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Herd-level risk factors associated with tuberculosis breakdowns among cattle herds in England before the 2001 foot-and-mouth disease epidemic

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A case–control study of the factors associated with the risk of a bovine tuberculosis (TB) breakdown in cattle herds was undertaken within the randomized badger culling trial (RBCT). TB breakdowns occurring prior to the 2001 foot-and-mouth disease epidemic in three RBCT triplets were eligible to be cases; controls were selected from the same RBCT area. Data from 151 case farms and 117 control farms were analysed using logistic regression. The strongest factors associated with an increased TB risk were movement of cattle onto the farm from markets or farm sales, operating a farm over multiple premises and the use of either covered yard or 'other' housing types. Spreading artificial fertilizers or farmyard manure on grazing land were both associated with decreased risk. These first case–control results from the RBCT will be followed by similar analyses as more data become available.

Keywords: bovine tuberculosis; case–control study; cattle movement; randomized badger culling trial; TB99

1. INTRODUCTION

Bovine tuberculosis (TB) is a major animal health problem in Great Britain. Over 4.5 million cattle tests were performed during 2003, resulting in the slaughter of over 23 000 cattle. In the State Veterinary Service (SVS) west region, one in seven herds experienced TB-related movement restrictions during the year, the majority owing to a TB 'breakdown'—at least one member of a cattle herd failing the conventional TB skin test or showing evidence of TB lesions at slaughterhouse inspection (TB statistics, Defra: http://www.defra.gov.uk/animalh/tb/stats/stats_dec2003.htm). To identify factors associated with the risk of a TB breakdown, a case–control study (known as the TB99 study) was initiated in 1999 (http://www.defra.gov.uk/animalh/tb/trans/p3tb99.htm). The TB99 study was based on cattle farms enrolled in the randomized badger culling trial (RBCT; Bourne *et al.* 1999; Donnelly *et al.* 2003) and was intended to complement the findings of the RBCT.

Case–control studies in the Republic of Ireland (Griffin *et al.* 1993, 1996), Northern Ireland (Denny & Wilesmith 1999) and Michigan, USA (Kaneene *et al.* 2002) have provided useful information on herd-level predictors of *Mycobacterium bovis* infection (the causative agent of bovine TB) and have led to recommendations on practices expected to reduce TB risk. The present study is the first such investigation in south-west England.

This paper describes an analysis of the risk of a TB breakdown in three RBCT regions (known as triplets) active before the 2001 foot-and-mouth disease (FMD) epidemic. The FMD epidemic interrupted data collection and so provided a clearly defined subset of data for analysis.

2. MATERIALS AND METHODS

All TB herd breakdowns that occurred in triplets A, B and C of the RBCT (table 1), after the initial proactive badger culls (the starting point of the RBCT) and before 1 January 2001, were eligible cases. Insufficient reports were obtained from the four other active RBCT triplets before the FMD interruption to warrant inclusion. Each case herd agreeing to participate triggered the selection of up to three control herds (one contiguous and two non-contiguous) matched on RBCT area. Eligible control herds had not experienced TB-related restrictions in the 12 months prior to the case breakdown and were selected randomly to reflect the herd size distribution of breakdowns within the RBCT areas in 1998. Each herd was included in the dataset only once, with subsequent case or control reports being excluded. Both the control and case reports were excluded if a farm completed one of each. All questionnaires were completed during an interview by trained staff from the local Animal Health Office.

Variables derived from the questionnaire covered a wide range of farm management, environmental and herd data and were screened using logistic regression, controlling for RBCT triplet and treatment (study design variables) and herd size to model the risk of a TB breakdown. (A full list of variables analysed is presented in the Electronic Appendix.) Non-categorical variables were ln transformed. All variables with a likelihood ratio test (LRT) p-value lesser than or equal to 0.15 compared with the forced covariates model (triplet, treatment and herd size) were made available for a final regression analysis. Models were constructed by backward elimination, considering the contribution of each variable to the variation in the data (by means of a LRT), the significance of the variable in the model and the stability of the remaining parameter estimates and standard errors when the variable was removed. Elimination of variables continued until a stable model was obtained. Interactions between all fitted and forced variables were examined, as were nonlinear terms for non-categorical variables.

The population attributable fraction (λ_{pop}: the proportion of the observed disease potentially prevented by removing exposure

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Table 1. Numbers of case and control reports available from each of the RBCT triplets for the various analyses.

triplet	region	start date	case reports	control reports	confirmed case reports
A	Gloucestershire/Herefordshire	January 2000	34	30	22
B	North Cornwall/North Devon	December 1998	61	34	47
C	East Cornwall	October 1999	56	53	42
	total		151	117	111

Table 2. Numbers of case and control farms reporting exposure to categorical variables made available to multiple logistic regression modelling.

variable	case farms		controls farms		likelihood ratio test p-value[a]
	positive	negative	positive	negative	
cattle brought on from markets	77	74	26	91	0.000
cattle brought on from farm sales	77	74	31	86	0.001
use of loose box housing	81	70	82	35	0.006
use of manure fertilizer	99	52	93	24	0.029
use of artificial fertilizer	130	21	109	8	0.031
use of covered yard housing	19	132	7	110	0.048
hired animals on the farm (such as breeding bulls)	19	132	6	111	0.076
mixed, deciduous wood land cover	72	79	38	79	0.080
presence of grazing premises (no housing provided)	120	31	102	15	0.083
use of 'other' housing types	103	48	65	52	0.098

[a] Compared with regression model containing the forced covariates (RBCT triplet, treatment and ln-transformed herd size) only.

to each factor) was calculated to compare factors in the regression model (Levin 1953)

$$\lambda_{\text{pop}} = p(E^+|D^+)((\psi_{\text{mult}} - 1)/\psi_{\text{mult}}))$$

where $p(E^+|D^+)$ is proportion of cases (D^+) exposed (E^+) to factor and ψ_{mult}, adjusted odds ratio (OR) for factor from multiple regression.

To calculate λ_{pop}, fitted non-categorical variables were converted to binary variables based on the median response. For protective factors, λ_{pop} was calculated using the inverse of ψ_{mult} and the proportion of cases not exposed to the factor ($p(E^-|D^+) = 1 - p(E^+|D^+)$).

The stability of the findings was examined by fitting alternative regression models. First, herd type (classified as dairy, beef or other) was included as an additional forced covariate. Second, cases were restricted to breakdowns confirmed by either culture of *M. bovis* or demonstration of visible lesions consistent with *M. bovis*.

3. RESULTS

In total, 151 case reports and 117 control reports from unique farms were analysed; 111 of the case reports referred to confirmed TB breakdowns (table 1). Case reports were received for 87% of eligible breakdowns. Seven case reports and 46 control reports were discarded as repeat visits. Ten categorical variables (table 2) and one non-categorical variable (total number of farm premises; cases: $n=151$, mean$=2.33$, s.e.m.$=0.15$; controls: $n=116$, mean$=1.74$, s.e.m.$=0.10$) passed the univariable screening, and were used in further analyses.

The effects of the forced covariates triplet and treatment reflected the relative numbers of cases and controls obtained from each triplet and treatment. There was no effect of herd size, as the controls were selected based on the expected distribution of case herd size.

Seven variables, in addition to the forced covariates, were included in the final regression model (table 3). Movement of cattle on to the farm from either markets or farm sales increased TB risk with odds ratios of 3.26 and 1.93, respectively. Two housing variables were associated with an increased risk of a breakdown, namely use of covered yard housing (OR$=$4.22) and use of 'other' housing types (OR$=$2.30). Operating herds over multiple premises also increased the TB risk (OR$=$1.79). Spreading of artificial fertilizers and farmyard manure on grazing land were both associated with a decreased TB risk (OR$=$0.21 and 0.42, respectively). None of the interaction terms was significant (using Bonferroni's correction for multiple tests) and neither were the nonlinear effects of herd size or number of premises. None of the factors was distinguished on the basis of λ_{pop} (range: 0.10 (use of covered yard housing) to 0.39 (use of 'other' housing types); table 3).

Similar risk factors were identified and consistent effects were found in the alternative models (table 4). Firstly, the inclusion of herd type as a forced covariate did not alter the composition of the model or the parameter estimates. Secondly, restricting the case definition to include only confirmed TB breakdowns resulted in the substitution of the protective factor use of artificial fertilizer with the presence of 'other' soil types on the farm as a protective factor. There was no appreciable change in the OR estimates of the conserved factors in the model but the confidence limits were somewhat wider.

4. DISCUSSION

A number of herd and farm management factors associated with TB risk have been identified in

Table 3. Logistic regression model of the risk of a TB breakdown showing the prevalence of exposure to the various factors among cases and population attributable fractions.

variable	estimate (s.e.m.)	odds ratio	95% confidence interval low	95% confidence interval high	exposure among cases[a] ($p(E^+\|D^+)$)	population attributable fraction (λ_{pop})
intercept	1.48 (1.10)	—	—	—	—	—
RBCT triplet						
A versus C	−0.23 (0.42)	—	—	—	—	—
B versus C	0.59 (0.36)	—	—	—	—	—
RBCT treatment						
proactive versus survey only	1.09 (0.40)	—	—	—	—	—
reactive versus survey only	0.57 (0.35)	—	—	—	—	—
herd size (ln)	0.16 (0.18)	—	—	—	—	—
use of artificial fertilizer	−1.54 (0.55)	0.21	0.07	0.63	0.14	0.11
use of manure fertilizer	−0.88 (0.37)	0.42	0.20	0.85	0.34	0.20
use of covered yard housing	1.44 (0.56)	4.22	1.41	12.65	0.13	0.10
cattle brought on from markets	1.18 (0.33)	3.26	1.71	6.21	0.51	0.35
use of 'other' housing types	0.83 (0.32)	2.30	1.22	4.33	0.68	0.39
cattle brought on from farm sales	0.66 (0.32)	1.93	1.03	3.60	0.51	0.25
use of two or more premises[b]	0.58 (0.31)	1.79	0.97	3.32	0.60	0.26

[a] For variables associated with a decreased risk (use of artificial fertilizer or loose box housing) of a TB breakdown calculated as $p(E^-|D^+)$.
[b] Variable included in model construction as a continuous variable but presented here as a binary indicator variable.

Table 4. Comparison of variations to the logistic regression model of the risk of a TB breakdown based on changes to the data being modelled and the forced covariates included.
(Variables included in the final models are shown with 95% confidence limits of the odds ratios from the models. Non-categorical variables converted to binary categorical variables based on the median response.)

variable	multiple regression model: all cases and all controls	all cases and all controls (herd type as additional forced covariate)	confirmed cases and all controls[a]
use of artificial fertilizer	(0.07, 0.63)	(0.08, 0.72)	(0.09, 0.96)[a]
use of manure fertilizer	(0.20, 0.85)	(0.16, 0.73)	(0.16, 0.78)
use of covered yard housing	(1.41, 12.65)	(1.52, 14.56)	(1.51, 16.95)
cattle brought on from markets	(1.71, 6.21)	(1.85, 6.89)	(1.67, 6.62)
use of 'other' housing types	(1.22, 4.33)	(1.10, 4.00)	(1.04, 4.30)
cattle brought on from farm sales	(1.03, 3.60)	(1.05, 3.77)	(1.22, 4.75)
use of two or more premises[b]	(0.97, 3.32)	(0.93, 3.23)	(0.96, 3.68)
'other' soil types on the farm			(0.11, 0.89)

[a] Artificial fertilizer use is presented here for comparison with the other models, although it was excluded from the final confirmed-cases model owing to its poor contribution to explaining variation in the data.
[b] Variable included in model construction as a continuous variable, but presented here as a binary indicator variable.

these analyses. Foremost were variables describing the movement of cattle on to the farm, namely sourcing cattle from markets or farm sales. Somewhat surprisingly, the risk did not increase with the number of cattle moved on to the farm or with moving specific cattle types, as observed by Griffin *et al.* (1993). Nonetheless, the consistent results for these factors suggest a significant risk of importing TB onto the farm. Griffin *et al.* (1996) did not show any risk associated with moving cattle onto the farm where a policy of pre-movement testing was in place, but instead found that cattle purchased since the last herd test were less likely to fail the subsequent test.

Operating the farm over multiple separated premises was associated with an increased TB risk beyond any effects of herd size and in the absence of an effect of total area farmed. Further study is required to determine whether this factor acts as a proxy for a combination of environmental or management variables that together increase risk. For example, more premises may include more contiguous herds or more badger setts, both identified as risks in other studies (Griffin *et al.* 1996; Martin *et al.* 1997; Denny & Wilesmith 1999).

Two housing-related factors were included in the various regression models, both associated with an increased risk of a TB breakdown: covered yards (open-walled housing for larger groups of cattle that may or may not be sub-divided) and 'other' housing types. The latter of these two was poorly defined and undoubtedly denotes a broad range of housing types, and so interpretation of its inclusion in the model is difficult. Kaneene *et al.* (2002) concluded that housing designed to minimize cattle–wildlife contacts (deer in this case) reduced TB risk. This was not demonstrated in the present study, although the importance of housing factors was highlighted. Better definition of housing types is needed, determining which cattle were kept in various housing types and for how long.

Fertilizer use on grazing land was found to be protective, irrespective of whether it was artificial fertilizer or manure. It is not clear why this is so, although there were few instances where farms did not use fertilizers on the grazing land. Griffin *et al.* (1993) observed that spreading slurry increased the risk of TB, although this variable did not appear in their final regression model.

Unlike the conclusions of Kaneene *et al.* (2002) and Griffin *et al.* (1993), the presence of a potential wildlife reservoir, measured here as active badger setts mapped to either the farm land or to within 1 km of the farm boundaries, made no appreciable contribution to the models. An alternative indicator of badger exposure, such as the distance to the nearest main sett or local badger density, may be more appropriate. The prevalence of TB in badgers assessed locally would be particularly relevant because prevalence can vary considerably between adjacent social groups (Rogers *et al.* 2003).

The design of the TB99 study was to include three controls per case, but this was never realized and there was therefore a potential for bias owing to the non-random loss of potential controls. This was investigated using farm data available from the SVS and RBCT databases by comparing those farms included as controls with those herds in the RBCT areas not included in the case–control study (see the Electronic Appendix). As expected from the selection procedure, control farms were larger than farms not included in the study in terms of herd size and farm area ($p<0.01$). Levels of consent to the RBCT differed between control farms and non-participating farms ($p<0.01$). There were no differences between the two groups with respect to herd type ($p=0.08$), number of land parcels ($p>0.1$) or the numbers of badger setts on the farm land ($p>0.1$) or within 1 km ($p>0.1$).

Possible causal interpretations of these conclusions must be treated cautiously, however, especially because of biases, potential unobserved confounders and the possibility that some explanatory variables are proxies for other, more biologically relevant, variables. While we have aimed to exclude alternative explanations as far as possible, ambiguities of interpretation apply to broad observational studies of this type.

Nonetheless, these analyses have identified factors associated with the risk of a TB breakdown in three RBCT triplets before the 2001 FMD epidemic. The results are broadly consistent with findings from studies elsewhere, although some differences were found, as would be expected from this complex disease system. Further investigations of factors will be possible as additional data become available.

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