected from any sample by bacteriologic culture (at one of three laboratories), or if acid-fast bacteria were detected in lesions by Ziehl Neelsen staining (Gallagher and Clifton-Hadley, 2000).

Isolates of *M. bovis* were genotyped by spacer oligonucleotide typing ("spoligotyping"; Kamerbeek et al., 1997). This allowed allocation of each isolate to one of the small number of readily identifiable *M. bovis* clones that occur in Britain (Smith et al., 2003); exploratory analysis revealed that an alternative typing method (using variable number tandem repeats; Frothingham and Meeker-O'Connell, 1998) provided no additional information.

Cattle TB data

Data on TB in cattle were taken from routine surveillance. In trial areas, surveillance involved annual tuberculin skin testing as well as continuous surveillance in slaughterhouses. If any herd showed evidence of *M. bovis* infection ("disclosure"), all skin test–positive animals were compulsorily slaughtered and subjected to necropsy. Within trial areas, protocol was to culture tissue samples from all compulsorily slaughtered cattle. A breakdown was considered "confirmed" (and hence prompted badger culling in reactive areas) only if lesions suggestive of TB were visible at necropsy, or if *M. bovis* was isolated following bacteriologic culture. Herd breakdowns were considered likely to be associated with purchased cattle if records showed that any of the skin test–positive cattle had been brought in from another herd during the previous 12 mo.

The median period between disclosure and slaughter was 21 days; confirmation through detection of TB lesions at necropsy was

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TABLE 1. Logistic regression model of *Mycobacterium bovis* infection prevalence in adult badgers, 1998–2003. Results are adjusted for overdispersion.

Predictor	Odds ratio (95% CI)	χ^2	d.f.	*P*
Triplet		186.16	9	<0.001
Sex		20.59	1	<0.001
male vs. female	1.45 (1.23–1.71)			
Age (tooth wear score)		7.35	5	0.196
2 vs. 1	0.95 (0.47–1.91)			
3 vs. 1	1.11 (0.55–2.21)			
4 vs. 1	1.09 (0.54–2.20)			
5 vs. 1	1.24 (0.60–2.57)			
not recorded vs. 1	0.23 (0.03–1.63)			
Carcass storage		8.90	1	0.003
>7 days vs. ≤7 days	0.59 (0.40–0.88)			
Necropsy laboratory		18.49	9	0.030
Culture laboratory		2.45	2	0.293
FMD		10.13	1	0.001
2002 vs. other years	1.49 (1.18–1.88)			
Cull type		25.78	5	<0.001
first reactive vs. first proactive	1.82 (1.27–2.61)			
subsequent reactive vs. first proactive	3.20 (1.82–5.63)			
second vs. first proactive	1.02 (0.76–1.35)			
third vs. first proactive	1.46 (0.93–2.29)			
fourth vs. first proactive	3.04 (1.75–5.29)			
fifth vs. first proactive	2.23 (0.91–5.47)			

immediate, whereas confirmation by culture took at least another 42 days. We therefore used slaughter date as a conservative estimate of confirmation date. All *M. bovis* isolates from cattle were spoligotyped as for badgers.

Statistical analyses of *M. bovis* prevalence

The prevalence of *M. bovis* infection among reactively and proactively culled badgers was compared using logistic regression models adapted from Woodroffe et al. (2006b). As in previous analyses, adults and cubs were analyzed separately because they showed very different patterns of *M. bovis* infection (Woodroffe et al., 2005c, 2006b; Jenkins et al., 2008). These models included several covariates known to influence the probability of infection: triplet, sex, age (measured as tooth wear for adults and days since 1 February for cubs), carcass storage, necropsy laboratory, culture laboratory, and date. Date was coded as a binary variable, which contrasted 2002 with all other years, since prior analyses had revealed that the suspension of cattle TB testing during the 2001 FMD epidemic was associated with elevated *M. bovis* prevalence in badgers in 2002 (Woodroffe et al., 2006b).

Prevalence was known to increase on successive proactive culls (Woodroffe et al., 2006b). To investigate whether prevalence likewise increased on successive reactive culls, and to compare baseline prevalence in reactively and proactively culled badgers, we developed a multilevel categorical variable called "cull type." This variable used initial proactive culls as the comparison group for subsequent proactive culling operations, as well as for reactively culled badgers taken on the initial, and all subsequent, culls conducted in a particular land parcel. Comparisons of prevalence under reactive and proactive culling excluded data from 2004–05 when reactive culling had been discontinued (Donnelly et al., 2003).

The results of the prevalence model were corrected for any overdispersion in the data, which might arise, for example, through clustering of infection among badgers from the same social group (Woodroffe et al., 2005c). Evidence for such overdispersion was investigated by testing for the significance of two interactions that, based on biologic knowledge, would be expected to be nonsignificant. Using the model reported in Table 1, we tested for significance of a triplet×sex interaction and a triplet×tooth wear interaction (corresponding to 9 and 45 degrees of

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freedom, respectively). The χ^2 statistics for these interactions were 13.92 and 55.23, respectively, indicating no significant effects in either case. However, to be conservative, an estimated overdispersion factor was obtained from the square root of the summed χ^2 values (13.92+55.23) divided by the summed degrees of freedom (9+45). This factor, 1.132, was used to enlarge the confidence intervals for estimates in the model presented in Table 1. Hence, these results allow for any clustering of infection among badgers.

Analyses of lesion prevalence and severity

The severity and distribution of lesions in *M. bovis*–infected badgers were assessed using an index developed by Jenkins et al. (2008). This index was calculated as:

Lesion index=(average score of lesioned sites)×(number of sites per affected body compartment)^2×(number of affected body compartments).

This index was based on the distributions, particularly the variances, of the three lesion variables included within it (Jenkins et al., 2008). For a badger with one lesioned site, the index was equal to the score at that site. The index was higher if more body compartments contained visible lesions and if lesions were visible in multiple sites in one body compartment. In case freezing influenced the detection of lesions, indices were not calculated for badgers that had been stored >7 days before necropsy.

Analyses of agreement between *M. bovis* spoligotypes from badgers and cattle

The *M. bovis* spoligotypes found in badgers on each reactive culling operation were compared with those detected in the cattle herd breakdown(s) that prompted the operation. For each operation, we calculated the weighted average probability that a randomly chosen badger (from those culled on that operation) would share the same spoligotype as a randomly chosen bovine from the associated breakdown(s). This probability provided a measure of the agreement between spoligotypes from badgers and cattle and was calculated as follows.

In operation i, let n_{iC} be the number of spoligotyped cattle, and let p_{ij} be the observed proportion of those cattle with spoligotype j. Likewise, let n_{iB} be the number of spoligotyped badgers from operation i, and let r_{ij} be the observed proportion of those badgers with spoligotype j. The observed proportions p_{ij} and r_{ij} have underlying probabilities π_{ij} and ρ_{ij}, respectively. Thus, for operation i, the estimated probability that a randomly chosen badger would share the same spoligotype as a randomly chosen bovine from the associated breakdown(s) is given by

$$\hat{\gamma}_i = \sum_j p_{ij} r_{ij},$$

where j is summed over all observed spoligotypes. By local linearization (the delta method), we have approximately that

$$\begin{aligned}\sigma_i^2 &= \mathrm{var}(\hat{\gamma}_i) \\ &= \sum_j \left\{ \rho_{ij}^2 \mathrm{var}(p_{ij}) + 2\sum_{j>k} \rho_{ij}\rho_{ik}\mathrm{cov}(p_{ij},p_{ik}) \right\} \\ &\quad + \sum_j \left\{ \pi_{ij}^2 \mathrm{var}(r_{ij}) + 2\sum_{j>k} \pi_{ij}\pi_{ik}\mathrm{cov}(r_{ij},r_{ik}) \right\}.\end{aligned}$$

Now, by the properties of the multinomial distribution, we have, for example,

$$\begin{aligned}\mathrm{var}(p_{ij}) &= \pi_{ij}(1-\pi_{ij})/n_{iC}, \\ \mathrm{cov}(p_{ij},p_{ik}) &= -\pi_{ij}\pi_{ik}/n_{iC} \quad (j \neq k).\end{aligned}$$

It follows that approximately

$$\sigma_i^2 = \left(\sum_j \rho_{ij}^2 \pi_{ij} - \gamma^2 \right) \Big/ n_{iC} + \left(\sum_j \pi_{ij}^2 \rho_{ij} - \gamma^2 \right) \Big/ n_{iB},$$

which is consistently estimated by replacing π_{ij} by p_{ij}, etc.

The weighted average probability that a randomly chosen badger would share the same spoligotype as a randomly chosen bovine from the associated breakdown(s) is given by:

$$\hat{\gamma} = \frac{\sum_i n_{iC}\hat{\gamma}_i}{\sum_i n_{iC}},$$

where n_{iC} is the number of spoligotyped cattle in operation i. The approximate variance of this weighted average is

$$\hat{\sigma}^2 = \sum_i n_{iC}^2 \hat{\sigma}_i^2 \Big/ \left(\sum_i n_{iC} \right)^2.$$

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To determine whether operations preferentially removed badgers with spoligotypes matching those in associated cattle, we calculated agreement measures for two comparison groups of badgers. For each reactive operation, we determined the probability that a randomly chosen bovine would share the same spoligotype as a randomly chosen badger from 1) the proactive culling area in the same triplet and year (except that in triplet A, proactive data from 1999 were compared with reactive data from 2000, since triplet A received no proactive culling in 2000); and 2) all other reactive operations conducted in the same triplet (across all years). These measures of spoligotype agreement with reference populations of badgers were then compared with those for the badgers captured on each reactive culling operation, on the basis of the weighted average within-operation difference. To make this comparison, we calculated

$$\hat{\delta}_i = \sum_j p_{ij}(r_{ij} - q_{ij}),$$

where q_{ij} is the proportion of spoligotyped badgers in the reference population with spoligotype j. If the spoligotype frequencies among the badgers from a particular reactive operation were no more similar to those of associated cattle than were those from the reference badgers, then this operation-specific measure would have mean zero and approximate variance

$$v_i = \sum_j p_{ij}(r_{ij} - q_{ij})^2 \Big/ n_{iC},$$

conditional on the observed r_{ij} and q_{ij}. Thus, the weighted average difference,

$$\hat{\delta} = \frac{\sum_i n_{iC}\hat{\delta}_i}{\sum_i n_{iC}},$$

is normally distributed with mean zero (if the spoligotypes from associated badgers are no more similar to those from cattle than are those from the reference badgers) and with approximate variance:

$$v^2 = \sum_i n_{iC}\left(\sum_j p_{ij}(r_{ij} - q_{ij})^2\right) \Big/ \left(\sum_i n_{iC}\right)^2.$$

We also calculated the agreement between spoligotypes from cattle slaughtered in the course of subsequent breakdowns that occurred in culling-associated herds but after culling operations had been conducted, and those from the original reactively culled badgers. This measure was compared with the spoligotype agreement between the same badgers and the cattle that prompted culling.

A similar approach was used to compare agreement values for operations conducted at different times after confirmation of infection in cattle, and in response to infection in single or multiple herds.

RESULTS

Descriptive data on cattle breakdowns and localized culling operations

There were 169 confirmed cattle herd breakdowns that prompted reactive culling, leading to 76 culling operations. The average herd breakdown involved the slaughter of 12.2 cattle (19.2 standard deviation [SD], range 1–134), of which 4.4 (7.5 SD, range 1–68) were confirmed to be infected (Table 2). The average reactive culling operation captured 27.2 badgers (22.6 SD, range 2–87), including 4.0 (4.5 SD, range 0–25) found to be infected with *M. bovis*.

Prevalence of *M. bovis* infection in badgers

Of 2,064 badgers taken on reactive culling operations for which culture data were available, 307 (14.9%) showed evidence of *M. bovis* infection. The prevalence recorded amongst adults (15.8%, n=1,654) was higher than that in cubs (10.7%, n=410).

After adjusting for other known predictors of *M. bovis* infection, adult badgers culled under the reactive strategy were more likely to show evidence of infection than were those taken on initial proactive culls (Table 1; comparing adult badgers taken on all reactive culls with those from initial proactive culls: odds ratio [OR]= 1.80, 95% confidence interval [CI]=1.25–2.58). Prevalence in badger cubs showed a comparable, albeit nonsignificant, trend in the same direction (OR=1.91, 95% CI= 0.75–4.91).

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TABLE 2. Descriptive data on reactive culling operations within nine Randomized Badger Culling Trial triplets; no reactive culling was conducted in triplet J.

	Herd breakdowns associated with culling				Years of reactive culling[a]			Reactive culling operations		Number of badgers captured on reactive culling operations		
Triplet	*n*	Cattle slaughtered[b]	Cattle with *M. bovis*[b]	Cattle with spoligotypes[b]	*n*	First	Last	Culls	Culls with *M. bovis*	Badgers caught[c]	Badgers with *M. bovis*[c]	Badgers with spoligotypes[c]
A	21	278 (13.2)	64 (3.0)	55 (2.6)	3	2000	2003	10	8	117 (11.7)	30 (3.0)	23 (2.3)
B	27	307 (11.4)	60 (2.2)	49 (1.8)	4	1999	2003	9	7	301 (33.4)	27 (3.0)	25 (2.8)
C	42	468 (10.4)	199 (4.7)	161 (3.8)	3	2000	2003	19	15	394 (20.7)	55 (2.9)	49 (2.6)
D	7	71 (10.1)	26 (3.7)	22 (3.1)	1	2003	2003	4	4	122 (30.5)	31 (7.8)	31 (7.8)
E	24	295 (12.3)	117 (4.9)	98 (4.1)	2	2002	2003	10	6	188 (18.8)	23 (2.3)	20 (2.0)
F	23	250 (10.9)	77 (3.3)	71 (3.1)	2	2002	2003	10	10	436 (43.6)	52 (5.2)	43 (4.3)
G	10	186 (18.6)	60 (6.0)	57 (5.7)	2	2002	2003	7	5	255 (36.4)	31 (4.4)	31 (4.4)
H	7	125 (17.9)	92 (13.1)	86 (12.3)	2	2002	2003	4	3	160 (40.0)	29 (7.3)	26 (6.5)
I	8	86 (10.8)	43 (5.4)	42 (5.3)	1	2003	2003	3	2	94 (31.3)	29 (9.7)	28 (9.3)
Total	169	2,066 (12.2)	738 (4.4)	641 (3.8)				76	60	2,067[d] (27.2)	307 (4.0)	276 (3.6)

[a] Badger years are defined as running 1st February–31st January.

[b] Total across breakdowns (mean per breakdown).

[c] Total across culling operations (mean per operation).

[d] Culture data were lacking for three of these animals.

As shown in Table 1, prevalence tended to be higher among reactively culled adults taken from land parcels where one or more (maximum four) operations had already occurred ($n=337$ animals) than among those taken from land receiving reactive culling for the first time ($n=1,317$).

Pathology of *M. bovis* infection in badgers

Of 247 *M. bovis*–infected reactively culled adult badgers for which pathology data were available, 103 (41.7%) had visible lesions suggestive of TB, and 19 (7.7%) were considered to have severe or widely distributed lesions (lesion indices≥8; Table 3). Equivalent figures for reactively culled cubs were 40.5% and 14.3%, respectively ($n=42$).

Infected badgers taken on proactive and reactive culls had similar probabilities of being visibly lesioned and also showed similar patterns of lesion severity (Table 3).

Comparison of infection patterns in cattle and badgers

Reactive culling was conducted in response to confirmed breakdowns in cattle; therefore, all herds considered here contained at least one confirmed infected bovine. Of 76 reactive culling operations, 60 (79%) captured one or more infected badgers. Logistic regression showed that the overall probability of capturing at least one infected badger increased with the (log transformed) total number caught (OR associated with doubling the number captured 1.76; $\chi^2=6.36$, $p=0.012$). However, some operations that caught no infected animals nevertheless captured large numbers of badgers (range 2–62).

Of 169 cattle herd breakdowns associated with reactive culling, 155 produced isolates of *M. bovis* that were successfully spoligotyped. Of these, 139 involved a single spoligotype, 14 involved two spoligotypes, and two involved three spoligotypes. Spoligotype frequencies recorded among cattle in breakdowns associated with reactive culling were broadly similar to those found in badgers culled in the

TABLE 3. Comparison of the prevalence of visible lesions and lesion indices among badgers taken on reactive (1999–2003) and proactive (1998–2005) culls. Numbers in parentheses are exact binomial 95% confidence intervals; *n* gives the sample size used to estimate each proportion.

	Adults		Cubs	
	Proactive	Reactive	Proactive	Reactive
% *Mycobacterium bovis*–infected animals with visible lesions	38.5% (35.5–41.6%) $n=1,020$	41.7% (35.5–48.1%) $n=247$	55.5% (47.0–63.7%) $n=146$	40.5% (25.6–56.7%) $n=42$
% *M. bovis*–infected animals with >1 body compartment lesioned	14.7% (12.6–17.0%) $n=1,020$	12.6% (8.7–17.3%) $n=247$	28.1% (21.0–36.1%) $n=146$	26.2% (13.9–42.0%) $n=42$
% *M. bovis*–infected animals with lesion indices ≥8	10.5% (8.7–12.5%) $n=1,020$	7.7% (4.7–11.8%) $n=247$	23.3% (16.7–31.0%) $n=146$	14.3% (5.4–28.5%) $n=42$

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same trial area (Table 4). While some spoligotypes were recorded in one species but not the other within a trial area, these never accounted for more than 16% of infections within a species (Table 4).

Of 76 reactive culling operations, 55 had spoligotype data from both badgers and associated cattle. Badgers and cattle were found to share at least one spoligotype on 51 (94%) of these operations. Overall, there was an estimated 80.3% probability (95% CI=75.3–85.4%) that a (spoligotyped) badger chosen at random from a particular reactive operation would share the same *M. bovis* spoligotype as a (spoligotyped) bovine chosen at random from the associated breakdown(s).

The spoligotype agreement between cattle from breakdowns prompting reactive operations and associated reactively culled badgers (80.3%) was greater than that between the same cattle and badgers taken on proactive culls in the same year and triplet (75.6%, difference 4.7% greater for associated reactively culled badgers, 95% CI=1.4–8.0% greater, $P=0.005$). However, this spoligotype agreement between associated cattle and badgers was not significantly different from that between the same cattle and all other reactively culled badgers from the same triplet (79.8%, difference 0.6% greater for associated reactively culled badgers, 95% CI=1.7% less to 2.8% greater, $P=0.62$).

The level of agreement between badger and cattle spoligotypes was similar for operations prompted by single- and multiple-herd breakdowns (73.9% and 82.1%, respectively; difference 8.2% less for single breakdowns, 95% CI=22.9% less to 6.4% more, $P=0.27$).

Possible effects of purchased cattle

Of the 169 cattle herd breakdowns that prompted reactive badger culling, 24 involved skin test–positive cattle that had been moved in from other herds within the previous 12 mo and might therefore have acquired infection elsewhere. These 24 breakdowns were associated with 21 badger culling operations. Although the purchased cattle might have acquired *M. bovis* infection elsewhere, the probability of catching one or more infected badgers on these operations (17/21 operations; 81%) was very similar to that recorded on breakdowns not involving purchased cattle (43/55 operations; 78%, $\chi^2=0.07$, d.f.=1, $P=0.79$).

There was likewise no evidence that the involvement of purchased cattle in herd breakdowns influenced the agreement between badger and cattle spoligotypes. The level of spoligotype agreement observed for reactive operations associated with infected purchased cattle (75.4%) was not significantly different from that for operations not involving purchased cattle (83.9%, difference 8.4% less for breakdowns involving purchased cattle, 95% CI=20.3% less to 3.4% greater, $P=0.16$).

Possible effects of time lags between detecting cattle infection and culling badgers

The median time lag between the first cattle slaughter date on a breakdown and the date the first badger was culled on the associated reactive operation was 211 days (interquartile range 146–323 days). Time lags that spanned the FMD epidemic (median 646 days, interquartile range 562–718 days, $n=22$ breakdowns) were longer than those that did not (median 186 days, interquartile range 139–285 days, $n=147$ breakdowns). When herd breakdowns were grouped into clusters (with each cluster consisting of the breakdowns that prompted a single culling operation), the median time lag between the earliest cattle slaughter date in the cluster and the first badger cull date was 254 days (interquartile range 166–453 days).

The extent of agreement between spoligotypes recorded in associated cattle and badgers appeared unrelated to this time lag. Time lags were arbitrarily considered "short" if ≤270 days elapsed between the median date of first cattle slaughter in a

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TABLE 4. Frequency of spoligotypes in reactively culled badgers and associated cattle herds. Data indicate the proportions of infected badgers and cattle (from breakdowns that prompted culling) in each triplet found to have each spoligotype of *Mycobacterium bovis*. The last line gives the numbers of *M. bovis* isolates available from each species in each reactive trial area.

	Triplet																	
	A		B		C		D		E		F		G		H		I	
Spoligotype[a]	Badger	Cattle	Badger	Cattle	Badger	Cattle	Badger	Cattle	Badger	Cattle	Badger	Cattle	Badger	Cattle	Badger	Cattle	Badger	Cattle
SB0129	–	–	–	–	0.02	–	–	0.05	–	0.01	–	–	0.94	1.00	–	0.01	–	–
SB0134	–	–	–	–	–	–	0.10	–	–	–	–	–	–	–	–	–	–	–
SB0140	0.04	0.04	0.96	0.88	0.92	0.98	–	–	0.25	0.13	–	0.03	–	–	–	–	–	–
SB0145	–	–	–	–	–	–	–	–	–	–	0.09	0.20	–	–	–	0.01	–	–
SB0263	0.91	0.95	–	0.04	0.06	0.01	0.84	0.95	0.75	0.86	0.02	–	–	–	–	–	0.21	0.71
SB0271	–	–	–	–	–	0.01	–	–	–	–	0.86	0.77	–	–	–	–	–	–
SB0272	–	0.02	–	–	–	–	0.06	–	–	–	0.02	–	0.06	–	0.12	–	0.79	0.21
SB0274	0.04	–	–	0.08	–	0.01	–	–	–	–	–	–	–	–	0.88	0.97	–	0.07
SB0275	–	–	0.04	–	–	0.01	–	–	–	–	–	–	–	–	–	–	–	–
SB1073	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	0.01	–	–
N	23	55	25	49	49	161	31	22	20	98	43	71	31	57	26	86	28	42

[a] International spoligotype identities; for equivalent Veterinary Laboratories Agency identities see http://www.mbovis.org/spoligodatabase/GBmetadata/frequency%20spoligo%20GB.html.

cluster of breakdowns and the subsequent associated badger cull. Time lags >270 days were considered "long." The probability of associated cattle and badgers sharing the same *M. bovis* spoligotype was similar for operations subject to "short" and "long" time lags (78.8% and 82.8%, respectively; difference 3.9% less for short time lags, 95% CI=13.4% less to 5.6% greater, $P=0.42$). Similarly, within clusters of TB-affected herds, particular breakdowns were considered "early" if they occurred on or before the median date for the cluster and "late" if they occurred after the median. The spoligotype agreement between cattle and badgers was similar for "early" and "late" breakdowns (84.9% and 86.0%, respectively; difference 1.1% less for early breakdowns, 95% CI=4.1% less to 1.9% greater, $P=0.46$).

Cattle herd breakdowns after badger culling

By the end of 2005, 79 further confirmed breakdowns had been recorded in the herds originally associated with reactive culling. These herds had been previously targeted by 42 culling operations, of which 31 provided spoligotype data for both host species (Table 5). The agreement between spoligotypes from cattle on these repeat breakdowns and those from the badgers culled previously was significantly lower than that between the same badgers and the breakdowns that originally prompted culling (82.5% vs. 86.7%; difference 4.2% less, 95% CI=2.0–6.4% less, $P<0.001$).

DISCUSSION

Associations between infections in badgers and cattle

The data presented here confirm that, in localized culling areas, *M. bovis* infections in badgers were associated with those in cattle. Badgers taken on reactive culls showed a higher prevalence of *M. bovis* infection than did those from proactive culls. This is consistent with a spatial association between infections in the two host species described previously (Woodroffe et al., 2005c): the practice of culling badgers in the vicinity of recent herd breakdowns would be expected to remove more infected badgers than would a less spatially localized form of culling. Furthermore, the spoligotype data presented here suggest that there may be a temporal association between infections in the two host species: *M. bovis* spoligotypes from reactively culled badgers were more similar to those from cattle slaughtered on the associated herd breakdowns than to those from cattle in the same herds that were slaughtered on subsequent breakdowns.

Most *M. bovis* spoligotypes were shared between badgers and associated cattle. Although the spoligotype agreement observed on reactive culls was higher than that expected based on spoligotype frequencies from proactively culled badgers, this difference was driven by two triplets where spoligotype frequencies were markedly different in proactive and reactive areas (Table 5). In triplet F, spoligotypes SB0140 and SB0145 accounted for, respectively, 56% and 44% of badger spoligotypes in the proactive area in 2002–03, but 0% and 9% of those in reactively culled badgers in the same years. Likewise, in triplet I, spoligotypes SB0263 and SB0272 accounted for 73% and 7% of badger spoligotypes in the proactive area in 2003, but 21% and 79% of those in reactively culled badgers. When cattle spoligotypes from particular reactive operations were compared with badger spoligotypes from nonassociated reactive operations conducted in the same trial area, the level of agreement was not significantly different from that with badgers taken on the associated operation. This indicates that, on the basis of spoligotype data, reactive culling appeared to be equivalent to random, rather than targeted, sampling of infected badgers in the vicinity of infected cattle.

There are several possible explanations for this pattern. One possibility is that the

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TABLE 5. Matching of *Mycobacterium bovis* spoligotypes from badgers taken on reactive culling operations with those from the original cattle herd breakdowns that prompted culling and with subsequent breakdowns involving the same herds. Data are restricted to operations with spoligotype data from both species; hence, numbers of animals reported as having spoligotype data differ from those given in Table 1.

	A	B	C	D	E	F	G	H	I	Total
Original breakdowns										
Operations with spoligotypes from both species	7	6	14	4	6	9	4	3	2	55
Operations with one or more spoligotypes found in both species	7	6	12	4	6	7	4	3	2	51
Badgers with spoligotypes	23	25	49	31	20	41	28	26	28	271
Cattle with spoligotypes	37	40	121	22	82	71	54	81	20	528
Probability associated cattle and badgers share same spoligotype (%)	89.3	81.7	78.6	80.3	69.0	67.6	99.6	85.2	91.7	80.3
Probability cattle share spoligotype with proactively culled badgers in same triplet and year (%)	83.8	92.5	96.4	93.0	53.3	13.8	99.8	96.3	43.3	75.6
Probability cattle share spoligotype with badgers from other reactive operations in same triplet (%)	86.6	89.6	89.6	79.4	71.8	67.6	91.5	85.6	9.2	79.8
Subsequent breakdowns										
Operations with spoligotypes from both species	4	6	8	1	4	4	1	1	2	31
Operations with one or more spoligotypes found in both species	4	6	8	1	4	4	1	1	2	31
Badgers with spoligotypes	14	25	31	4	17	15	4	17	28	155
Cattle with spoligotypes	32	81	45	4	51	5	4	7	5	234
Probability associated cattle and badgers share same spoligotype (%)	92.9	92.7	83.7	75.0	66.4	93.2	100	84.6	91.7	86.7
Probability repeat cattle share spoligotype with badgers culled on previous reactive operation (%)	92.0	96.0	77.4	75.0	54.2	93.3	100	75.6	85.7	82.5

amalgamation of multiple breakdowns into a smaller number of culling operations led to sampling of badgers on a spatial scale larger than that on which cattle and badger infections are associated. However, the similar level of agreement between badger and cattle spoligotypes in operations associated with single and multiple breakdowns provides no support for this hypothesis.

An alternative explanation is that the comparatively small number of spoligotypes in each trial area (Table 4) provided insufficient precision to link infections in cattle and badgers. While this is consistent with the localized geographic distribution of most *M. bovis* clones in Britain (Smith et al., 2003), we were able to detect differences in spoligotype agreement with badgers between breakdowns that prompted reactive culls and subsequent breakdowns in the same herds. This suggests that spoligotyping offered sufficient precision to detect temporal associations between infections in the two host species and might therefore have been able to detect spatial associations.

A final explanation is that not all infections in cattle and badgers may have been causally linked. It is likely, on the basis of national patterns, that some breakdowns that prompted reactive culling were caused by cattle-to-cattle transmission (Cox et al., 2005; Gilbert et al., 2005; Johnston et al., 2005) rather than originating in badgers. Such cattle-to-cattle transmission would tend to dissociate infection patterns in badgers and

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cattle. However, we could find no support for this hypothesis using this data set: there was no evidence that the involvement of recently purchased cattle in herd breakdowns reduced the probability of capturing infected badgers, or of capturing badgers with spoligotypes similar to those found in cattle. Despite this, our analyses cannot rule out the possibility that herd breakdowns caused by cattle-to-cattle transmission reduced agreement between infections in cattle and badgers, because such infections may not always be detected in the purchased cattle themselves, and because transmission could also occur through contact between herds rather than through cattle purchase. The possible role of cattle-to-cattle transmission in explaining the patterns presented here could be investigated in future by tracing cattle on a case-by-case basis, although the imperfect sensitivity of the tuberculin test (Morrison et al., 2000) means that some breakdowns could have been caused by infected cattle that remained undetected.

Although the data presented here indicate that infections in cattle and badgers were associated with one another, they provide little insight into the relative importance of badger-to-cattle vs. cattle-to-badger transmission in generating this association. Badgers with gross TB lesions are often assumed to be much more infectious than are badgers without visible lesions (Gallagher and Clifton-Hadley, 2000). If this were the case, the lack of any difference between badgers taken from reactive and proactive areas in the prevalence or severity of lesions might be taken to suggest that badger-to-cattle transmission was relatively unimportant. However, cattle are known to be able to shed *M. bovis* bacilli without having visible TB lesions (McCorry et al., 2005), and the same is suspected for badgers (Jenkins et al., 2007b). These lesion data may therefore provide little indication of the direction of *M. bovis* transmission.

Spoligotype data likewise give little indication of the direction of transmission. Although spoligotypes detected among cattle subsequent to badger culling were relatively dissimilar to those found in badgers, these subsequent breakdowns occurred following management that was intended to remove both the infected badgers and the infected cattle from the previous breakdown. It is not known, therefore, whether subsequent infections were brought into the area by recolonizing badgers, by cattle-to-cattle contact, or by failure to remove infected animals of either host species.

Why did localized badger culling fail to reduce the incidence of cattle TB?

The data presented here suggest that the badgers removed by localized reactive culling were likely to be epidemiologically associated with TB-affected cattle herds. Lowering the local density of infected badgers would therefore be expected to reduce the risk of subsequent cattle herd breakdowns, whether the cattle acquired infection from these badgers, or vice versa, and whether or not every infected badger was removed by culling. Why, then, did no such reduction occur (Donnelly et al., 2003)?

The data presented here show that, like proactive culling (Woodroffe et al., 2006b), reactive culling was associated with an increased prevalence of *M. bovis* infection in badgers. Detailed analyses indicate that this rising prevalence was related to repeated culling (which was asynchronous across triplets) rather than reflecting a simple year-on-year increase (Woodroffe et al., 2006b). This rising prevalence is likely to have been caused by increased mixing among badgers as a result of culling-induced disruption of social and territorial organization (Woodroffe et al., 2006a; Pope et al., 2007). Since localized culling was, by definition, restricted to comparatively small areas of land, recolonization appears to have been rapid (Woodroffe et al., 2006a), and local badger densities were reduced only slight-

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ly (Woodroffe et al., 2008). The increased prevalence of *M. bovis* infection prompted by localized badger culling may therefore have offset any benefits for cattle of somewhat reduced badger density. This argument is consistent with the observation of greater spatial dispersion of cattle infections following repeated reactive culling (Jenkins et al., 2007). It is worth noting that increased badger ranging might increase badger-cattle contact (and hence disease transmission) in the absence of elevated *M. bovis* prevalence; however, the prevalence increase reported here would entail further negative consequences for cattle.

Could a more effective localized culling strategy be devised?

A localized badger culling strategy might in principle be more beneficial for cattle TB control if it more efficiently targeted badgers associated with herd breakdowns. In principle, greater efficiency might be achieved by removing badgers more rapidly, in greater numbers, or by using a diagnostic test to identify and remove infected animals.

We investigated the effect of varying time lags between the confirmation of infection in cattle and culling of badgers. Such time lags were an inevitable component of reactive culling within the RBCT, since 1) reactive operations were often postponed until herds contiguous with the original breakdown herd had been tested, to ensure inclusion of all land associated with a cluster of breakdowns; 2) additional field surveys were needed to prepare for culling; 3) reactive and proactive operations were conducted by the same teams, requiring that the two strategies follow complementary timetables; and 4) no culling could be conducted during the closed season. However, as we found no difference in spoligotype agreement between operations associated with "long" and "short" time lags, there is no evidence to suggest that more rapid removal of breakdown-associated badgers would greatly increase the effectiveness of reactive culling as a disease control strategy.

The problems encountered with the reactive treatment are likely to apply to other strategies involving localized culling. Other ways of targeting culling at "the right badgers" entail their own problems. A serologic test developed for badgers lacked sufficient sensitivity to identify infected animals or social groups (Woodroffe et al., 1999). More recently, molecular methods have been used to detect mycobacteria in the environment (Courtenay et al., 2006), but positive sample rates are extremely high, and specificity, as well as relevance to transmission, are unknown.

An additional concern is that any form of localized culling is likely to cause behavioral change in badgers and, hence, lead to increased transmission of infection. Although *M. bovis* infections are clustered in badgers, the edges of these clusters are not sharply defined (Delahay et al., 2000; Woodroffe et al., 2005c); so, even if every infected animal, or every member of an infected social group, could be identified and removed, it is likely that some animals immigrating into the cleared area would be infected, especially as infected badgers appear to disperse further than do uninfected animals (Pope et al., 2007). Imperfect detection of infection in badgers and imperfect badger removal elevate the chances of increased contact rates leading to increased transmission, constraining the ability of localized culling to reduce TB risks to cattle.

In conclusion, our findings confirm that *M. bovis* infections in cattle are associated with those in badgers, but they suggest that localized badger culling, using currently available methods, is unlikely to positively contribute to future strategies for cattle TB control in Britain.

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