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Original Research

Spatial pattern in prevalence of paratuberculosis infection diagnosed with misclassification in Danish dairy herds in 2009 and 2013

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ABSTRACT

Paratuberculosis is a chronic infection of economic importance to the dairy industry. The infection may be latent for years, which makes diagnostic misclassification a general challenge. The objective of this study was to identify the spatial pattern in infection prevalence, when results were adjusted for covariate information and diagnostic misclassification. Furthermore, we compared the estimated spatial pattern with the spatial pattern obtained without adjustment for misclassification. The study included 1242 herds in 2009 and 979 herds in 2013. The within-herd prevalence was modelled using a hierarchical logistic regression model and included a spatial component modelled by a continuous Gaussian field. The Stochastic Partial Differential Equation (SPDE) approach and Integrated Nested Laplace Approximation (INLA) were used for Bayesian inference. We found a significant spatial component, and our results suggested that the estimated range of influence and the overall location of areas with increased prevalence are not very sensitive to diagnostic misclassification.

1. Introduction

Paratuberculosis is a chronic infection in cattle caused by *Mycobacterium avium* subsp. *paratuberculosis* (MAP) (Sweeney, 2011). A MAP infection may be latent for the major part of an animal's life, or infection may develop to infectious and affected disease states (Nielsen and Toft, 2008). The possibility for latent infection makes diagnostic misclassification a general challenge. Infectious animals shed MAP in faeces and the resulting contamination of the environment may lead to transmission of MAP to susceptible animals. Furthermore, MAP can be transmitted *in utero* from a dam to her calf (Whittington and Windsor, 2009), and via milk and colostrum from infectious animals (Streeter et al., 1995). MAP infection is of economic importance to the dairy industry, since infected cows may experience a reduced milk yield and increased mortality (Hendrick et al., 2005). Therefore, control programmes on MAP have been established in several countries (Geraghty et al., 2014). In Denmark, a voluntary control programme was initiated in 2006 by the Danish Cattle Federation (Nielsen, 2007). The programme aims at reducing the prevalence of MAP infected cattle and providing farmers with tools to manage the MAP infections. The programme is offered to all dairy farmers. Infection status is assessed by screening of individual milk samples for detection of MAP specific antibodies.

Verdugo et al. (2015) found a decreasing trend in the MAP prevalence among Danish control programme herds from 2011 to 2013, and estimated the true within- and between-herd prevalence to be 0.07 and 0.77, respectively,

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in 2013. Bihrmann et al. (2012) did a descriptive spatial analysis to describe the spatial pattern in MAP prevalence across Denmark in late 2008 – early 2009, and identified geographical areas with higher prevalence. It is not known how this spatial pattern developed over time, and the study by Bihrmann et al. (2012) did not take any covariate information into account. This might influence their findings since, for example, MAP infection has been associated with herd size (Wells and Wagner, 2000), which is not randomly distributed across the country. Furthermore, assessment of MAP infection status is subject to misclassification, especially low sensitivity of the diagnostic test used in the control programme (Nielsen et al., 2013). To our knowledge, the effect of adjustment for diagnostic misclassification in estimation of the spatial pattern has not been assessed.

The objective of this study was to identify the spatial pattern in prevalence of MAP infection in Danish dairy herds, including (1) location of areas with increased prevalence and (2) investigation of development over time (2009–2013), when results were adjusted for covariate information and diagnostic misclassification. Furthermore, we compared the estimated spatial pattern with the spatial pattern obtained without adjustment for misclassification. We modelled the within-herd prevalence of MAP using a hierarchical logistic regression model and included a spatial component to describe any residual spatial pattern. The spatial component was modelled by a continuous Gaussian field. In large data sets, Bayesian inference in such a model has only recently been made possible by the so-called Stochastic Partial Differential Equation (SPDE) approach (Lindgren et al., 2011), which utilises Integrated Nested Laplace Approximation (INLA) (Rue et al., 2009) for inference.

2. Material and methods

2.1. Data

All Danish cattle herds are registered in the Danish Cattle Database (hosted by SEGES, Aarhus N, Denmark). Relevant information on all herds in two separate study periods (1st quarter of 2009, and 1st quarter of 2013) was retrieved from the database, including unique cow identification number, unique herd identification number, and geographical coordinates (UTM-format) of the farm location. In total, the study included 26,076 herds in 2009, and 20,651 herds in 2013. All herds with at least one record in the Danish milk recording system were categorised as dairy.

All dairy herds enroled in the voluntary control programme on MAP perform 4 annual screenings at regular intervals. Non-enroled dairy herds may also perform occasional screenings. Screening results from both enroled and non-enroled herds were included in the study. In the analysis, enrolment was defined by enrolment status on January 1st. If a herd performed multiple screenings during a study period (1st quarter, 2009 or 1st quarter, 2013), then one of these screenings was randomly chosen for analysis. In total, 1304 herds performed screening in 2009 (84% enroled in the control programme), and 1012 herds performed screening in 2013 (93% enroled in the control programme). Herds located on the remote island Bornholm (2009: 8, 2013: 4) were excluded from the analysis, as were herds with less than 10 tested cows (2009: 46, 2013: 22), and a small number of herds which had been vaccinated against paratuberculosis (2009: 8, 2013: 7). Within each herd, tested cows younger than 2 years of age were excluded from analysis. In total, $N_{2009} = 1242$, and $N_{2013} = 979$ herds were included in the study. Among these, 794 herds were included in both 2009 and 2013.

All lactating cows within a screened herd were tested using a milk antibody ELISA (ID-Screen®, ID-Vet, Montpellier, France) detecting MAP specific antibodies. Samples were automatically collected through the Danish milk recording system. A cow was defined to be test-positive if the test had a sample-to-positive ratio of 0.30. If at least one cow within a herd was test-positive, the herd was defined to be test-positive. The sensitivity and specificity of the test for MAP were estimated by Nielsen et al. (2013). They modelled the age-dependent sensitivity by

$$\log\left(\frac{\mathrm{SE}(x)}{1-\mathrm{SE}(x)}\right) = \beta_0 + \beta_1 \exp(-\beta_2 x),$$

where $\mathrm{SE}(x)$ is the sensitivity at age $x \in \{2\text{ years}, 3\text{ years}, \ldots, 10\text{ years}\}$. Based on a sample-to-positive ratio of 0.30 to define a positive test, the estimated parameter values were $\beta_0 = 1.28$, $\beta_1 = -9.31$, and $\beta_2 = 0.66$, whilst the estimated specificity SP was 0.9935 (unpublished results based on data and model in Nielsen et al. (2013)). In order to have a sensitivity SE that was independent of age, we calculated an average value using the actual age distribution of the cows included in this study. Hence, SE was calculated as

$$\sum_{x=2}^{10} \mathrm{SE}(x)\, P(\text{age of cow} = x),$$

where $P(\text{age of cow} = x)$ is the proportion of cows at age x in the study. This gave an average sensitivity of 0.5332 in 2009 and 0.4913 in 2013.

The following covariate information, all on herd level, was collected or derived from the Danish Cattle Database and included in the analysis: (1) mean age of the tested cows on the day of testing in each herd, (2) herd size, (3) herd density, defined as the number of herds (both dairy and non-dairy) per km^2 within a radius of 5 km, (4) organic production or not, (5) proportion of purchased cows in the herd, and (6) proportion of Jersey cows within the herd. Items (4), (5), and (6) were all defined on February 15th in each study period. For analysis, herd size was log transformed, since the distribution was skewed. Based on their distributions, the proportion of purchased cows in the herd was classified into three groups (none, below 5%, above 5%) and the proportion of Jersey cows was classified into two groups (below or above 80%).

2.2. Statistical model

Let p_i denote the apparent within-herd prevalence of MAP (i.e. the proportion of test-positive cows) in herd $i, i = 1, \ldots, N$, and let π_i denote the true within-herd

prevalence (i.e. the proportion of truly infected cows) in herd $i, i = 1, \ldots, N$. Unless we have a perfect diagnostic test, π_i will be different from p_i. Given sensitivity SE and specificity SP of the test, the apparent prevalence can be written as

$$p_i = \mathrm{SE}\pi_i + (1 - \mathrm{SP})(1 - \pi_i), \quad i = 1, \ldots, N. \tag{1}$$

Using (1) as a link between the observed number of test-positive cows and the unobserved number of truly infected cows, the true prevalence π_i was modelled as

$$\mathrm{logit}(\pi_i) = \boldsymbol{\beta}\boldsymbol{X}_i + U_i + W(s_i), \quad i = 1, \ldots, N \tag{2}$$

where $\boldsymbol{X}_i, i = 1, \ldots, N$ is a vector of herd level covariates, and $\boldsymbol{\beta}$ is a vector of regression parameters. The random effect $\boldsymbol{U} = (U_i)_{i=1,\ldots,N} \sim \mathrm{N}(0, \sigma_u^2 \boldsymbol{I})$ was included to account for the hierarchical structure given by the clustering of cows within herds, and $\boldsymbol{W} = (W(s_i))_{i=1,\ldots,N} \sim \mathrm{N}(0, \boldsymbol{\Sigma})$ is a realisation of a latent stationary Gaussian field (GF) representing the spatial dependence between herds located at sites $\boldsymbol{s} = (s_i)_{i=1,\ldots,N}$. The spatially structured covariance matrix $\boldsymbol{\Sigma}$ is given by the Matérn covariance function

$$\mathcal{C}(h) = \sigma_w^2 \frac{(\kappa h)^{\lambda}}{2^{\lambda-1}\Gamma(\lambda)} K_{\lambda}(\kappa h), \tag{3}$$

where $h = \|s_i - s_j\|, i = 1, \ldots, N, j = 1, \ldots, N$, σ_w^2 is the marginal variance, Γ is the gamma function, and K_λ is a modified Bessel function of the second kind and order λ. The smoothness parameter λ was fixed at 1, and κ is a scaling parameter. The range of influence (corresponding to the distance at which the correlation is close to 0.1) is defined as $\sqrt{8\lambda}/\kappa$ (Lindgren et al., 2011).

The model given by (2) is referred to as the IID+GF model (since the U_i's are Indedependent, Identically Distributed) with adjustment for misclassification. Substituting the true prevalence π_i in (2) with the apparent prevalence p_i, we have an IID+GF model without adjustment for misclassification. The model given by omission of the GF $\boldsymbol{W}$ in (2) is referred to as the IID model (with or without adjustment for misclassification depending on the prevalence parameter).

2.3. Inference

The Integrated Nested Laplace Approximation (INLA) approach (Rue et al., 2009) was used for Bayesian inference in all models. This approach applies Laplace approximations to provide deterministic approximations to the posterior marginal distribution of all parameters. All analyses were done in R (R Core Team, 2013) using the INLA package (www.r-inla.org).

Inference in the IID+GF model was based on the so-called Stochastic Partial Differential Equation (SPDE) approach, developed by Lindgren et al. (2011). The basic idea in this approach is to represent the GF by a Gaussian Markov random field (GMRF) defined on a triangulation of the spatial region (i.e. Denmark). This representation offers huge computational advantages since the GMRF is given by a sparse precision matrix $\boldsymbol{Q}$, as opposed to the dense covariance matrix $\boldsymbol{\Sigma}$ of the GF. The precision $\boldsymbol{Q}$ of the GMRF depends on the parameters σ_w^2 and κ, just like $\boldsymbol{\Sigma}$. The SPDE approach is included in the INLA package, which also includes a function for creating the required triangulation of the spatial region. The triangulation, referred to as a mesh, was based on the observation sites with additional mesh nodes added to create a regular mesh. The

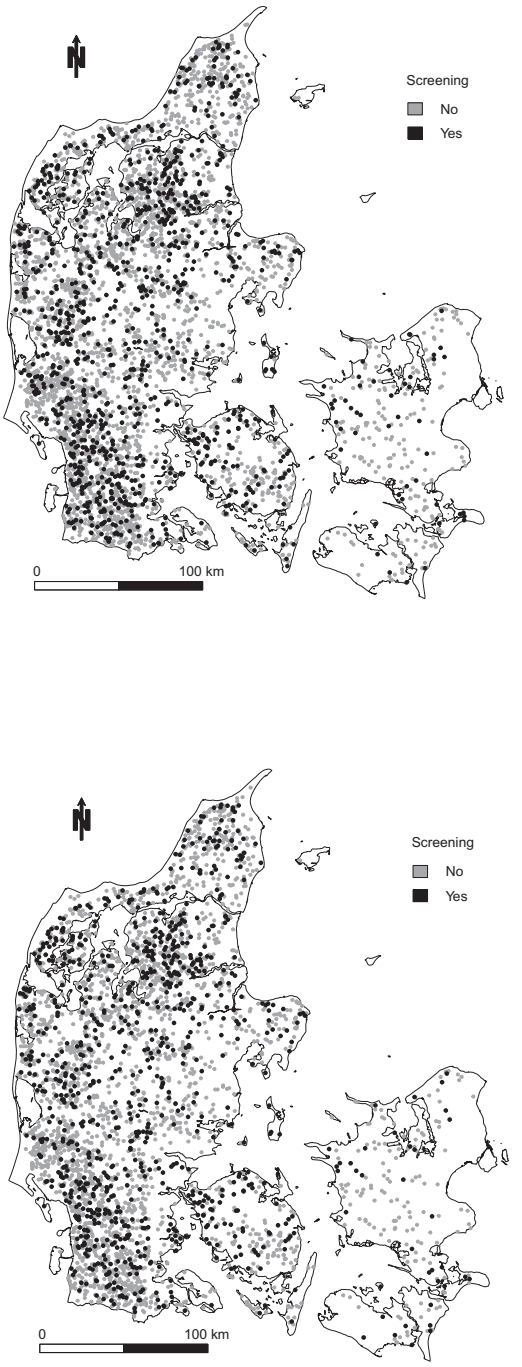

Fig. 1. Location of all Danish dairy herds with status on screening for MAP, 1st quarter 2009 (top) and 1st quarter 2013 (bottom).

mesh was extended beyond the observation area to correct for edge effects. The maximum allowed triangle edge length was 5 km inside the area and 50 km outside the area. The cutoff (minimum allowed distance between nodes) was 5 km. The mesh consisted of a total of 2012 nodes with 2009 data, and of 1995 nodes with 2013 data. A sensitivity analysis was performed to assess the impact of the mesh on the parameter estimates (2009 data only). The cutoff (which could be changed and still produce a regular mesh) was changed to 6 km (1410 nodes), to 4.5 km (2431 nodes), and to 2.5 km (5198 nodes).

Reported parameter estimates were based on mean, standard deviation, and 95% credible intervals from the marginal posterior distributions. The Deviance Information Criteria (DIC) was used to compare the fit of the different models, and Moran's I (Moran, 1950) was used to test for spatial correlation in residuals. Linearity of continuous covariates was assessed by plotting the estimates obtained when classifying each variable in 20% quantiles and assigning the median value to each interval. By visual inspection of these plots, all continuous covariates showed a non-linear pattern, and the categorised versions were therefore included in the analyses. For comparison of the analyses in 2009 and 2013, the categorisation in the 2013 data followed the cut points of the 2009 data.

The estimated spatial pattern (i.e. the Gaussian field) was illustrated on a map by projecting the posterior mean and standard deviation of $\boldsymbol{W}$ from the mesh nodes to a 5 km by 5 km grid across Denmark. The predicted prevalence of MAP was calculated as the posterior mean of the fitted value π_i at each herd site $s_i, i = 1, \ldots, N$, and the spatial distribution was illustrated by a smooth surface created by inverse distance weighting (5 km by 5 km grid).

2.4. Prior distributions

Prior distributions must be assigned to all parameters. The regression parameters were assigned independent zero-mean Gaussian prior distributions with precision 0.001. The log of the precision $\tau_u = 1/\sigma_u^2$ of the random effect $\boldsymbol{U}$ was assigned a log Gamma(1, 0.0005) prior (default of the INLA package). The marginal variance σ_w^2 of the GF was parametrized as $\sigma_w^2 = 1/(4\pi\kappa^2\tau_w^2)$, where π is the mathematical constant π (and hence not related to the true within-herd prevalence π_i). The hyper parameters $(\log(\kappa), \log(\tau_w))$ were assigned zero-mean Gaussian prior distributions with precision 0.001. A sensitivity analysis was performed to assess the impact of the prior distributions. This involved changing the Gamma parameter from 0.0005 to 0.001 and 0.00001, and changing the Gaussian precision from 0.001 to 0.1 and 0.00001. The sensitivity SE and specificity SP of the test for MAP were fixed at given values (SE=0.5332 in 2009, SE=0.4913 in 2013, and SP=0.9935).

3. Results

Fig. 1 shows the location of the Danish dairy herds in 2009 and 2013. Most herds were located in the north-western and south-western part of the country. Only a limited number of herds were located in the eastern part of the country. From 2009 to 2013, the number of dairy herds decreased while the total number of cows increased (Table 1). The proportion of herds performing screening for MAP was fairly constant through the period, but the total proportion of tested cows dropped. The proportion of test-positive cows was reduced, which was accompanied by a reduction in the proportion of test-positive herds.

In both 2009 and 2013, the GF+IID model had a lower DIC and hence provided a better fit to the data than the IID model, regardless of adjustment for misclassification or not (Table 2).

This indicated the presence of spatial variation in the data, which was supported by Moran's I showing significant spatial correlation in the residuals from the IID model. Except for 2009 with adjustment for misclassification, the spatial variation was adequately modelled by the GF, since no spatial correlation was found in the residuals from the GF+IID model. In general, the models without misclassification had the lowest DIC.

The estimated range of influence (corresponding to the distance at which observations were no longer correlated) changed slightly from 16 km in 2009 to 14 km in 2013 (with adjustment for misclassification), but the uncertainty of the 2009 estimate was large with the 95% credible interval reflecting a skewed posterior distribution with a heavy right tail (Table 2). The estimated range of influence was not substantially affected by adjustment for misclassification.

The estimated GF with standard deviation is mapped in Fig. 2 (2009) and Fig. 3 (2013). The GF shows the residual spatial pattern after covariate information has been accounted for. Hence, an area with increased MAP prevalence after adjustment for covariates was indicated by a positive value (red colour) in the maps. A number of distinct areas with increased prevalence were seen across the country in 2009 and 2013. The standard deviation reflected the location of the herds, and was large compared to the value of the GF, especially with adjustment for

Table 1
Summary of data from the two study periods (1st quarter 2009, 1st quarter 2013) showing the total number of Danish dairy herds/cows, the number of herds/cows screened for MAP and included in the study, and the number of included herds/cows that were test-positive for MAP.

	2009		2013	
	Herds (%)	Cows (%)	Herds (%)	Cows (%)
Dairy	4301 (100)	548,779 (100)	3623 (100)	562,550 (100)
Screening	1242 (28.9)	155,354 (28.3)	979 (27.0)	122,808 (21.8)
Test-positive	1035 (83.3)	7580 (4.9)	733 (74.9)	3932 (3.2)

Table 2
Selected results of fitting different hierarchical logistic regression models to the within-herd prevalence of MAP infection in Danish dairy herds with or without adjustment for diagnostic misclassification. The models included an independent random effect of herd and a spatial component modelled by a Gaussian field (IID+GF), or just an independent random effect of herd (IID). All models included covariate effects.

	2009				2013			
	Without adj. for miscl.		With adj. for miscl.		Without adj. for miscl.		With adj. for miscl.	
	IID+GF	IID	IID+GF	IID	IID+GF	IID	IID+GF	IID
DIC[a]	6056	6061	6105	6108	4234	4239	4282	4289
IID precision $1/\sigma_u^{2\,b}$	1.7 (1.5; 2.0)	1.6 (1.4; 1.8)	1.2 (1.1; 1.4)	1.1 (1.0; 1.3)	1.4 (1.2; 1.8)	1.3 (1.1; 1.5)	1.0 (0.8; 1.2)	0.9 (0.7; 1.0)
Range of influence[b,c]	17 (8;109)	–	16 (8;202)	–	14 (6; 48)	–	14 (6; 36)	–
GF marginal variance $\sigma_w^{2\,b}$	0.03 (0.01; 0.1)	–	0.03 (0.01; 0.2)	–	0.08 (0.04; 0.2)	–	0.1 (0.07; 0.4)	
Moran's I residuals[d]	0.19	0.001	0.013	0.0005	0.77	0.020	0.61	0.018

[a] Deviance information criteria.
[b] Posterior mode (95% credible interval).
[c] Extent of spatial correlation between herds (in km).
[d] Test for residual spatial correlation (p-value).

misclassification. The standard deviation increased with adjustment for misclassification. In general, the overall location of areas with increased prevalence did not change between models with and without adjustment for misclassification. In 2009, however, the estimated spatial pattern was much more smooth with adjustment for misclassification than without. In 2013, the opposite was the case.

The values of the GF were larger in 2013 than in 2009 (different scales in Figs. 2 and 3), indicating larger spatial differences in 2013. These were mainly seen in the western part of the country, where an area to the south had the highest increase in prevalence. Areas in the south-eastern parts of the country with increased prevalence in 2009 were not persistent in 2013.

The distribution of the covariates included in the analysis changed from 2009 to 2013 (Table 3).

The age at screening, herd density, and the proportion of purchased animals within the herds decreased, whereas herd size increased. Less non-enroled herds were screened. Increased MAP prevalence was mainly associated with purchase of animals and Jersey herds (Table 3). Herds with organic production tended to have a lower MAP prevalence than herds with non-organic production (not significant). Control programme herds had a significantly lower prevalence than the non-enroled, screened herds in 2013. This difference was not seen in 2009.

In all but a very few exceptions, the odds ratios estimated without adjustment for misclassification were closer to 1 (the null) and had more narrow credible intervals than the odds ratios estimated with adjustment for misclassification.

The predicted prevalence with adjustment for misclassification within each tested herd is mapped in Fig. 4. The predicted prevalence decreased across the country from 2009 to 2013, which is clear from the change in colouring from red to green. In 2013, only very local spots of high prevalence were seen.

For comparison, we identified and analysed the 794 herds included in both 2009 and 2013. In 2013, the range was estimated to 12 km (5; 37) with adjustment for misclassification. The overall spatial pattern did not change, but some of the very local spots of high predicted prevalence disappeared (not shown).

3.1. Sensitivity analysis

The regression parameter $\boldsymbol{\beta}$, the precision $\tau_u = 1/\sigma_u^2$ of the random effect $\boldsymbol{U}$, and the hyper parameter $\log(\kappa)$ of the GF were not sensitive to the chosen prior distributions. The hyper parameter $\log(\tau_w)$ of the GF changed slightly (7.5%) when increasing the precision of the prior distribution from 0.001 to 0.1 (the default of the INLA package) in the model without adjustment for misclassification. However, a decrease in precision from 0.001 to 0.00001 did not affect the estimate, and 0.001 was concluded to be a satisfactory precision of the prior.

Changing the mesh did not affect the estimates of the regression parameter or the random effect $\boldsymbol{U}$. Without adjustment for misclassification, the estimated range of influence varied slightly (between 10 km and 17 km) when

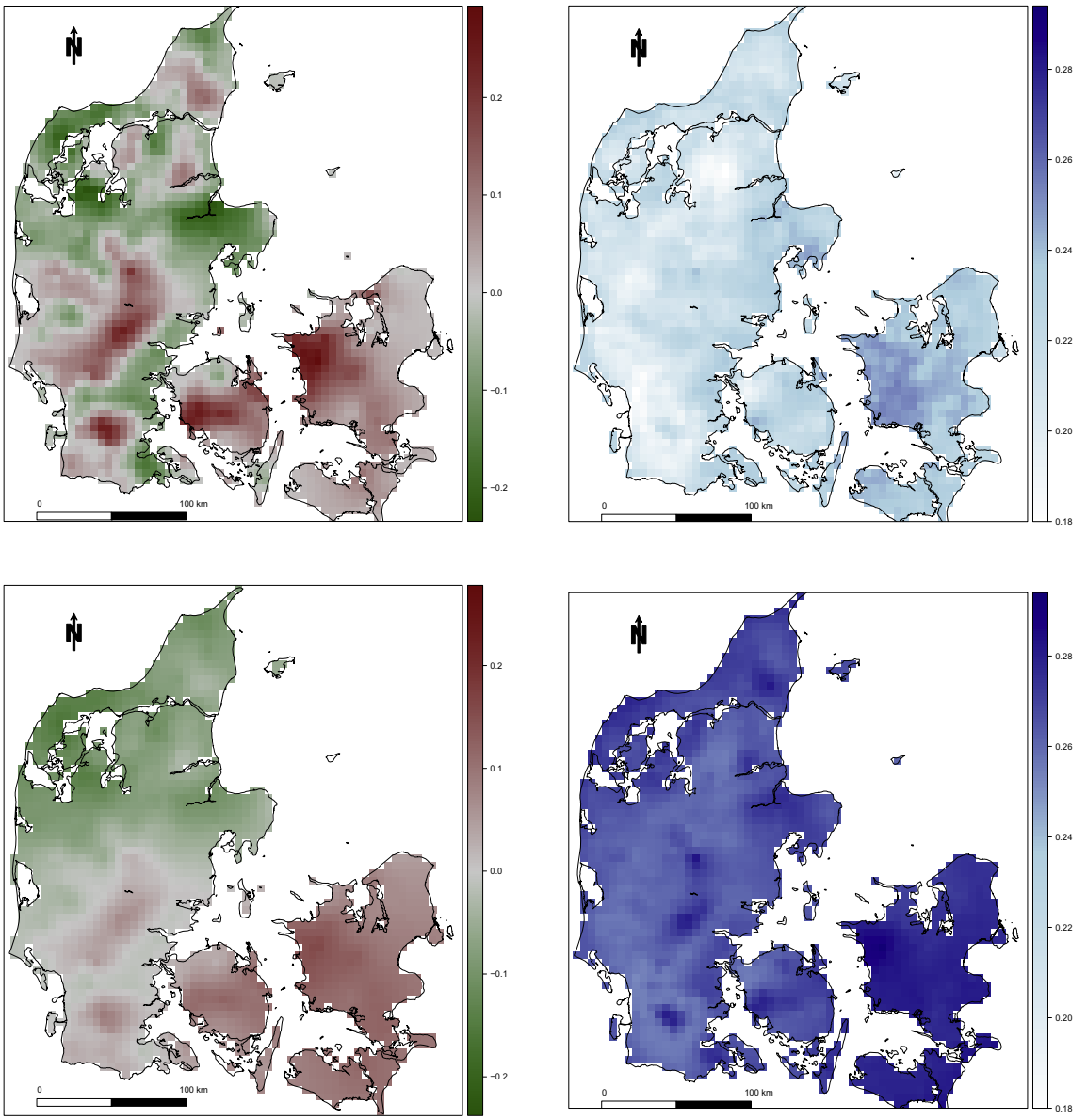

Fig. 2. Estimated Gaussian field (left) with standard deviation (right) showing the residual spatial pattern in within-herd prevalence of MAP infection in Danish dairy herds in 2009 without (top) and with (bottom) adjustment for diagnostic misclassification. Red colour indicates an area with increased prevalence. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

changing the mesh, but variation was small considering the uncertainty of the estimate. With adjustment for misclassification, the range of influence could not be estimated with the reduced mesh consisting of 1410 nodes (result: 0.4 km (−27; 655)). Estimates obtained with 2012 and 2431 nodes were essentially alike. With 5198 nodes, the analysis demanded more memory than available in our standard laptop (Intel Core Duo CPU, 2.8 GHz, 3 GB RAM).

4. Discussion

The main source of between-herd transmission of MAP is considered to be movement of infected animals (Sweeney, 1996; Nielsen and Toft, 2011). In 2000-2009, the median distance of movement of cattle within Denmark was 15.3 km (Mweu et al., 2013). This corresponds well with the range of influence, which measures the spatial extent of the correlation between herds, being estimated to 14–16 km in the present study. Bihrmann et al. (2012) estimated the range of influence from a semivariogram without taking diagnostic misclassification and covariate effects into account, and obtained a similar result as in the present study (16.8 km). Furthermore, their estimated spatial pattern in within-herd prevalence in 2009 was very similar to our result in terms of location of areas with increased prevalence. The predicted within-herd

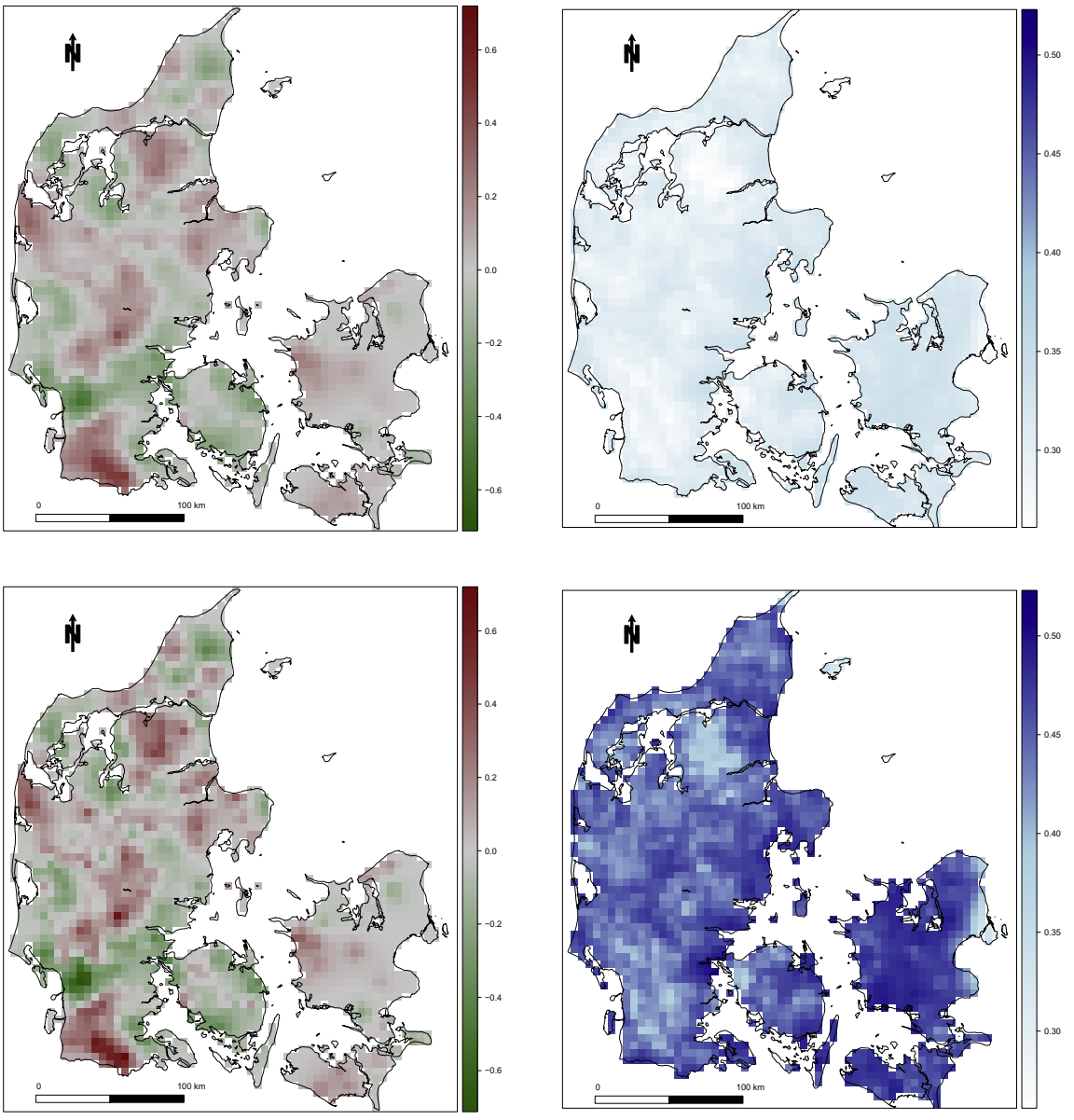

Fig. 3. Estimated Gaussian field (left) with standard deviation (right) showing the residual spatial pattern in within-herd prevalence of MAP infection in Danish dairy herds in 2013 without (top) and with (bottom) adjustment for diagnostic misclassification. Red colour indicates an area with increased prevalence. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

prevalence, however, was lower in the study by Bihrmann et al. (2012). Although some of this difference may be explained by the diagnostic misclassification, it may also be attributable to the fact that we used inverse distance weighting to produce the map of predicted within-herd prevalence, and the result was less smooth than the kriged map by Bihrmann et al. (2012). In the present study, we did not use kriging, since a semivariogram could not be very well fitted to the within-herd prevalence obtained as fitted values from the model.

That movement of cattle is important in relation to the spread of MAP was confirmed in the present study by the within-herd prevalence being associated with purchase of animals. Furthermore, MAP prevalence was found to be higher in Jersey cows (compared to mainly Holstein cows), which was also previously shown by Jacobsen et al. (2000). The observed changes in the distribution of the covariates from 2009 to 2013 reflected a general trend in Denmark towards fewer, but larger herds. The expansion of the dairy herds leads to a lower mean age, and the proportion of purchased animals is affected by the increasing use of sex-sorted semen in some herds, which may lead to a reduced need for purchase of animals.

Adjustment for misclassification adds uncertainty to the model. This resulted in wider credible intervals of the estimated odds ratios and increased standard deviation of

Table 3
Estimated odds ratios (OR) with 95% credible intervals (CI) obtained by fitting a hierarchical logistic regression model including a spatial component to the within-herd prevalence of MAP infection in Danish dairy herds with or without adjustment for diagnostic misclassification.

	2009					2013				
		Without adj. for miscl.		With adj. for miscl.			Without adj. for miscl.		With adj. for miscl.	
	N (%)	OR	95% CI	OR	95% CI	N (%)	OR	95% CI	OR	95% CI
Organic production										
No	1070 (86)	1	Ref.	1	Ref.	840 (86)	1	Ref.	1	Ref.
Yes	172 (14)	0.86	(0.73; 1.02)	0.83	(0.68; 1.01)	139 (14)	0.84	(0.67; 1.05)	0.81	(0.60; 1.05)
Control programme										
Yes	1062 (86)	1	Ref.	1	Ref.	932 (95)	1	Ref.	1	Ref.
No	180 (14)	1.05	(0.90; 1.22)	1.04	(0.86; 1.24)	47 (5)	1.69	(1.23; 2.26)	2.00	(1.35; 2.86)
Age[a]										
[2,3.30]	250 (20)	1	Ref.	1	Ref.	583 (60)	1	Ref.	1	Ref.
(3.30; 3.47]	248 (20)	1.08	(0.91; 1.27)	1.10	(0.89; 1.34)	140 (14)	1.01	(0.82; 1.22)	0.99	(0.76; 1.26)
(3.47; 3.63]	246 (20)	1.18	(0.99; 1.39)	1.24	(1.01; 1.52)	103 (11)	1.08	(0.85; 1.34)	1.09	(0.81; 1.43)
(3.63; 3.86]	254 (20)	1.08	(0.91; 1.28)	1.12	(0.91; 1.37)	153 (16)[b]	0.94	(0.71; 1.20)	0.89	(0.65; 1.19)
(3.86; 7.55]	244 (20)	1.37	(1.14; 1.64)	1.49	(1.19; 1.84)	–	–	–	–	–
Herd size[a]										
0–97	249 (20)	1	Ref.	1	Ref.	156 (16)	1	Ref.	1	Ref.
98–131	248 (20)	1.14	(0.94; 1.38)	1.19	(0.94; 1.48)	148 (15)	1.09	(0.81; 1.46)	1.11	(0.76; 1.58)
132–157	243 (20)	1.19	(0.97; 1.43)	1.22	(0.97; 1.53)	159 (16)	1.14	(0.85; 1.51)	1.18	(0.82; 1.66)
158–204	248 (20)	1.22	(1.00; 1.47)	1.27	(1.00; 1.59)	221 (23)	1.23	(0.94; 1.60)	1.26	(0.89; 1.75)
205–1400	254 (20)	1.31	(1.07; 1.59)	1.39	(1.09; 1.75)	295 (30)	1.08	(0.82; 1.40)	1.05	(0.74; 1.44)
Herd density[a]										
[0; 0.54]	260 (20)	1	Ref.	1	Ref.	387 (40)	1	Ref.	1	Ref.
(0.54; 0.69]	245 (20)	1.18	(0.98; 1.39)	1.23	(1.00; 1.51)	299 (31)	1.01	(0.84; 1.21)	1.03	(0.81; 1.27)
(0.69; 0.80]	228 (20)	1.13	(0.94; 1.35)	1.17	(0.94; 1.45)	154 (16)	1.24	(0.98; 1.54)	1.33	(0.99; 1.75)
(0.80; 0.94]	257 (20)	1.05	(0.88; 1.26)	1.07	(0.86; 1.32)	139 (14)[b]	0.94	(0.73; 1.19)	0.90	(0.65; 1.21)
(0.94; 1.50]	252 (20)	1.13	(0.93; 1.36)	1.17	(0.93; 1.45)	–	–	–	–	–
Purchase										
None	291 (23)	1	Ref.	1	Ref.	390 (40)	1	Ref.	1	Ref.
Below 5%	348 (28)	1.38	(1.16; 1.61)	1.51	(1.24; 1.84)	284 (29)	1.41	(1.17; 1.68)	1.60	(1.26; 2.00)
Above 5%	603 (49)	1.64	(1.40; 1.92)	1.85	(1.52; 2.24)	305 (31)	1.96	(1.63; 2.34)	2.41	(1.91; 3.00)
Jersey										
Below 80%	1065 (86)	1	Ref.	1	Ref.	813 (83)	1	Ref.	1	Ref.
Above 80%	6177 (14)	2.03	(1.73; 2.35)	2.35	(1.95; 2.81)	166 (17)	1.68	(1.39; 2.01)	1.98	(1.56; 2.47)

[a] Cut points based on the 20% quantiles of the distribution in 2009.
[b] Includes the last group due to small numbers.

the Gaussian field. This is, however, needed to account for the noise induced in the observed data by the diagnostic misclassification. Otherwise, the variation will be underestimated. Furthermore, the induced noise caused the covariate estimates to be biased towards the null without adjustment for misclassification. That is always the case with non-differential misclassification, whereas the direction of the bias could change in case of differential misclassification (Copeland et al., 1977). In the present study, misclassification was assumed non-differential, but the sensitivity actually depended on the age of the tested cow. This could not be incorporated in the model, since data were aggregated at herd level. The latter was done, since the model cannot handle multiple observations (i.e. one for each cow) at the same location.

The diagnostic misclassification was independent of the spatial location of the herds, since all milk samples in the Danish control programme on MAP are analysed in the same laboratory. Hence, the spatial pattern would be expected to be depleted by the random noise added to the data by the misclassification. This was seen in 2013, where the estimated Gaussian field was more smooth without adjustment for misclassification than with adjustment for misclassification. In 2009, however, the smoothness of the estimated Gaussian field increased with inclusion of misclassification in the model, which was unexpected. We have no real explanation for this. It may somehow be related to the misclassification depending on age, since the age of the tested herds was actually not randomly distributed across the country (2009: Moran's I $p = 0.001$). Furthermore, the age distribution changed from 2009 to 2013, which could explain the different behaviour of the estimated Gaussian fields in 2009 and 2013 (2013: Moran's I $p = 0.01$). At the same time, the spatial structure of the 2009 data was not satisfactorily described by the model with misclassification, since spatial correlation was still found in the residuals from this model. This suggested that the spatial component estimated with adjustment for misclassification in 2009 was actually too smooth.

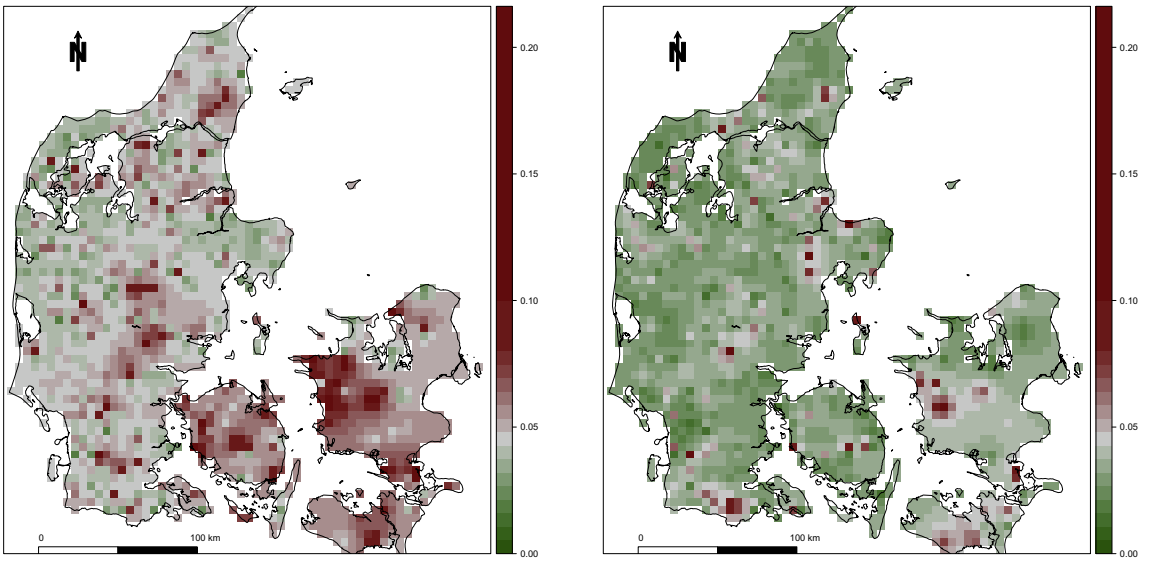

Fig. 4. Predicted within-herd prevalence of MAP infection in Danish dairy herds with adjustment for diagnostic misclassification in 2009 (left) and 2013 (right).

Overall, however, the estimated spatial pattern in terms of the range of influence and the location of areas with increased prevalence did not depend on adjustment for misclassification. Berke and Waller (2010) studied the effect of non-spatial diagnostic misclassification on the observed spatial pattern in a case study on data aggregated in polygons. They considered the semivariogram, Moran's I, and spatial scan statistics and also concluded that, with large sample sizes, the spatial pattern was not seriously affected. Bihrmann et al. (2014) studied conditional autoregressive (CAR) models in a small simulation study on spatial binary data with diagnostic misclassification. The CAR models, however, do not provide any estimate of the spatial pattern, and can only be used to account for spatial correlation in data.

In the present study, the DIC suggested a better fit of the models without adjustment for misclassification than with adjustment for misclassification. The two models may, however, not be truly comparable, since modelling the true prevalence instead of the apparent prevalence may be considered a change of data. In any case, the model with adjustment for misclassification may be preferable because of the biased estimates obtained without adjustment for misclassification.

This study was based on data from a voluntary control programme. Therefore, the studied herds are not necessarily representative of the total Danish dairy herd population. In 2011, the estimated median true within-herd MAP prevalence was 7.4% among the herds participating in the control programme (Verdugo et al., 2015), and 5.4% among dairy herds with no screening for MAP infection (Kirkeby et al., submitted for publication). This suggests a slightly higher prevalence of MAP infectionin the herds participating in the control programme. In the 2009 analysis, 14% of the herds were actually not enroled in the programme. These herds might be suspected of performing screening because of experiencing problems with MAP infection, but their within-herd prevalence was similar to the within-herd prevalence of the enroled herds (OR 1.05 (0.90; 1.22)).

It is assumed that the full effect of the control programme in terms of a decrease in the within-herd MAP prevalence is not observed until after 4–8 years of enrolment (Nielsen and Toft, 2011). In 2009, the herds had only been enroled for a maximum of 3 years (Mar 2006–Apr 2009). In 2013, however, 81% of the analysed herds had been enroled in the control programme since at least 2009, i.e. at least 4 years. The decrease across the country from 2009 to 2013 in within-herd prevalence found in this study is therefore likely to reflect the effect of the control programme, and thereby not be applicable to the non-participating dairy herds.

The non-tested herds may be considered a missing data problem. Bihrmann and Ersbll (2015) studied the estimate of the range of influence in case of missing data in a simulation study. In general, the estimate did not change much, but with 75% missing data, corresponding to the situation in the present study, large variation between data sets were observed. In the simulation study, the missing data did not depend on spatial location. Spatial differences in the participation in the control programme on MAP has, however, been found (Bihrmann et al., 2012). This may not necessarily affect the estimated range of influence, but the estimated spatial pattern may be influenced. For example, an area with low estimated prevalence may simply be the result of none of the herds within that area being tested. This was not accounted for in the present study, and could be a topic for future research.

A strength of the data used in this study is the availability of the exact location of each measurement. Hence, there is no bias introduced by aggregating data in more or less random polygons defined by e.g. administrative regions, also known as the modifiable areal unit problem (MAUP) (Openshaw and Taylor, 1979).

In conclusion, this study presented a model to describe the spatial pattern in infection prevalence, when the prevalence is subject to diagnostic misclassification and covariate effects. We used the model to estimate the spatial pattern in within-herd prevalence of MAP infection in Danish dairy herds in 2009 and 2013, and found a significant spatial component. The smoothness of the estimated spatial pattern was affected by diagnostic misclassification, but our results suggested that the estimated range of influence and the overall location of areas with increased prevalence are not very sensitive to diagnostic misclassification.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.sste.2015.10.001.

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