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Original article

BSE, feed and cattle in Switzerland: Is there a spatial relation?

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Abstract – Cross-contamination of cattle feed with meat and bone meal (MBM) allowed in feed for other species is regarded as the current hypothesis for the infection pathway of Bovine Spongiform Encephalopathy (BSE) cases occurring after the implementation of a ban on feeding MBM to cattle. This study was aimed at establishing a spatial relation between BSE cases in Switzerland and the findings of MBM in cattle feed. A cluster analysis and a cohort study were performed. Two hundred sixteen BSE cases born after December 1990 and detected until August 1st 2005, screening data of 504 feed producers between 1996 and 2001 and population data from the Swiss 2001 cattle census were included. The cluster analysis showed feed producer, positive for MBM contaminations in cattle feed, as possible cluster centres for BSE cases. In the cohort study, farms within a radius of 2 and 10 km around positive feed producers showed significantly higher odds to have a BSE case than the control group. The odds ratio and its 95% confidence interval were 2.23 (1.26–3.93) for the 2 km radius and 1.38 (1–1.9) for the 10 km radius. The results provide evidence for a spatial relation between cross-contamination and BSE occurrence. These findings support the hypothesis of cross-contamination to be an important route for BSE transmission after a feed ban.

bovine spongiform encephalopathy / compound feed / cluster / spatial analysis / feed producer

1. INTRODUCTION

The first cases of Bovine Spongiform Encephalopathy (BSE), a progressive neurodegenerative disorder of adult cattle, were recognised in the United Kingdom (UK) in 1985 due to their spatial and temporal clustered emergence [16]. In 1990, the first native case of BSE found in Switzerland indicated the spread of the disease to other countries [3]. In the beginning of the epidemic in the UK, the clustered appearance provided a useful starting point to investigate the transmission pathways of BSE, leading at that time to the theory of transmission through commercial compound feed harbouring infected meat and bone meal (MBM) [17]. Measures reducing the exposure of the national cattle populations to infectivity have resulted in a reduction of cases in most countries. In Switzerland, a ban on feeding MBM to ruminants became effective in December 1990. Cases occurring in bovines born after the feed ban (BAB cases) have been explained by cross-contamination of cattle rations with MBM intended for use in pig or poultry feed in the UK [8], France [1],

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Ireland [14] and Switzerland [6]. Evidence for this was established mainly on a spatial relation between the BSE occurrence and the intensity of pig or poultry production [1, 9, 13], as an indication of the likelihood of cattle feed cross-contamination with MBM from pig or poultry feed in local feed producers.

To strengthen the logical evidence for cross-contamination as a cause for BSE cases from this spatially established relationship, several conditions have to be fulfilled: (A) a localised market for cattle feed, (B) production of cattle and pig/poultry feed in the same premises to make cross-contamination possible, (C) spatial relation between pig or poultry production and local feed production for these species, (D) no spatial heterogeneity in the distribution of infectivity in MBM. Other factors concerning different surveillance systems and population data, which could influence the spatial distribution of detected cases, are not dealt with in this study.

Modelling exercises have established further evidence for the link between MBM contamination and BSE. It is most likely that the variability in feed infectivity (which is determined by both the amount and infectivity load of the MBM in the feed) between different producers or the variation in feed utilisation between different farms explains the observed spatial pattern [8]. Recently, Sheridan et al. [14] demonstrated a spatial relation between feed distributors and areas with a significant increased risk of BSE. However, there was no information on the occurrence of cross-contamination in these studies. For Switzerland, a time dependency between the percentage of cattle feed positive for MBM contaminations detected in the Swiss feed screening programme, and the number of BSE cases born has been proposed (Fig. 1).

The purpose of this study was to establish a spatial relation between the

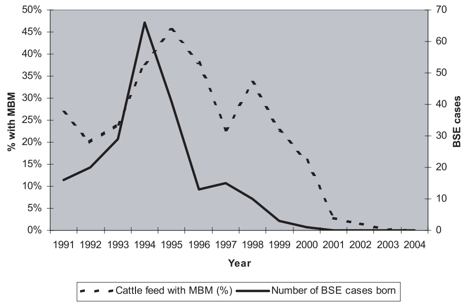

Figure 1. Percentage of cattle feed batches where MBM was found in the feed surveillance and number of BSE cases recorded in the national Swiss surveillance programme by August 1st 2005 by year of birth.

occurrence of BSE cases and the results from the Swiss screening programme for MBM in cattle feed. The intention was to strengthen the evidence for cross-contamination in the production process being the main risk factor for propagation of BSE infections after a ban on feeding MBM to ruminants.

2. MATERIALS AND METHODS

2.1. Data sources

Switzerland is administratively segregated into 26 cantons that have their own veterinary services, each headed by a cantonal veterinarian. Until August 2005, 216 BSE cases born after the introduction of the feed ban in December 1st 1990 were confirmed by the Swiss reference laboratory for spongiform encephalopathies. The case with the most recent birth date was born in January 2000.

The national BSE case database, which is maintained by the Swiss Federal Veterinary Office (SFVO), supplied data on all BSE cases diagnosed in the national Swiss surveillance programme. Before 1999, the surveillance programme focussed on clinical suspects only. In January 1999 an active surveillance system was implemented, which included testing of all fallen stock, emergency slaughtered bovines over 30 months and a sample of healthy slaughtered bovines over 30 months. The active surveillance in healthy slaughtered bovines was intensified in 2001, when 70% of all healthy slaughtered bovines over 30 months were tested [12]. Epidemiological data on BSE cases was collected by cantonal veterinarians using a standardised questionnaire. This data included the date of birth, date of death, date of BSE diagnosis and the exact geographic coordinates of the farms where the cases spent most of their first year after birth. It was assumed that the cases were exposed with the BSE agent on these locations [2]. One hundred and eleven cases were found as clinical suspects, 84 in the active surveillance system and 21 in the voluntary testing.

Data on animals that were clinically suspected of having BSE but subsequently tested negative for BSE between January 1991 and August 2005, was collected in a central database at the SFVO. The spatial reference for clinical BSE suspects was the canton where the suspicion was raised.

Livestock population data for 2001 were derived from the Swiss agricultural animal and animal holding census database (AGIS) and served as study population data. This database included 48 160 farms with at least one bovine over 2 years of age and 819 827 bovines over 2 years of age.

The location of 504 feed producers active between 1996 and 2001 and results from the surveys on MBM contamination in feed conducted from 1996 to 2001 were derived from the Federal Research Station for Animal Production (RAP). The survey was designed to include each feed producer at least once each year. Larger feed producers or such where contaminations were found previously were sampled more often. Feed producers where at least one charge of cattle feed was found to be contaminated with MBM are referred to as "positive", producers where no contamination was found are referred to as "negative". The diagnosis was made by microscopic examination. Contaminations are defined to be below a threshold of 0.1% MBM in the feedstuff [7]. More than 0.1% MBM in the produced feed indicates intentional inclusion of MBM, not an inherent process contamination. Below this threshold, the results cannot be quantified down to the detection limit of 0.01% [7]. Sensitivity and specificity of the method depend on the laboratory, but currently it is the best method and can reach up to 100% sensitivity and specificity[1].

2.2. Statistical methods

2.2.1. Analysis of clusters

The presence and location of spatial clustering of positive feed producers and farms of origin of BSE cases were assessed using the Cuzick-Edwards (C&E) test [5] and the spatial-scan statistic included in the software SatScan™ [10]. Geographic coordinates of cases and controls (reference system CH1903) were used to test for spatial clustering of cases while adjusting for the spatial distribution of the population at risk. For the analysis of feed producers, all negative feed producers served as controls, for the analysis of farms all cattle farms without a reported BSE case served as controls in the C&E test and all farms served as population for the spatial-scan statistic.

The C&E test is a nearest neighbour test and able to identify the presence of clustering in spatial data for a population at risk which has an underlying non-random distribution. The 1st–10th order (k) nearest

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neighbours (NN) for each case were identified and the observed number of NN cases (T_k) was compared with the expected number of NN cases assuming random distribution of cases and controls ($E(T_k)$) within a possibly clustered population at risk as follows:

For each level of k

$$T_k = \sum_{i=1}^{n} \delta_i d_{ik}$$

with $\delta_i = 0$ if the index point was a control, and $\delta_i = 1$ if the index point was a case, $d_{ik} = 0$ if the k^{th} NN was a control, and $d_{ik} = 1$ if the k^{th} NN was a case, $n = n_0$ (number of cases) + n_1 (number of controls), and

$$E\,(T_k) = pkn \text{ with } p = \left(\frac{n_0}{n}\right)\left(\frac{n_0 - 1}{n - 1}\right).$$

Observed and expected number of the first 10 NN cases within the population were compared. Clustering of cases in the study region was tested for statistical significance using a one-sided test with "presence of a cluster" as the alternative hypothesis. The significance level was set to P-value < 0.05. P-values for each individual k^{th} level as well as two measures for combined P-values (multiple testing), the Bonferroni P and the Simes P, were calculated.

The spatial scan statistic compares the number of cases inside a circular area to the outside and identifies the presence of a spatial cluster location. Essentially the method examines circles of continuously varying size centred on different locations. These locations are either derived from the locations in the dataset or from a specific file where the centroids for the circles are defined. For each circle, a likelihood ratio is computed for the alternative hypothesis that there is an increased (search for high-risk areas) or decreased risk of disease (search for low risk areas) inside the circle against the null hypothesis that the risk inside the circle is the same as the risk outside. The "most likely cluster" is that with the largest likelihood ratio. The statistical significance of this largest likelihood ratio is assessed by determining its distribution under the null hypothesis through a Monte Carlo simulation. This approach takes into account the multiple testing inherent in the procedure.

In a first step, the C&E test was used to explore whether there was clustering present in both the dataset of feed producers and the dataset of farms. In the next step, the sat scan statistic was used to identify clusters of positive feed producers and therefore an indication of local causes for MBM contamination.

Identification of clusters of farms with BSE cases and areas with low BSE risk was done in a twofold approach using SatScan™. In the unfocussed approach only farm data was used, whereas in the focussed approach positive feed producers represented potential cluster centres. The unfocussed analysis with farms as potential cluster centres was used to confirm the presence of clusters identified before [6] and ascertain their precise location with the actual datasets. These locations of clusters should be compared with the results of the focussed analysis with positive feed producers as potential cluster centres. The aim of the analysis with positive feed producers as potential centres for low risk areas was to confirm the spatial relation of positive feed producers and clusters of BSE cases, but only in the absence of such low risk areas.

In the unfocussed approach, BSE case farms were expected to follow a Poisson distribution under the null hypothesis. For the focussed approach, cases and controls were tested against a null hypothesis with a Bernoulli distribution. The settings for the SatScan™ software were 1 000 iterations and a maximum window width of 50%. These settings offered a good balance between computing time and cluster detection power.

2.2.2. *Retrospective cohort study*

A farm was considered to be exposed if there was a positive feed producer within either 2 km, 10 km or 20 km. A farm was considered to be unexposed, if there was a negative but no positive feed producer within either 2 km, 10 km or 20 km. Unadjusted odds ratios (OR) with 95% confidence intervals (log approach) were used to assess whether the odds to experience a BSE case differed significantly between exposed and unexposed farms. The OR were used instead of the relative risk, since the incidence in both groups was very low and the values were close to 1. A potential overestimation of the exposure effect, by using the OR in a cohort study was therefore assumed negligible. The logarithmic approximation of the 95% confidence interval (CI) is applicable if all cells exceed five observations, as in the dataset.

2.2.3. *Regional distribution of clinical BSE suspects*

Crude OR with 95% CI (log approach) were used to assess whether suspect BSE case reporting was significantly different between the cantons. The reporting level of the three cantons Lucerne, Appenzell and St. Gall was compared to the reporting level of all other cantons combined. Previously these three cantons had mainly contributed to the observed case clusters.

All test statistics were considered statistically significant either for *P*-values below 0.05 (C&E test, spatial scan statistic), or if the 95% CI excluded the value of one (odds ratios, OR). Data management and descriptive statistics were conducted with MS Access and MS Excel (Office 2000 Professional, Microsoft). Statistical calculations were performed with NCSS for Windows and WinEpiscope 2.0. The calculation of the C&E test was done with ClusterSeer (BioMedware), the estimation of the spatial scan statistic was done with SatScan 2.1 and geographic data management was done with ArcView 8.2 (ESRI).

3. RESULTS

Eighty-two feed producers were positive. No statistical evidence for clustering of positive feed producers was found using the C&E test or SatScan^{TM}. *P*-values were > 0.05 at all 10 nearest neighbour levels and in the summary statistics.

Clusters of BSE cases were found. The C&E test showed *P*-values < 0.001 at all 10 nearest neighbour levels and in the summary statistics. In the unfocussed analysis using SatScan^{TM} two high risk cluster regions ($P < 0.001$) for BSE cases were detected (Fig. 2 and Tab. I). In the focussed analysis the same two high risk regions were identified ($P < 0.001$). No evidence for low risk areas was found in the focussed analysis. In Figure 2, the cluster's exact locations are displayed together with the locations of cattle farms, BSE cases and positive and negative feed producers. The eastern cluster area covers parts of Appenzell and St. Gall, the western cluster area covers a part of Lucerne. The cross-hatched area is the overlapping area of the clusters found with each method. In each area, the cluster found in the unfocussed analysis and the cluster found in the focussed analysis overlap and most of the cases found in each analysis contribute to both clusters. Both cluster areas are situated in lowland regions passing into mountainous regions of the Alps in the south.

Farms in the proximity to positive feed producers (2 km, 10 km and 20 km) showed higher odds to have a BSE case than unexposed farms. The OR was significantly higher ($P < 0.05$) on farms within the defined 2 km or 10 km radius around a positive feed producer (Tab. II).

Between 1991 and 2005 the three cantons Lucerne, Appenzell and St. Gall were less likely to report animals with clinical

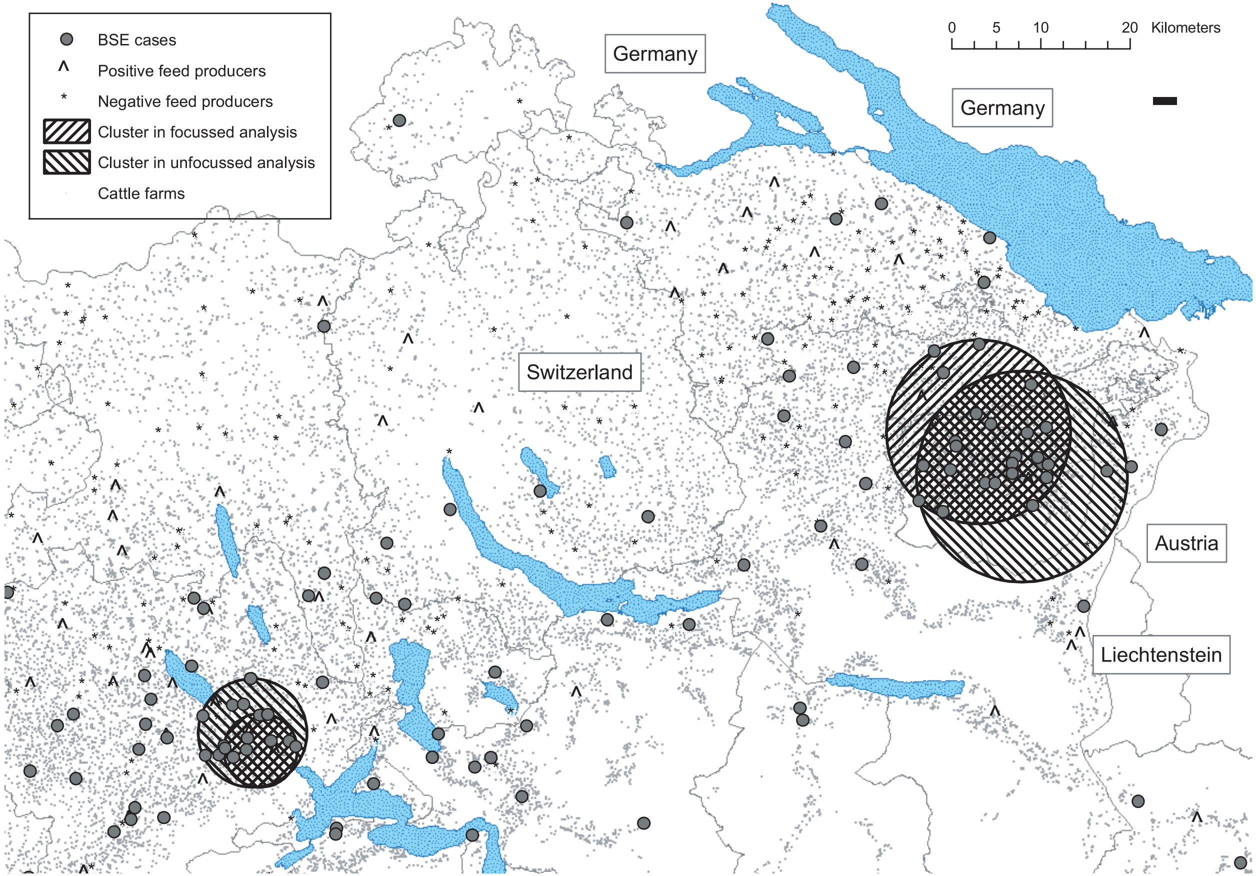

Figure 2. Regions in Switzerland with clusters of BSE cases born after December 1st 1990 as identified with SatScan™ either unfocussed with farms or focussed with positive feed producers as possible cluster centres.

Table I. Results of the SatScan™ statistics. 'hr' indicates tests for high risk areas, 'lr' for low risk areas. Geographic reference system for coordinates is CH1903 with one meter as the distance unit.

Data	Type	Cluster (*P*)	Location (x/y)	Affected cantons	Radius (km)	Cases in cluster
BSE cases	Unfocused hr	East ($P < 0.001$)	747'600/243'940	Appenzell, St. Gall	11.6	21
		West ($P < 0.001$)	661'360/215'770	Lucerne	5.5	15
BSE cases	Focused hr	East ($P < 0.001$)	742'570/249'540	Appenzell, St. Gall	10.5	23
		West ($P < 0.001$)	662'510/213'320	Lucerne	4.2	9
BSE cases	Focused lr	no				
Feed producer	hr	no				

BSE signs, tested negative for BSE, than all other regions combined (OR = 0.84; 95% CI 0.73–0.98).

4. DISCUSSION

4.1. Cluster analysis

An overview over the main possibilities for cluster analysis can be found in Carpenter [4]. For detection of global clustering within the datasets the C&E test was used. In contrast to other cluster tests, the C&E test has the capability to adjust for the underlying population structure [5] and has a high power to detect the presence of clustering [11]. Since all 1st–10th orders were assessed and gave similar results, the ability of the C&E test to detect clusters of a certain size was not influenced by the choice of the order. However, it is a global test that only assesses whether clustering is present within the population of interest, but not how many clusters are present and where they are located. The SatScan™ provides the location, size and significance of identified case clusters. The circular shape of the scanning window has been described as a major limitation of SatScan™ [6]. However, without additional information, in this study the idea of a circular window seemed the best suiting approach. In the analysis for areas with high BSE risk, clusters were detected in regions where areas of high density of cattle farms border the high mountain area without cattle farms. To avoid erroneous results, care should be taken when using SatScan™ in regions along natural or artificial borders (rivers, lakes, country borders) [6].

Two important points should be emphasised: firstly, in any cluster analysis, two tests based on different methods should be applied to point out that clustering is present at all [4]. This was fulfilled by application of the C&E test and the spatial scan test. Although the combination of Cuzick and Edwards' method and the SatScan™ was (in our view) the method of choice for our situation, there is limited information about the power of the analysis for detecting different types of clusters in the Swiss setting. Secondly, the distribution of the population at risk should be reflected as accurate as possible in the test. We included the data of the Swiss cattle population as controls, therefore no bias should be introduced by control selection.

Table II. Odds Ratio (OR) with 95% confidence interval (95% Cl) for the association between the farm of origin of BSE cases and the proximity to a positive/negative feed producer. Exposition to a positive/negative feed producer was defined for the distances 2 km (A2), 10 km (A10) and 20 km (A20).

Categories	Number of farms				OR	95% Cl	
	Exposed; with BSE	Not exposed; with BSE	Exposed; without BSE	Not exposed; without BSE		Lower	Upper
A2	19	32	2472	9236	2.226	1.26	3.934
A10	54	127	9729	31603	1.376	1	1.893
A20	54	140	10426	34764	1.286	0.939	1.762

Clinical BSE suspects were less frequently reported from the cantons where the BSE high risk areas were identified than from all other regions of Switzerland. Therefore, the higher risk for BSE in the high-risk areas is unlikely due to higher reporting levels. In the active surveillance system, either all adult cattle are tested (fallen stock and emergency slaughtered cattle) or the sampling is stratified on a cantonal level according to the canton's cattle population (healthy slaughtered cattle). For voluntary testing of healthy slaughtered cattle, a sampling bias cannot be excluded. However, a large proportion of healthy slaughtered cattle is tested voluntarily and only a small proportion of BSE cases has been detected in this stream. Furthermore, voluntary testing takes place mainly in large abattoirs that slaughter cattle originating from all over Switzerland. Hence, a small sampling bias cannot be excluded but is unlikely to have occurred in the surveillance system.

4.2. Study aim

This study focussed on the establishment of evidence for the spatial relation between BSE occurrence and contamination of cattle feed with MBM. Evidence was provided for a spatial relation between the farm of origin of reported BSE cases and positive feed producers. Four preconditions had to be fulfilled to maintain logical evidence for this relation in previous studies. In this study, two needed not to be considered: precondition B, production of cattle and pig or poultry feed on the same premise and precondition C, spatial relation between pig or poultry production and local feed production for these species. Since MBM was found in cattle feed, the occurrence of cross-contamination is highly likely for these feed producers and no indirect evidence derived from the preconditions B and C is required. The intention of this study was to strengthen the evidence for cross-contamination in the production process being a major risk factor for propagation of BSE infections after a ban on feeding MBM to ruminants.

Only the two remaining preconditions needed to be considered in this study. The general conditions in Switzerland fulfil the precondition on spatial equality in the distribution of infectivity in MBM (precondition D). Since 1996, MBM for pig or poultry feed was produced in only one enterprise with material originating from the whole country. As a result, the indigenous infectivity entering the process has been collected and distributed as evenly as possible. But infectivity might have been present in only a part of the produced batches of MBM, because it is unlikely that infectivity was present in the raw material for each batch produced, given the prevalence of BSE cases in Switzerland after 1996.

The precondition expressing the local market for cattle feed (precondition A) can be assumed to be fulfilled at least in the areas where a number of small feed producers are active. The small feed producers do compete on the local market and it is unlikely that farmers buy in from small local feed producers far away. However, large and medium sized feed producers do sell regionally. Since the relevance of local feed producers was not known in this study, we calculated OR for increasing distances from 2 km to 20 km (Tab. II). The assumption was that OR would decrease with increasing distance, since the effects of local factors should decrease. The 2 km distance equals the average distance between villages (and therefore local feed producers) in the areas with a high density of feed producers. The 10 km and 20 km distances were chosen according to the radii of identified clusters of BSE cases. The decrease of the OR with increasing radius supports the hypothesis of a local feed market.

Since the analysis of the cohort study is univariate, confounding is not taken into account. Confounders for BSE might be the age structure or the breeds of the cohorts compared. Since the OR are not much bigger than 1, neglecting confounding might result in erroneous inference. But since the cohorts were grouped according to exposure and no spatial clustering of positive feed producers was found, no regional selection bias (for example production systems are different in the Alps and in the lowland) was introduced and thus it is unlikely that the internal validity is violated by regional selection. Anyway, since no data on the regional distribution of the production systems was available as detailed as needed for inclusion in the analysis, it was not possible to study the influence of possible confounders on the results.

The SatScan^{TM} test revealed clusters in both the unfocussed and focussed analyses in only two regions. But BSE cases and MBM contaminations have been found elsewhere in Switzerland (Fig. 2), therefore clustering had to be expected also in other areas if a causation between both was to be deduced from the SatScan^{TM} results. In this study, only the spatial relation of MBM contaminations in cattle feed and BSE cases was investigated. Thus clustering of BSE cases might be due to other reasons, related to MBM contaminations or not, for example higher levels of MBM contaminations, higher infectivity in the MBM used or differences in either feeding practices or other farm management items.

In the analysis, other known local risk factors for BSE such as pig density or poultry density were not included, because the interest was focussed on the spatial relation of occurrence of BSE cases and MBM contamination in cattle feed. Currently, these other risk factors are mainly recognized as a surrogate marker for the local probability of MBM contamination occurring. In the investigations into spatial relation between the occurrence of BSE cases and pig density in France [1], UK [15] and Switzerland [6], pig density was valued as a surrogate for the risk of cross-contamination in local feed producers. Since the data on the occurrence of cross-contamination was available, the surrogates were not needed. But it is possible that the relation between cross-contamination and pig density could also be based on other mechanisms, for example (un)intentional feeding of pig feed to cattle being more likely in regions with higher pig density. This can be examined on the farm level, and should show higher odds of BSE cases for mixed farms (cattle and pigs) compared to farms with cattle only [13]. This study provides evidence for a major impact of cross-contamination of cattle feed on local BSE risk. It indicates that an effectively implemented total feed ban or a well-controlled system of dedicated feed mills is necessary to break the recycling of BSE infectivity.

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