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## Article

Gabrielle E. Kelly\*

# Joint Spatio-Temporal Modeling of *Mycobacterium bovis* Infections in Badgers and Cattle – Results from the Irish Four Area Project

**Abstract:** In Ireland and in the UK, bovine tuberculosis (bTB) infects cattle and wildlife badgers (*Meles meles linnaeus*) and badgers contribute to the spread of the disease in cattle. Isotropic and anisotropic spatio-temporal models are fitted to cattle herd and badger sett bTB incidence data from the Four Area Project using sequences of linear geostatistical models. An association was found between the spatial distribution of the disease in cattle and badgers in two of three areas. The limited association may be due to irregularity of sett territories, fragmentation of farms, TB-test insensitivity, temporal lags associated with transmission or non-spatial transmission. A statistical methodology is outlined whereby hypotheses related to spatial correlation structure may be tested.

**Keywords:** association between bTB infection in badgers and cattle, spatio-temporal modeling, geostatistical models, Four Area Project

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## 1 Introduction

As humans have moved cattle around the world, bovine tuberculosis (bTB), causative agent the bacterium *Mycobacterium bovis* (*M. bovis*), has also spread. It has now a global distribution with a range of wildlife maintenance hosts, including possums in New Zealand, white-tailed deer in North America and buffalo in Africa and these wildlife are implicated in spreading the disease in cattle (Etter et al. 2006).

In Ireland and in the UK, *M. bovis* can infect and cause bTB in both cattle and the European badger (*Meles meles linnaeus*) and badgers are a known reservoir of

infection for cattle (Bourne et al. 2007; Donnelly et al. 2007; Griffin et al. 2005). Kelly et al. (2010) and Kelly and More (2011) found spatial correlation of the disease in badgers and cattle separately. Here the question of spatial association across the species is considered, to further the understanding of the spatial structure of the disease together with the role of underlying geography.

Recent genetic evidence shows badgers in Ireland and Great Britain (GB) have different origins that may influence diet, roaming patterns and habitats (Sleeman and Mulcahy 2005; Kelly et al. 2010; O'Meara et al. 2012). Irish badgers exhibit more wide ranging behavior and there are also differences in badger social group size and these factors may result in a different spatial structure of the disease between Ireland and GB. In addition, a study in south-west England found that badgers visited farm buildings that were mostly feed stores with a peak in visits in spring and summer (Tolhurst et al. 2009). Thus dietary preferences influence when and how often British and Irish badgers visit farm buildings and their roaming patterns and the latter may not be the same for both (Sleeman, Davenport, and Fitzgerald 2008, Keohane and McCarthy 2009). This in turn affects associated risks of bTB transmission across species.

Differences in cattle breeding systems, environmental conditions and control measures between Ireland and the UK lead to different epidemiological situations also making it difficult to extrapolate between studies from the two countries (Gordejo and Vermeersch 2006).

However, in both countries badgers contribute to failure of bTB eradication programs in cattle and control strategies in the UK are a subject of intense national debate involving environmentalists, farmers, animal rights advocates and the general public (e.g. 21 June 2011, <http://www.bbc.co.uk/news/uk-wales-politics-13854902>; 25 September 2012, <http://www.bbc.co.uk/news/uk-19709033>).

In Ireland cattle owners are legally obliged to present their animals for a full herd test each year and disclosure of bTB in a herd involves slaughter of the affected cattle, movement control of the herd and additional repeated testing. Reactive culling of badgers may take place, following bTB disclosure and an epidemiological inspection by the District Veterinary Inspector, as described in Griffin et al. (2005) and Kelly et al. (2008). Typically, a radius of approximately 2 km around the index farm is chosen for the reactive cull. Disease clustering is an important consideration in this choice and finding optimal control strategies is a subject of on-going research.

In this study data are drawn from a large scale field trial, the Four Area Project (FAP), a formal badger removal project undertaken in four counties in Ireland from September 1997 to August 2002, to assess the effect of badger culling on the incidence of bTB. The aims of this study are:

1. to establish if there is a relationship between spatial association of *M. bovis* in cattle and spatial association of *M. bovis* in badgers;
2. to establish if spatial associations changed over the 5-year period in which data are considered;
3. to outline a statistical methodology whereby the hypotheses in 1 and 2 may be tested.

Questions 1 and 2 will be examined for each county separately for reasons given below.

In previous spatial analyses related to bTB in cattle herds, Kelly and More (2011) restricted attention to isotropic spatial correlation, while Kelly (2011) and Kelly (2012) do account for possible anisotropy in different ways. In this study, anisotropic spatial correlation is considered using geometric anisotropic correlation structures not considered previously.

In Section 2 we introduce the data and present preliminary analyses. Section 3 outlines a sequence of linear geostatistical models (LGM's) (Diggle and Ribeiro 2007) for modeling the joint spatial distribution of the disease in cattle and badgers. Section 4 presents the results of the joint modeling while in Section 5 the results are interpreted and discussed.

## 2 Cattle and badger data

The data used in this study are drawn from the FAP. Briefly, the FAP was conducted in matched removal and reference areas (average area of 245 km<sup>2</sup>) in four counties

in Ireland: Cork, Donegal, Kilkenny and Monaghan. Badger culling was carried out proactively in the removal areas with minimal culling in the reference areas. The geographical location of the areas is shown in Figure 1. The study design and its results are published in detail in Griffin et al. (2005).

Only data from removal areas are considered since culling was minimal in reference areas and relevant badger data not available for them. The removal areas are for the most part surrounded by fixed natural boundaries (e.g. rivers, mountain ranges and sea inlets), outside of which neighbors do not exist, as can be seen in Figure 2. Where natural barriers were absent, the areas up to 6 km in width, at the boundary of each selected removal area, were labeled "buffer areas," although badger removal was also proactive in these areas. In this study buffer and removal areas combined are referred to as removal areas. In an area isolated by natural boundaries, the spatial process discontinues at the boundaries as noted in Henley (1981). However, there was some permeability in the FAP and limited immigration of badgers into the removal areas occurred during the study period (Griffin et al. 2005; Sleeman et al. 2009). Thus the problem of edge effects arises and for counties Cork, Donegal and Kilkenny this was limited to the first 2 years for the most part while in Monaghan it continued throughout the study period (Griffin et al. 2005). Therefore the data are considered both as a unit and in two stages. Stage 1 denotes the first two culling years and stage 2 the last three culling years of the FAP. The variable stage is used rather than year for reasons described below but mainly because of sparsity of data (low rates of bTB positive herds) for subsequent modeling and in the case of badgers the majority of badgers were culled in the first two culling years of the study.

All badgers culled during the 5-year period 1997–2002 for which the infection status, sex and age were known are included for study. The badger sett is the unit of analysis and number of badgers captured per sett is available as well as the geographical information system (GIS) coordinates of the sett at capture. Beginning in September 2007 two culls took place on an annual basis – around September and May of each year and thus September–September shall be referred to as the culling year. A sett is regarded as bTB positive if any badger captured in the sett was bTB positive. As stated in Kelly and More (2011), the culture method used underestimates the true infection prevalence. Badger setts are at best incompletely culled out via snare traps (Sleeman et al. 2009) and thus the same sett may form

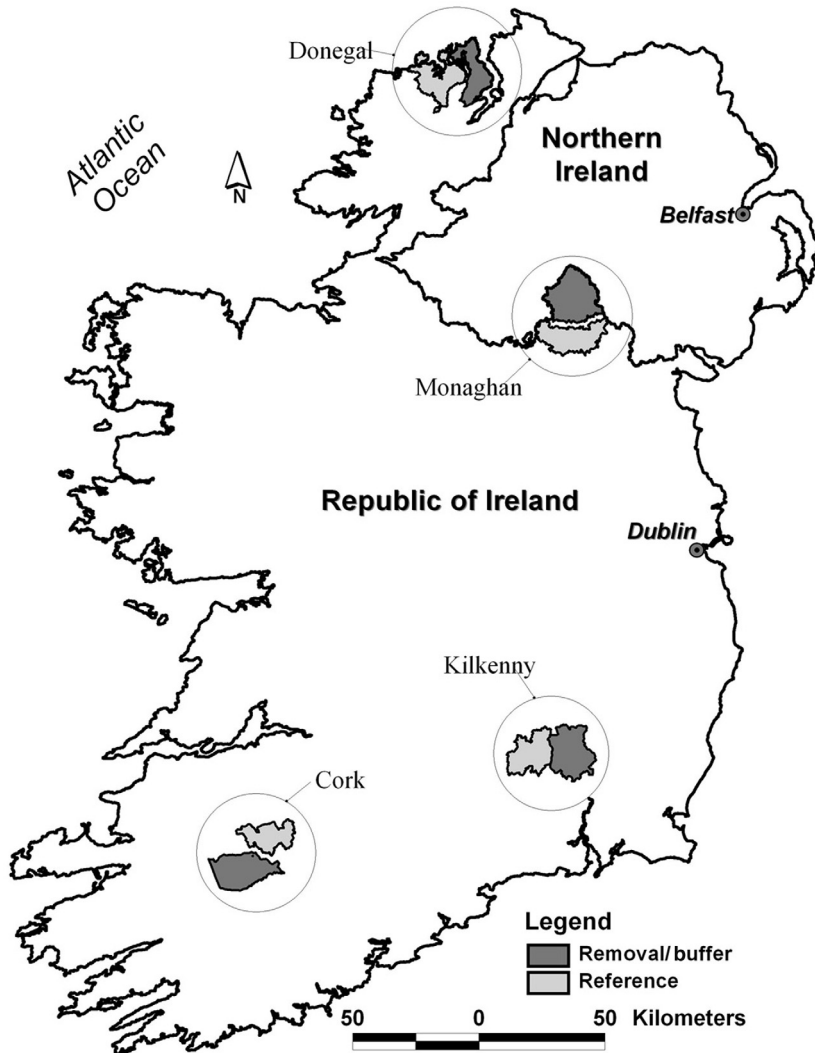


Figure 1 Location of the matched removal and reference areas in counties Cork, Donegal, Kilkenny and Monaghan of the FAP.

part of the data for both stages 1 and 2. There is also evidence that setts are not persistently infected (or for that matter, not repopulated).

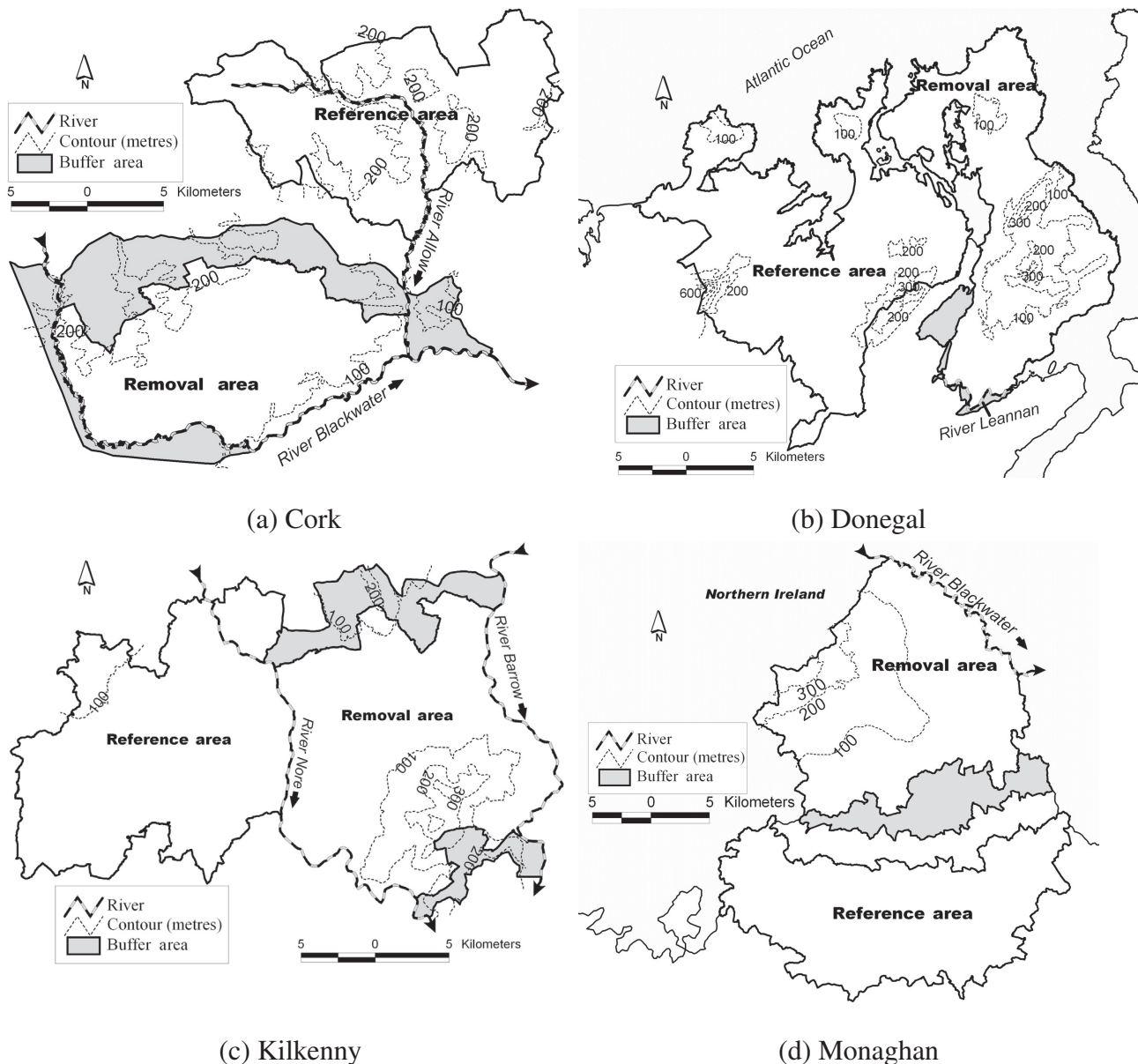
Herd data were also taken from the removal areas of the FAP for comparative purposes. A herd was designated infected in a year if it contained at least two cattle that tested positive for bTB in that annual yearly Single Intradermal Comparative Tuberculin Test (SICTT), as in Kelly and More (2011). This test has sensitivity 52.9–60.8% and specificity 99.2–99.8% of which further details can be found in Clegg et al. (2011). As a herd may be located on multiple parcels of land, GIS coordinates of the herd are taken as the centroid of the main parcel of land. The advantages and disadvantages of this choice is discussed in detail in Kelly and More (2011).

## 3 Modeling

### 3.1 Preliminary data analyses

We begin with preliminary exploratory data analyses. Table 1 shows descriptive statistics for the incidence of bTB in the two species by area and stage.

County Cork: Over the 5-year period, there were 1,870 observations (i.e. annual full herd tests) corresponding to 422 distinct herds. During this period some herds ceased operating (i.e. had 0 cattle) and others began, but 88% of herds had at least four annual tests. There were 83 cases, i.e. 83 bTB reports involving 68 distinct herds. In a logistic non-spatial model fitted to herd bTB status (positive/negative) in each year, history of bTB in the previous year



**Figure 2** The removal (including buffer) and reference areas within counties (a) Cork, (b) Donegal (c) Kilkenny and (d) Monaghan of the Four Area Project September '97–August '02.

(ph, yes/no), log(herd size) and year are statistically significant ( $p < 0.0001$  in each case). Using the variable stage instead of year gave a slightly better fit by Akaike's Information Criterion (AIC).

274 badger setts were culled in the 5-year culling period. 124 infected setts were observed during the period (124 had a badger with bTB, i.e. 45.3% of setts). Infected badgers were culled from 27 setts in both stages. The variable number of badgers culled in the sett constituted a significant fixed effect ( $p < 0.0001$ ) in a logistic model fitted to sett bTB status in each year, with stage also being significant ( $p = 0.0222$ ).

County Donegal: There were 1,710 observations corresponding to 397 distinct herds. Only 0.3% of herds were infected over the period, a number too small for statistical modeling.

133 badger setts were culled in total, 35 of which were infected (26.3% of setts). 7 setts had infected badgers culled from them in both stages. The number of badgers culled in the sett was significant ( $p = 0.0009$ ) in a logistic model fitted as above, with stage not significant ( $p = 0.44$ ).

County Kilkenny: There were 1,103 observations corresponding to 261 distinct herds with 22 cases. 85%

**Table 1** Numbers of badgers culled/setts and number of herds and percentage of these with positive bTB status, in the badger removal areas in four counties of Ireland during 1 September 1997 to 31 August 2002. Stage 1 denotes the first two culling years and stage 2 the final three years.

County	Stage	No. of setts	% setts positive	No. of badger	% badger positive	No. of herds	% herds positive
Cork	1	274	45.3	574	27.9	417	12.2
Cork	2	90	30.0	211	15.2	405	5.9
Cork	Total	274	45.3	785	24.5	422	15.2
Donegal	1	133	26.3	243	14.4	387	0.3
Donegal	2	42	16.7	75	12.7	385	0.0
Donegal	Total	133	26.3	318	13.5	397	0.3
Kilkenny	1	191	29.3	335	13.7	255	4.3
Kilkenny	2	91	55.3	199	15.1	252	4.0
Kilkenny	Total	191	29.3	534	14.2	261	8.4
Monaghan	1	183	40.4	327	20.2	793	3.7
Monaghan	2	116	25.0	245	13.5	775	3.4
Monaghan	Total	183	40.4	572	17.3	807	6.3

of herds were observed for at least 4 years. In the logistic model fitted to herd bTB status, ph ( $p = 0.51$ ), log(herd size) ( $p = 0.11$ ) and year ( $p = 0.63$ ) were not statistically significant. The AIC for the model with stage replacing year was considerably better but stage was not statistically significant in the better model either ( $p = 0.20$ ).

191 setts were culled in total, 56 of which were infected (29.3% of setts). 23 setts had infected badgers culled from them in both stages. The number of badgers culled in the sett constituted was significant ( $p < 0.0001$ ) with a logistic model fitted as above, while there was no effect of stage ( $p = 0.95$ ).

County Monaghan: There were 3,425 observations corresponding to 807 distinct herds with 58 cases. 84% of herds had at least 4 years of observation. In the logistic model fitted to herd bTB status, ph ( $p = 0.0012$ ) and log(herd size) ( $p < 0.0001$ ) were statistically significant while year was borderline significant ( $p = 0.1221$ ). Replacing year by stage gave a better fit by AIC, with stage significant in the model ( $p = 0.0439$ ).

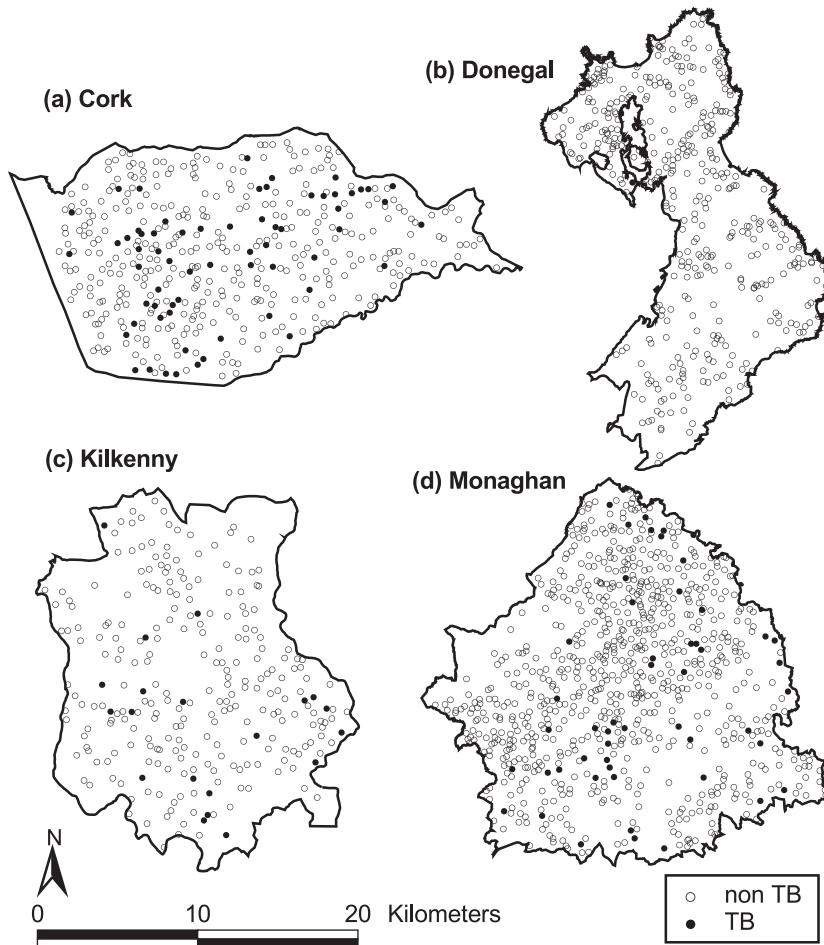
183 setts were culled in total, 74 of which were infected (40.4% of setts). 29 setts had infected badgers culled from them in both stages. The number of badgers culled in the sett was significant ( $p < 0.0001$ ) in the logistic model, with stage also significant  $p = 0.0549$ .

From Table 1 it is clear there is considerable variation in bTB status across counties both for badgers (and setts) and cattle herds. For all areas for the logistic model for herd bTB, models with the first two and last three culling years grouped (i.e. stage 1 and 2) fit equally well if not better than the model with year and standardized Pearson residuals were obtained from this model for

each county. Covariates other than ph, log(herd size) and stage were not considered based on previous analyses of these data (Griffin et al. 2005; Kelly and More 2011). We note that for Kilkenny none of these covariates were statistically significant due perhaps to the small number of herds at risk and small number of cases. Similarly for badger setts, bTB models with years grouped into the two stages fit equally well as year and the standardized Pearson residuals from this model were obtained for each county. Covariates other than the number of badgers culled in a sett and stage were not considered based on the analyses of Kelly et al. (2010). These residuals for cattle herds and badger setts were then pooled by county for further analyses.

Initial plots were made of the response variables infected/not infected (Figures 3 and 4), as well as the pooled standardized Pearson residuals of infected herds and infected badgers setts from the respective logistic models described above, versus the associated GIS coordinates separately for each county. There was no “apparent” visual clustering of cases in badgers and cattle but some clustering in cattle herds in counties Cork and Monaghan can be seen in the 2-D plots of Figure 3.

Directional semi-variograms based on the above Pearson residuals of positive herds and badger setts were then constructed separately for each county. Semi-variograms based on combined species residuals are difficult to interpret as the residuals differ by a scale factor over the species. In county Cork the semi-variograms showed spatial variation within each species separately with more spatial variation along the east–west axis than north–south. In county Donegal there was little evidence of spatial clustering among badgers. In counties Kilkenny



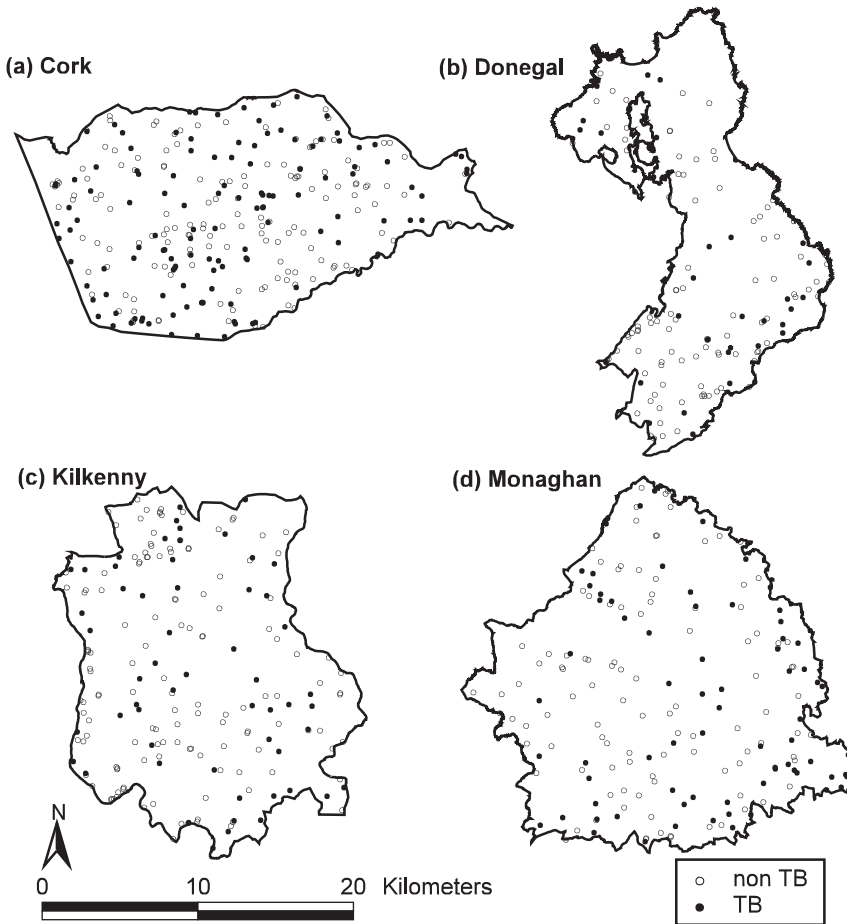
**Figure 3** Scatterplots of locations of bTB infected and non-infected herds in the badger removal areas of four counties in the period 1997–2002.

and Monaghan the directional semi-variogram for badgers and cattle combined had some additional structure than those for badgers and cattle separately. As noted in Diggle and Ribeiro (2007), these types of three-dimensional plot require more data than their two-dimensional counterparts (the ordinary empirical semi-variogram) and yield only gross directional effects and thus are not shown here.

### 3.2 Joint species spatial models

In examining the spatial structure for these data, the question arises firstly whether data from the four counties should be combined or analyzed separately. This depends on whether the correlation structure within a species differs for all four counties. It is not possible to fit one spatial model to badger data combined over four counties. One cannot expect spatial correlation between badger setts in different counties. If data are combined,

badger setts with the same inter-distances from different counties are pooled. Thus if correlation between setts is modeled as a function of the inter-distances, we can expect a value of zero. This is in fact the result when this is done. Therefore one can just fit separate spatial structures to each county and compare them. In Kelly and More (2011) and Kelly (2011) estimates of spatial parameters for cattle herds were found to differ for the four counties for these data and in Kelly et al. (2010) estimates of spatial parameters for badger setts varied with county also. In Griffin et al. (2005) estimated parameters in the mean model varied with county and in addition there was a significant effect of county. Since both Cressie (1993) and Diggle and Ribeiro (2007) state fixed effects are useful to describe large scale spatial trends, this latter result also indicates differences in spatial correlation structure between counties. Therefore, we assume here, as it has already been established, the correlation structure within a species differs for all four counties.



**Figure 4** Scatterplots of locations of bTB infected and non-infected badger setts in the badger removal areas of four counties in the period 1997–2002.

Spatial models for badgers and cattle combined present additional difficulties than single species models as different covariates are associated with the disease in each species, thus presenting problems when combining data. In addition, the scale of spatial association may vary with species and this also needs to be accounted for. Generally in epidemiology the interest is in the covariates (risk factors). Once these are identified, the residual autocorrelation is investigated. However, since these data have been extensively analyzed and important covariates identified with the results published elsewhere, these analyses shall not be re-iterated here and the focus shall be on spatial autocorrelation. Having removed the effects of differing covariates for the two species using models described in Section 2, the standardized Pearson residuals from these two models were pooled for spatial modeling. The pooled residuals are either positive or negative corresponding to positive or negative bTB infection status and therefore cannot be assumed to be normally distributed. Thus four groups of residuals are

identified corresponding to: positive/negative cattle herds and positive/negative badger setts. A fixed effect for these groups is included in all models since the sets of residuals may be of different order of magnitude. This categorical variable “group” distinguishes residuals from cattle herds and badger setts and infected from non-infected animals.

Attention is restricted here to fitting geometrically anisotropic and isotropic LGMs to these residuals. These are linear models extended to include spatially correlated random effects. GIS coordinates are used to model the spatial correlation. The models assume the spatial process is second-order stationary and is isotropic, i.e. spatial correlation does not depend on direction but can be extended to include possible anisotropy. They have been used to describe spatial association of bTB in badgers and separately in cattle herds using data from the FAP by Kelly et al. (2010), Kelly and More (2011) and Kelly (2011). LGMs can describe small-scale variation and can estimate the scale of this variation, i.e. range of

clustering. Fitting an LGM to the residuals is equivalent to fitting a marginal spatial generalized linear model to the original binary observations positive/negative, as described in Schabenberger and Gotway (2005, section 6.3.5) but without iterating between estimation of the mean and spatial covariance structures. Since what is aimed at here is first to remove any large-scale fixed effects and then estimate spatial correlation structure, this iteration is not performed. This issue is discussed in Diggle and Ribeiro (2007, section 5.2.5). Modeling the combined residuals also has the advantage that it circumvents the extra computational difficulties that arise, due to differences in scale of the mean structure, when fitting generalized linear geostatistical models (GLGMs) to the combined binary data of the two species.

LGMs with exponential covariance structure are fitted as described in Schabenberger and Gotway (2005, section 6). The LGM model used is as follows:

Let  $r(s_i)$  be the residual for the animal at the  $i$ th location  $s_i$ . Let  $u(s_i)$  be a spatial random effect at location  $s_i$ . We assume the  $u(s_i)$  follow an exponential isotropic model initially with covariance matrix  $F$  with  $(i,j)$ th element is given by

$$F[i, j] = \text{Cov}[u(s_i), u(s_j)] = \sigma^2[\exp(-d_{ij}/\rho)] \quad [1]$$

where  $d_{ij}$  is the distance between the locations  $s_i$  and  $s_j$ . We thus have a Gaussian linear model with a constant term and a random effect  $u(s_i)$  with spatial exponential covariance structure. The variance-covariance matrix of the data is thus  $\text{Var}[r(s)] = F$ . The parameters  $\sigma^2$  and  $\rho$  refer to the geostatistical parameters “sill” and “range”, respectively. Covariance in this model reaches zero only asymptotically, thus the practical range is defined as the distance at which covariances are reduced to 5% of the sill, i.e.  $3\rho$ . Since we have repeated measures on cattle herds (data over 5 years) and also on some badger setts, all models include nugget terms, representing yearly variation within herds or setts. A nugget term is included by using

$$\text{Var}[r(s)] = \sigma_1^2 I + F \quad [2]$$

All models are also fitted including possible terms for anisotropy that is modeled geometrically as

$$F[i, j] = \sigma^2[\exp(-d_{ij}(\theta, \lambda))/\rho] \quad [3]$$

i.e. geometric anisotropy is corrected by applying a rotation  $\theta$  and scaling  $\lambda$  to the coordinate system, and  $d_{ij}(\theta, \lambda)$  represents the Euclidean distance between two

points in the transformed space. If a process is geometrically anisotropic in coordinate system  $c = [c_1, c_2]$ , then it is isotropic in the coordinate system

$$Ac = \begin{pmatrix} 1 & 0 \\ 0 & \lambda \end{pmatrix} \begin{pmatrix} \cos\theta & -\sin\theta \\ \sin\theta & \cos\theta \end{pmatrix} c = c^*$$

The model has four unknown parameters. The scaling parameter  $\lambda$  represents the ratio of the range parameters in the direction of the major and minor axis of the correlation contours (Diggle and Ribeiro 2007, section 3.7). Fixing  $\lambda = 1$  reduces the model to an isotropic one for any angle of rotation – this provides a test for anisotropy. Kelly (2012) used a different model for anisotropy but the geometric representation here with estimation of angle and scale provides models that are more practically useful and interpretable.

Parameter estimates are obtained via restricted maximum likelihood together with a measure of goodness-of-fit of the model:  $-2$  residual log(likelihood) or AIC or AIC corrected (AICC), a version of AIC that is adjusted for the effects of estimating parameters (Schabenberger and Gotway 2005, section 6.2). Models with the same mean structure but nested covariance structures are compared by taking the difference of  $-2$  residual log(likelihood) and referring it to a  $\chi^2$  distribution with degrees of freedom the difference in number of covariance parameters in the models, i.e. a likelihood ratio test (LRT). Since we are testing whether certain variance components are zero, the parameters lie on the boundary of the parameter space and for a test involving one variance parameter only we divide the  $p$ -value obtained from  $\chi_1^2$  by 2 (Self and Liang 1987, case 5). If we are simultaneously testing several covariance parameters equal to zero, the distribution theory is more complicated but the  $p$ -value obtained from a  $\chi^2$  test will provide an upper bound (Self and Liang 1987). By case 9 of Self and Liang, if for example, the variance-covariance matrix is diagonal and we simultaneously test four variance components to be zero, the asymptotic distribution of the likelihood ratio statistics is a mixture of  $1/16\chi_0^2$ ,  $4/16\chi_1^2$ ,  $6/16\chi_2^2$ ,  $4/16\chi_3^2$  and  $1/16\chi_4^2$ . By the arguments of Stram and Lee (1994, Case 4), if the variance-covariance matrix is block diagonal and we are testing simultaneously the elements of a  $4 \times 4$  variance-covariance matrix to be zero, i.e. one of the blocks is a 0 matrix, estimation of the off-diagonal elements has no effect on the asymptotic distribution of the LRT and thus it is again given by the above mixture of  $\chi^2$ . This can also be seen by applying Hölder’s inequality since if all variance terms are zero the covariance terms are necessarily zero. These tests will be referred to as

modified LRTs and associated  $p$ -values are obtained by simulating the percentiles of the relevant mixture of  $\chi^2$  distributions. In some testing situations, a lower bound for the  $p$ -value may suffice. For the  $4 \times 4$  variance–covariance matrix above, the  $p$ -value associated with a mixture of  $1/16\chi_0^2$  and  $15/16\chi_1^2$  provides such a lower bound. Nested models are compared using AIC or AICC.

If the estimated  $\rho = 0$  then this seems to imply observations separated by more than 0 km are not spatially correlated. Then a modified LRT test of the hypothesis, spatial correlation does not depend on distance but is a constant  $\sigma^2$ , is carried out. As a model with  $\rho = 0$  and  $\rho = \infty$  fit equally well (as we can switch between the two by re-parameterization) a value  $\rho = 0$  may be due to just general spatial heterogeneity (unobserved spatial variables that could influence incidence). A further modified LRT test can be carried out to test if  $\sigma^2 = 0$ , i.e. if the partial sill is zero.

A model with a separate geometric anisotropic structure and a separate nugget for each “group” by stage is the most general model. But proceeding in a stepwise procedure from this considering all possible ways of amalgamating “groups” and stages that do not differ significantly does not necessarily lead to a coherent model. Therefore, the following stepwise model fitting procedure was adopted.

Step 1:

- Model 1: The spatial correlation structures in badger setts is determined separately. A model is fitted with a separate spatial structure and nugget for each stage for positive and negative setts.
- Model 2: The number of distinct nuggets in model 1 is determined using modified LRTs.
- Model 3: Proceeding from model 2 the number of distinct groups of geometric anisotropic parameters is determined again using modified LRTs. For badger setts, for example, a model may be fitted with a separate spatial correlation structure and nugget for each stage for positive and negative setts and compared to a model with a single spatial correlation structure for the combined setts for the stage. If the latter model fitted better than this indicated no spatial clustering of the disease in badger setts for that stage.
- Model 4: A separate spatial correlation model is fitted to each of the distinct “groups” as determined in model 3.

Step 2: A similar procedure as in Step 1 is carried for cattle herds.

Step 3: For each distinct spatial correlation group of badger setts and cattle herds determined in Steps 1

and 2, the corresponding data on badger setts and cattle herds are combined.

- Model 5: For each set of data in Step 3, a model with a separate spatial correlation structure and a separate nugget for each species is fitted to the combined two groups of species residuals.
- Model 6: For each set of data in Step 3, a model where one spatial correlation structure is assumed for badger setts and cattle herds is fitted. Model 6 allows for spatial association across the species while Model 5 specifies there is none. Thus the hypothesis of no cross-infection was tested by comparing  $-2$  residual log(likelihood) from Models 5 and 6 by modified LRTs.

The Gaussian and spherical covariance structures are also fitted in all models to see if fit is improved (Schabenberger and Gotway 2005). The scale in all models is km. Effects with  $p$ -values  $< 0.05$  are regarded as statistically significant. The statement significant spatial correlation structure means the partial sill was significantly different from 0.0.

Models are estimated using Proc Mixed of SAS 9.2 version 9, SAS Institute Inc., Cary, NC, USA.

## 4 Results

### 4.1 Cork

A comparison between a model fitted to combined positive and negative badger setts in stage 1 indicated one spatial correlation structure ( $p = 0.60$  in comparison with a model with two spatial correlation structures) and one nugget. Models fitted to stage 2 badger setts positive and negative combined showed a model with two spatial correlation structures ( $p < 0.0001$  in comparison with a model with one spatial correlation structure) and one nugget fitted best. Then positive and negative badger setts were considered separately for stage 2.

In stage 2, for positive badger setts a spatial correlation model had scale 0.0, indicating clustering along the major axis only while for negative badger setts the partial sill was 0.0, i.e. no spatial correlation.

For negative badger setts, spatial correlation structure differed between the two stages ( $p < 0.0001$ ), while for positive badger setts it did also ( $p < 0.0001$ ).

In summary, positive badger setts showed spatial clustering of disease in stage 2.

A comparison between a model fitted to combined positive and negative herds in stage 1 indicated two spatial correlation structures ( $p < 0.0001$  in comparison with a model with one spatial correlation structure) and one nugget. Models fitted to stage 2 herds positive and negative combined showed a model with two spatial correlation structures and one nugget fitted best also ( $p < 0.0001$  in comparison with a model with one spatial correlation structure).

For bTB positive cattle herds the nugget did not differ between the two stages but spatial correlation structure did ( $p < 0.0001$ ). The estimated range was 0.0, but the partial sill differed significantly from zero in both stages. Similarly, for bTB negative cattle herds, the nugget did not differ between the two stages but spatial correlation structure did ( $p < 0.0001$ ). The estimated range was 0.0, but the partial sill differed significantly from zero in both stages.

In summary, cattle herds show spatial clustering of disease in both stages 1 and 2.

Then positive badger setts and positive cattle herds in stage 1 were modeled. A model with one nugget fitted best and when a model with separate spatial orthogonal correlation structures for badgers setts and cattle herds was compared with a model with a single spatial correlation structure, the modified LRT had  $p < 0.0001$ . The same procedure was carried out for stage 2 with the same result. The modified LRT had  $p < 0.0001$ . The models indicated similar angles but different scale parameter estimates for setts and herds in each stage but the estimated range was 0.0 for cattle herds always.

For completeness, negative badger setts and negative cattle herds in stage 1 were also modeled (these groups have larger sizes than bTB positive groups). Using the same analysis as just described, a model with separate spatial correlation structures for badgers and cattle fitted better than a model with one spatial correlation structure by a modified LRT ( $p < 0.0001$ ). The models indicated similar angles and different scale parameter estimates for setts and herds but the same estimated range of 0.0. For stage 2, there was a similar result by a modified LRT ( $p < 0.0001$ ) but angle, scale and  $\rho$  estimates all differed by species.

These results show no evidence of cross-infection between badger setts and cattle herds in stage 1 or stage 2.

In conclusion, there was no evidence of cross-infection by species in either stage, but in stage 2 there was significant spatial clustering of disease in badger setts and separately in both stages for cattle herds with clustering in the latter extending over the whole area in a particular direction.

## 4.2 Kilkenny

A comparison between a model fitted to combined positive and negative badger setts in stage 1 indicated two separate spatial correlation structures ( $p < 0.0001$ , versus a model with one spatial correlation structure) and one nugget, while a similar comparison for stage 2 indicated one spatial structure ( $p = 1.0$ ). For positive badger setts, the nugget did not differ between the two stages but spatial correlation structure did ( $p < 0.0001$ ). For stage 1, an isotropic model fitted best, but the partial sill did not differ significantly from 0.0 ( $p = 0.35$ ), while for stage 2 the partial sill was 0.0 ( $p = 1.0$ ), i.e. no spatial correlation.

For negative badger setts, the nugget did not differ between the two stages but spatial correlation structure did ( $p < 0.0001$ ). However, when stages were analyzed separately the partial sill was 0.0 in both stages 1 and 2 ( $p < 1.0, 0.98$ ) respectively.

A comparison between a model fitted to combined positive and negative cattle herds in stage 1 indicated two separate spatial correlation structures ( $p < 0.0001$  versus a model with one spatial correlation structure) and one nugget. Therefore positive and negative cattle herds were considered separately. There was no spatial correlation among positive cattle herds ( $p = 0.99$ ) while for negative cattle herds there was ( $p < 0.0001$ ) with clustering on the major axis only and the estimated  $\rho$  was 0.0. There was a similar result for stage 2.

For positive cattle herds the nugget did not differ between the two stages but spatial correlation structure did ( $p < 0.0001$ ).

Similarly for negative cattle herds the nugget did not differ between the two stages but spatial correlation structure did ( $p < 0.0001$ ).

In summary, the results indicate spatial clustering of disease in badgers in stage 1 but not stage 2. There was evidence for spatial clustering of the disease in positive cattle herds, but numbers are very small. Negative cattle herds did show significant underlying spatial correlation structure, differing to positive herds, and this spatial correlation structure differed with stage. The results for cattle indicate spatial clustering of the disease in cattle with a large scale parameter.

Then positive badger setts and positive cattle herds in stage 1 were modeled. A model with one nugget fitted best and when a model with separate spatial orthogonal correlation structures for badgers setts and cattle herds was compared with a model with a single spatial correlation structure, the modified LRT had  $p = 1.0$ . In the former model the estimated angle for badgers was near 0.0 while

for cattle it was 0.0, i.e. essentially identical. The model with one spatial correlation structure had estimated partial sill that was non-zero with borderline significance ( $p = 0.15$  by modified LRT). The same procedure was carried out for stage 2 but the model with two spatial correlation structures fitted best (the modified LRT had  $p < 0.0001$ ). The model indicated distinct angles parameter estimates for setts and herds, the estimated scale was 0.0 for both species while the estimated partial sill was 0.0 also for badgers.

For completeness, negative badger setts and negative cattle herds in stage 1 were also modeled (these groups have larger sizes than bTB positive groups). Using the same analysis as just described, a model with separate spatial correlation structures for badgers and cattle fitted better than a model with one spatial correlation structure by a modified LRT ( $p < 0.0001$ .) A similar result was found for stage 2.

These results show strong evidence for cross-infection between badger setts and cattle herds in stage 1 and none in stage 2.

### 4.3 Monaghan

A comparison between a model fitted to combined positive and negative badger setts in stage 1 indicated a model with two spatial correlation structures ( $p = 0.12$ , borderline significance compared to a model with one spatial correlation structure) and no nugget fitted best. Spatial models fitted to stage 2 badger setts, positive and negative combined, showed no difference between positive and negative. A geometric anisotropic model fitted to positive badger setts stage 1 showed significant spatial correlation structure ( $p < 0.0001$ ). For stage 2 there was also evidence of spatial correlation structure ( $p = 0.0003$ ). In both stages clustering was anisotropic and the estimated  $\rho$  was 0.0, but spatial correlation structures differed by stage ( $p < 0.0001$ ).

A comparison between a model fitted to combined positive and negative cattle herds in stage 1 indicated two separate spatial correlation structures and one nugget. There was a similar result for stage 2. Therefore, positive and negative cattle herds were considered separately. For positive herds there was no difference in spatial correlation structure between the stages and a model with no spatial structure and a single nugget fitted best. For negative cattle herds there was spatial correlation in stage 1 ( $p < 0.0001$ ), but the scale was zero and there was a similar result for stage 2 but the spatial correlation structure did differ by stage ( $p < 0.0001$ ). Spatial

clustering was seen in the negative herds rather than positive, but this implicitly implies a spatial effect among positive herds also.

In summary, there was evidence of spatial clustering of disease in badger setts in stages 1 and 2. There was significant spatial clustering of disease in cattle herds also in stages 1 and 2.

Then positive badger setts and positive cattle herds in stage 1 were modeled. A model with one nugget fitted best and when a model with separate spatial orthogonal structures for badgers setts and cattle herds was compared with a model with a single spatial structure, the modified LRT had  $p < 0.0001$ . The same procedure was carried out for stage 2 with the same result. The modified LRT had  $p < 0.0001$ . The models indicated distinct angles and scale parameter estimates for setts and herds in each stage but the same estimated range.

For completeness, negative badger setts and negative cattle herds in stage 1 were also modeled (these groups have larger sizes than bTB positive groups). Using the same analysis as just described, a model with separate spatial correlation structures for badgers and cattle fitted better than a model with one spatial correlation structure by a modified LRT ( $p < 0.0001$ ). The models indicated distinct angles and scale parameter estimates for setts and herds but the same estimated range. For stage 2, a model with one spatial correlation structure fitted best by a modified LRT ( $p < 0.0001$ ) and by a modified LRT the estimated partial sill was non-zero ( $p < 0.0001$ ) although the estimated  $\lambda$  was 0.0 and scale was 1.0. Finally negative badger setts and positive cattle herds stage 2 were considered and a model with two spatial correlation structures fitted best ( $p < 0.0001$ ).

These results show no evidence of cross-infection between badger setts and cattle herds in stage 1 while there is evidence for this in stage 2.

### 4.4 Donegal

Donegal differs to the other areas in that there were very few confirmed herd restrictions in the removal area for the 5-year period 1997–2002. Low levels had been achieved in the county prior to removal and these persisted (Griffin et al. 2005). Numbers of infected herds are thus too small to permit spatial modeling.

However, badger setts where capturing occurred were examined for spatial correlation structure. For stage 1, a model was fitted with different spatial correlation parameters for the positive and negative setts and no covariance between these two groups and with two

**Table 2** Summary of spatial model fitting results to standardized Pearson residuals of infected herds from a logistic model fitted to herd bTB incidence and infected badger setts fitted to sett bTB incidence separately for the removal areas of counties (a) Cork, (b) Donegal (c) Kilkenny and (d) Kilkenny of the Four Area Project September '97–August '02. Stage 1 denotes September '97–August '99 and stage 2 September '99–August '02. The table indicates whether or not significant spatial clustering of disease was found classified by county, species and stage.

County	Badger setts		Cattle herds		Cross-species infection	
	Stage 1	Stage 2	Stage 1	Stage 2	Stage 1	Stage 2
Cork	No	Yes	Yes	Yes	No	No
Donegal	Yes	Yes	–	–	–	–
Kilkenny	Yes	No	Yes	Yes	Yes	No
Monaghan	Yes	Yes	Yes	Yes	No	Yes

nuggets. The same model with one nugget fitted better. The model with separate spatial correlation structures fitted better than a model with a single spatial correlation structure ( $p < 0.0001$ ). For stage 2, there was a similar result. Thus, positive and negative badger setts were then analyzed separately.

For infected setts, a model with one nugget but separate spatial correlation structures for the two stages fitted marginally better than one spatial structure ( $p = 0.0780$ ).

Considering the negative setts, a model with one nugget fitted best. Also a model with a single spatial correlation structure for the two stages fitted better than a model with two spatial structures ( $p < 0.0001$ ).

In summary, the results show differences in location of badger setts between the two stages and there was evidence of spatial clustering of disease in both stages.

Results for the four areas are summarized in Table 2. For all counties, there was a nugget effect when modeling cattle herds, indicating correlation between repeated measures on the same herd. The nugget effect was small in relation to the partial sill, indicating high degrees of spatial structure (Schabenberger and Gotway 2005). Models without spatial random effects but with corresponding group effects had higher AICs than models that incorporated spatial effects, for all counties.

Gaussian models when they converged, gave very similar estimates to the exponential models.

#### 4.5 Hessian issues and estimated parameter standard errors in the spatial models

For some models convergence criteria of the fitting algorithm were met but the final Hessian was not positive definite. This can indicate a surface saddlepoint or linear dependencies among the parameters. It may also be due to some final estimates of parameters being equal to the

boundary constraints. Where a variance term is zero, the corresponding random effect can be dropped from the model. The results from modeling cattle and badgers separately were used to confirm these indications. Another issue that arose was individual spatial covariance parameter estimates were often not significant using Wald type tests, although the model had spatial structure. Since covariance parameter estimates are typically not normally distributed, unless some transformation is applied, such tests are not appropriate here and in all cases modified LRT tests were carried out to test the significance of covariance parameters.

## 5 Discussion

The results of the model fitting showed spatial association of bTB in badger setts varies over time, between areas and with direction within an area. Significant spatial association of bTB in badger setts was found in all four counties – in counties Donegal and Monaghan in both stages while in Cork and Kilkenny it varied with stage. The spatial correlation was geometrically anisotropic in all four counties. The results build on those in Kelly et al. (2010) who found spatial clustering of disease in badger setts in all counties using isotropic models. In that study, using estimated intensity functions, locations where particular strains of bTB clustered were also identified. If clustering is anisotropic then isotropic models will “average” parameter estimates over the entire area and may find significant clustering.

Differences in spatial correlation structure between stages was found among badger setts. In badgers when spatial correlation of disease persisted over both stages the direction of clustering changed. Even when spatial correlation of disease was not present in both stages, the geometry of where badger setts were located did change

in all counties, i.e. there were different angles and scales of general location between the stages. The results support the theory of increased badger movement and changes in sett location and social organization following culling (O'Corry Crowe et al. 1996; Tuytens et al. 2000; Woodroffe et al. 2006). The changing geometry may also be due in part to edge effects, caused by immigration of badgers back into an area, as stated in Section 2. Differing results between stages in counties may also in part be due to edge effects. In the logistic model fitted to badger setts, the number of badgers captured at a sett was significant in the model for all counties. This may be synonymous with small-scale spatial correlation. This indicates widespread local transmission rather than a single epidemic affecting the entire trial area. This was indicated also by Kelly et al. (2010).

Significant spatial clustering of disease in cattle herds was also found in three of four counties and in each stage. In counties Cork and Kilkenny there was anisotropic spatial clustering of disease in cattle herds in both stages 1 and 2 with the direction of clustering changing between stages. For bTB positive cattle herds, there was a change in spatial structure from stage 1 to 2 but no change in nugget. In counties Kilkenny and Monaghan, spatial clustering was seen in the negative herds rather than positive but this implies a spatial effect among positive herds also. In all counties the estimated range parameter was 0, indicating clustering extended in a particular direction across the entire area. The results are in agreement with Kelly (2012) who in a study of county Cork only, using a different modeling approach, found spatial clustering only in an East–West direction in the removal area. A temporal effect was also found in that study. In Kelly (2011) spatial clustering of disease in cattle herds was found in the removal areas of Cork, Donegal and Monaghan. In that study possible anisotropy was adjusted for, by dividing each area into subregions, and comparing semi-variograms across the subregions. Spatial clustering was found in only one subregion of Kilkenny and Monaghan while it was found in two subregions in county Cork although in one of these the practical range extended to the entire subregion and thus could be general spatial heterogeneity. These results support that of this study, in that clustering is seen mainly in one direction – that of the major axis.

Differences in spatial structure between stages was also found in infected cattle herds. It is difficult to examine time-varying spatial dependence here mainly due to sparsity of data. There are also other confounding factors – the incubation period of the disease, time difference between annual bTB test and disease onset,

discussed in more detail in Kelly et al. (2010) and Kelly and More (2011). Edge effects will be almost the same when comparing the same area over time for cattle herds (as the herd population changes little between the two stages). A change in spatial disease clustering in cattle herds over two stages may be a natural temporal change or may be due to the changing badger population, perturbation of the badger population or other factors. In GB, perturbation of the badger population has been associated with increased risk of bTB incidence in cattle herds (Donnelly et al. 2007), a result not observed in the FAP (Griffin et al. 2005). Clustering in the cattle herd data in this study was spatially heterogeneous (estimated range parameters extending to the entire areas). Heterogeneity could be due to cattle movements leading to introduced infection and a relatively dispersed spatial pattern of infection (Ashe et al. 2009). Costello et al. (1999) record that a large number of bTB genotypes in cattle were found in the same area of Ireland. In Ireland by retrospective calculation, 6–7% of current herd restrictions are due to the recent introduction of an infected animal (Clegg et al. 2008). Spatial clustering in cattle herds hypothetically may also be due to shared access routes, pasture or road transport. Other studies (Griffin et al. 1996; Kaneene et al. 2002) have found contiguity with other bTB restricted herds was a significant risk factor for herd bTB.

There was significant evidence for cross-infection between badger setts and cattle herds in county Kilkenny in stage 1 and county Monaghan in stage 2. The results on cross-infection are unique. In Monaghan it is known permeability of the area and immigration of badgers continued into stage 2. No cross-infection was found in county Cork in this analysis. This area differed to the other two in that spatial clustering of disease in badgers was only seen in stage 2 and not in stage 1. Cork also had the highest rate of infected badger setts and cattle herds and it could be the case that cross-infection occurred in a spatially heterogeneous way due to the large numbers of infected animals involved.

There is a large body of evidence that badgers contribute to the spread of bTB in cattle and this was seen in some counties for some stages here. Possible reasons why it was not seen for all stages may be the use of centroids of home farms or the location of the sett where a badger is captured in calculating distances from badger setts to cattle herds. Limitations of this approach are firstly an infectious badger sett may have a large home range and cover the centroids of a number of farms many a great distance from it (Sleeman and Mulcahy 1993) and secondly the degree of overlap of the home range with a

farm is not taken into account (Laffan et al. 2011). This is of particular importance in Ireland where the degree of fragmentation of farms is high, leading to a high degree of overlap between badger territories and farms (O’Corry-Crowe et al. 1996). Also there will have been both false negative badger groups and cattle herds, diluting spatial association and this issue is discussed in more detail in Kelly and More (2011). Finally, transmission-related processes may be only partially or non-spatially related and may have time lags between them.

Anisotropy terms are required when modeling spatial association of infection in either badger setts or cattle herds. A major assumption of isotropy is that of spatial homogeneity over the area considered. This assumption means, in particular, that use of the conclusions at a very local level would not be justified. Thus, the anisotropy results indicates the direction of culling is important. Moreover, the differing estimates of covariance parameters in different regions and time periods has implications for control policy indicating a single global culling scale may not be suitable for badgers or a single scale be specified epidemiological investigations. This is discussed in Kelly et al. (2010), Kelly and More (2011), Kelly (2011) and Kelly (2012). A limitation of this study is that types of anisotropy other than geometric, as discussed in Schabenberger and Gotway 2005, Section 4, are not considered here. For example, in a process exhibiting zonal anisotropy, the covariance function depends on only some components of the lag vector and partial sills may also vary with direction. This was indicated by some models where the estimated scale parameter  $\infty$  was very large or 0 and could be modeled using an isotropic function that involved only the easting (or northing coordinate). To this extent only, are forms of anisotropy other than geometric considered. Fitting more complex anisotropic structures or fitting both large-scale spatial effects and local spatial effects requires more specific data and larger population sizes of infected/non-infected animals than the data available here.

In the analyses we did not attempt to consider the geography of a landscape itself directly – i.e. how much can be explained simply by the differing geography of the landscape. The herds or setts may not be randomly scattered over an area and may exhibit some spatial structure. However, in all cases spatial association was established in the first instance, by a comparison of infected and non-infected animals from the same area. If infected animals differed in spatial correlation structure from the non-infected then this was evidence for spatial association of disease. For infected animals, when clustering was found in a particular direction and extended

across the entire area, i.e. the estimated range parameter was or 0, if the estimated partial sill was non-zero (by a modified LRT) then this was evidence of spatial association of disease. Infection may be associated with a particular kind of geography, e.g. poor land for instance, and anisotropic models may account for this if the poor land is in a particular direction. However, this would require a separate study.

Spatial models fitted to combined cattle and badger data cannot be compared to a model fitted separately to cattle and to badgers as the mean structure is different (Schabenberger and Gotway 2005). The results from these latter models are not presented in detail here and conclusions from them are in agreement with previous analyses (Kelly et al. 2010; Kelly and More 2011). The models presented here are attempts to model infection cross-species with associated computational and interpretability problems. Different models may fit equally well but practical conclusions from the models may be similar (Kelly 2011). Many spatial models other than those detailed here, were fitted separately to badgers and cattle and to the combined data. We follow the recommendations of Schabenberger and Gotway in choosing the “best” model: “When fitting several competing models, for example, models that differ in their covariance structure ....One should not necessarily adopt the model with the smallest information criterion, but a model in the group that is parsimonious and interpretable”.

Other methods for examining spatial association in populations include those of kernel-based nonparametric regression estimators – but these are not guaranteed to give conditionally negative-definite covariance estimates (Huang, Hsing, and Cressie 2011). McGrath et al. (2009) used hexagon maps to display the relative risk of bTB in cattle herds across Ireland by dividing summarized disease data with summarized population data in each hexagon and expressing it as a percentile. In maps such as these, the size of hexagon determines the trends that can be seen visually and important covariates such as herd size are not accounted for. Similarly, distance-based methods as in Woodroffe et al. (2005) and Jenkins et al. (2007) do not adjust for covariates nor do spatial scanning statistics (Kulldorff and Nagarwalla 1995).

In conclusion, in terms of spatial analysis there is strong evidence that spatial association of bTB in badger setts and separately in cattle herds is anisotropic. Some evidence for spatial association of disease across the species was also found. The limited extent of this may be because spatially the infection occurs non-linearly as discussed above or because the relative contribution of infection of cattle herds by badgers is small as was seen

in the FAP and Randomized Badger Culling Trial in GB (Griffin et al. 2005; Donnelly et al. 2007).

In Ireland, approximately two-thirds of all standard reactors are found in approximately one-third of the agricultural land. It is now recognized that the movement of infected cattle between epidemiologically separate locations (translocation) is probably the main mechanism whereby bTB spreads from areas of high bTB incidence to areas of low incidence devoid of a wildlife reservoir (Sheridan 2011). Thus at the global level, the additional controls of pre-movement testing and enhanced clearance procedures for high risk herds have been identified as important in the context of eradication (Sheridan). Several studies have mentioned the importance of biosecurity as a control measure (Griffin et al. 1996; Macdonald, Riordan, and Mathews 2006; O’Corry-Crowe et al. 1996; Sheridan 2011) and a renewed focus on this may be important.

Extrapolation from Irish studies to other countries needs to proceed cautiously due to the ecological and

genetic differences already mentioned. However, the spatial methodology outlined here is widely applicable and enables important spatial hypotheses to be tested without which control programs and preventive measures cannot be designed optimally nor evaluated appropriately.

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