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Is there a decline in bovine spongiform encephalopathy cases born after reinforced feed bans? A modelling study in EU member states

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SUMMARY

Occasional cases of classical bovine spongiform encephalopathy (BSE) still continue to occur within the European Union (EU) for animals born after reinforced feed bans (BARBs), which should in theory have eliminated all risk of infection. The study aimed to determine (i) whether a common rate of decline of BSE infection was evident across EU member states, i.e. to determine whether control measures have been equally effective in all member states, (ii) whether there was any evidence of spontaneous occurrence of BSE in the data and (iii) the expected date for the last BSE case in UK. It was found that there was no significant difference in the rate of decline of BSE prevalence between member states, with a common rate of decline of 33·9% per annum (95% CI 30·9–37%) in successive annual birth cohorts. Trend analysis indicated an ultimate decline to 0 prevalence, suggesting that spontaneous occurrence does not explain the majority of cases. Projecting forward the trends from the back-calculation model indicated that there was approximately a 50% probability of further cases in the UK, and should the current rate of decline continue, there remains the possibility of further occasional cases up until 2026.

Key words: Back-calculation methods, BARB cases, bovine spongiform encephalopathy, maximum likelihood methods, trends.

INTRODUCTION

Bovine spongiform encephalopathy (BSE) was first detected in November 1986, with the key route for transmission subsequently being identified as the inclusion of contaminated meat and bone meal (MBM) in cattle rations [1]. This led to a number of control measures in the United Kingdom (UK), and later across the European Union (EU), to reduce the probability of contamination of animal feed from infectious material. Ultimately, a reinforced feed ban was introduced in the UK on 31 July 1996, which prohibited the feeding of any mammalian-derived meat and bone meal (mMBM) to livestock. Equivalent bans were subsequently introduced in Ireland (IE) on 17 October 1996 and across the EU on 1 January 2001 [2]. Active surveillance was also introduced across the EU at 1 January 2001 in the form of the testing of animals over 24 or 30 months of age from

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the following groups: healthy slaughter animals, fallen stock, emergency slaughtered animals and animals with clinical signs at ante-mortem (with several subsequent revisions of the age of testing).

These control measures appear to have been very effective in controlling classical BSE [3], with exponential decline in the birth cohort prevalence within the UK [4], IE (unpublished results) and across the EU as a whole [5]. This has resulted in a steady decline of BSE cases across the EU since the introduction of EU-wide active surveillance from a peak of around 2215 cases in 2001 to two in 2016 [6]. However, there continue to be BSE cases from animals born after the introduction of the reinforced feed ban.

Cases of classical BSE in cattle that were born after the reinforced feed ban are referred to as born after reinforced feed ban (BARB) cases. Of all the EU member states (MSs), the highest number of BARB cases has been in the UK; to date, there have been 178 confirmed BARB cases in the UK (Table 1). Cattle born after 31 July 1996 should not have had any exposure to banned feedstuffs; therefore, there has been much interest and speculation about the aetiology of classical BSE BARB cases. A case–control study exploring the possible causes of the continued occurrence of BSE in BARBs in the UK [7] concluded that the results did not contradict the working hypothesis of an exogenous foodborne source, originally proposed by [8], i.e. cross-contamination between legitimately traded mMBM and imported feed ingredients during storage, processing or transportation could result in potential exposure to the domestic Great Britain (GB) (and hence UK) cattle population. However, the higher number of cases born within the UK since 2001 than other MSs makes this hypothesis look less credible than when originally proposed, at which time it was too early to assess the impact on UK BSE cases of the recently introduced reinforced feed ban within mainland Europe.

The aim of this study was to use statistical methods to examine the decline of BSE across the EU and determine whether the decline provided any insight into possible reasons for the continued occurrence of cases. Specifically, the study aimed to determine first whether a common rate of decline is evident across the EU MSs, thus indicating that control measures were equally effective across the EU. Second, since the possibility of spontaneous occurrence of BSE could be a potential source of BSE cases, as a human equivalent (Creutzfeld–Jacob disease) naturally occurs within the human population at a rate of approximately 1 per million around the world [9], the study aimed to determine whether there is any evidence of spontaneous occurrence in the data. Finally, the study also aimed to estimate the expected date for the last BSE case in the UK, to get an idea of how long the outbreak might still persist.

Table 1. *The total number of classical BSE cases born after the reinforced feed ban in each EU member state included in a study to estimate the trend of BSE*

Member state	BARB start date	Total (up to 31 March 2016)
Ireland	17 October 1996	48
United Kingdom	1 August 1996	178
Germany	1 January 2001	2
Spain	1 January 2001	7
France	1 January 2001	2
Italy	1 January 2001	1
Luxembourg	1 January 2001	1
The Netherlands	1 January 2001	1
Portugal	1 January 2001	2

METHODS

Data

The demographic and surveillance data used to populate the model, i.e. the population sizes and the number of positive and tested animals from active surveillance (fallen stock, clinical suspects, healthy slaughter and emergency slaughter) for each MS, were centrally collected and maintained by the European Commission (EC) and the European Food Safety Authority (EFSA). These data contained the details of over 91 million cattle tested within the EU25 surveillance scheme from 2002 to 2011 and have been used to inform previous EFSA scientific opinions [10].

Statistical methods

A back-calculation modelling approach was adopted [11, 12] to estimate the prevalence of infection by birth cohort, based on BSE occurrence in active and passive surveillance. In short, this involved using a maximum likelihood approach to estimate the number of infected cattle in each birth cohort that would be required in order to match the number of detected cattle, taking into account the age distribution of the standing population, the age at infection, incubation period and the sensitivity of the diagnostic test. The model used has been described in full elsewhere

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[13, 14], with the age distribution in 12 months intervals of standing, fallen and slaughtered cattle provided by EU MSs from EC and EFSA held data, the age at infection and incubation period from [12] and the sensitivity of the diagnostic test relative to the stage of the incubation period from [15].

Due to the small number of cases in recent birth cohorts in most MSs (Table 1), countries with fewer than 10 cases were grouped together for the birth cohort trend analysis. This resulted in three groups: UK, IE and other-EU (consisting of Germany, Spain, France, Italy, Luxembourg, the Netherlands and Portugal). The trend analysis covered the period from 1 January 1997 for UK and IE, 1 January 2001 for the other-EU, up to 31 March 2016 (all). EU MSs with no BARB cases were excluded from the study, although their inclusion would not have influenced the trend estimates (it would have merely reduced the estimates of prevalence). Poland and the Czech Republic, which had BARB cases (three and one, respectively) were also excluded from the analysis as they did not implement the EU-wide surveillance and control measures until joining the EU in May 2004, and it was considered that it was not possible to construct a reasonable trend analysis for these MSs.

A model of the form $A\exp(-Bt)$ was fitted to the infection prevalence by birth cohort for each group, where t was the birth cohort, and A and B were estimated from the data using maximum likelihood techniques; A determining the level of BSE and B determining the rate of BSE decline. Two models were fitted to the data; a nine-parameter model, with different values of A and B for every group, j, $Y_9 = A(j)\exp(-B(j)t)$ and a seven-parameter model where the value of B was the same for every group, $Y_7 = A(j)\exp(-Bt)$. As the seven-parameter model was nested within the nine-parameter model, a likelihood ratio test was used to determine whether the rate of decline was significantly different between the groups. For convenience of interpretation, the estimates of B were converted into percentage annual rates of decline $(1 - \exp(-B))$. The confidence intervals of individual parameters were obtained via profile likelihood.

In order to test whether there was any evidence of spontaneous occurrence of BSE in the data, a second model was fitted to the data of the form $A\exp(-Bt) + C$, where C represents a constant prevalence that is not declining over time, i.e. the estimated prevalence of spontaneous occurrence. A likelihood ratio test was carried out to test whether the model with the additional parameter C provided a significantly better fit to the data than the model without C and thus whether there was any evidence of spontaneous occurrence in the data.

To gauge expectations of how long BSE cases may continue to occur, the model was set up to estimate the likely final year in which a BSE case would be observed. The model was used to represent UK, it being the MS with the highest infection prevalence. The infection prevalence in future birth cohorts was estimated by assuming the estimated rate of annual decline in birth cohort prevalence would continue into future years. It was assumed that animals were tested from the age of 48 months in the fallen stock and emergency slaughter stream, with no testing of healthy slaughter, in line with current EU policy. The year of the final BSE case was estimated by simulating the number of cases each year, with 10 000 replicates, assuming a Poisson distributed number of cases in each stream, with expected value given by the back-calculation model. The expected number of infected cattle in each birth cohort was also estimated, based on the infection prevalence multiplied by the number born in that birth cohort.

RESULTS

Exponential rate of decline in BARB cases

Each of the three groups of countries showed an exponential decline in their number of BSE cases in each BARB birth cohort, suggesting that the choice of an exponential model fit was appropriate (Fig. 1). While there was a faster rate of decline estimated for the other-EU group (44·5% per annum, 95% CI 30·6–59·5%) compared with the UK (35·4% per annum, 95% CI 32–39·1%) and IE (26·8% per annum, 95% CI 20·8–33·4%), a likelihood ratio test indicated that there was no significant difference between the rates of decline ($P = 0{\cdot}12$), with a common rate of decline of 33·9% per annum (95% CI 30·9–37%) across EU MSs included in the study.

No evidence of spontaneous occurrence

There was no significant improvement in model fit to the birth cohort prevalence when adding a spontaneous (non-declining) element to the trend models, i.e. likelihood ratio tests suggested that the parameter C was not statistically significantly different from zero when estimated for UK, IE and other-EU grouped together ($P = 0{\cdot}80$). Therefore, the best fitting model was one

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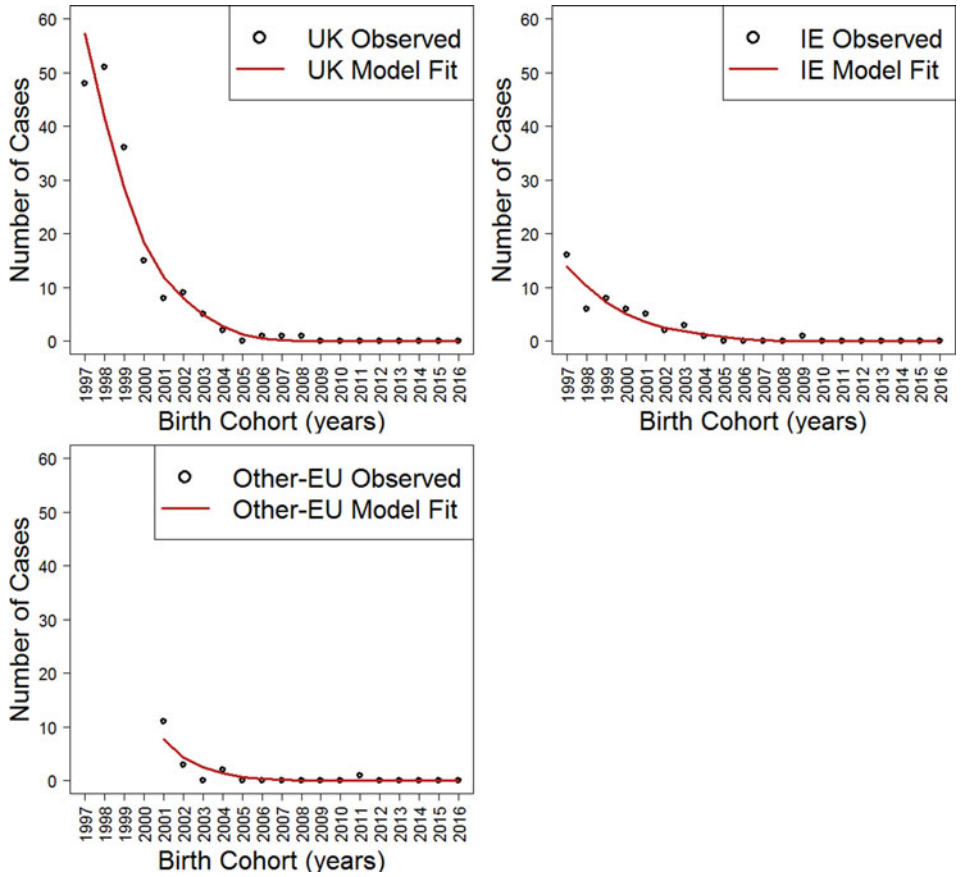

Fig. 1. The fit of the back-calculation model to the United Kingdom (UK), Ireland (IE) and other-EU (France, Germany, Italy, Luxembourg, the Netherlands, Portugal, Spain) data for the number of BSE cases in each BARB birth cohort.

where the birth cohort prevalence was ultimately declining to zero for all the MS groups.

Expected date for the last classical BSE case in UK

There is a 44·9% probability that the final BSE case in the UK occurred in 2015 (Fig. 2), i.e. that there will be no further cases. However, there was still the possibility of later cases, with a 55·1% probability that the last case would occur in 2016 or later. While the prevalence in each birth cohort is declining each year, it is not until the 2011/12 cohort that there is less than one infected animal expected (Fig. 3). Since even with only one infected animal in a birth cohort there is still the possibility of detecting a case – there was an extremely low but non-zero probability of having a detected case as late as 2026 (0·02%).

DISCUSSION

In this paper, we present a statistical analysis to investigate if the rate of decline of BARB cases differs between EU MSs. It should also be noted that this study is restricted to classical BSE and its findings are not relevant for atypical BSE, which appears to have a non-feedborne source of transmission and may occur sporadically [16]. This analysis was conducted in response to the greater number of BARB cases in recent born cohorts in the UK and whether this implied that there was a slower rate of decline in the UK, compared with the rest of the EU. This study has found no evidence that the rate of decline differs between EU MSs, and thus the data do not support a slower rate of decline in the UK. This suggests the process driving the reduction in BARB cases is the same across the EU, with no difference in the effectiveness of the various control measures between countries. Thus, the greater prevalence of BSE in more recent birth cohorts in the UK, and to a lesser extent IE, compared with other EU MSs is simply due to the higher BSE prevalence at the time of introduction of the re-inforced feed ban (1996 for UK and IE and 2001 for the other EU MSs). However, there remains high uncertainty in the cause of continued occurrence,

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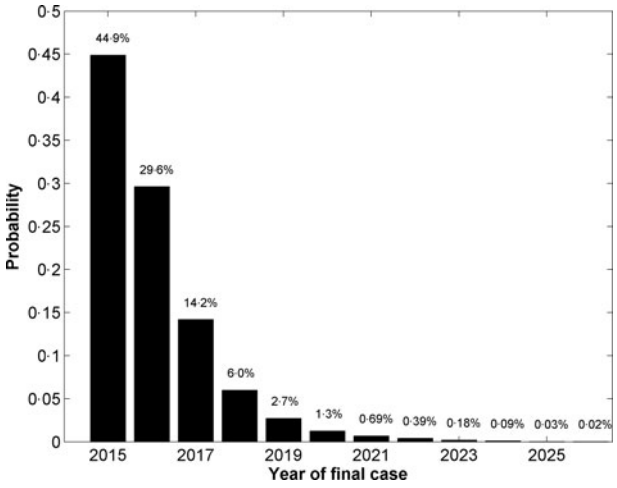

Fig. 2. Histogram showing the distribution of the probability of the estimated year of detection of the final BSE case in the UK from the results of a simulation model.

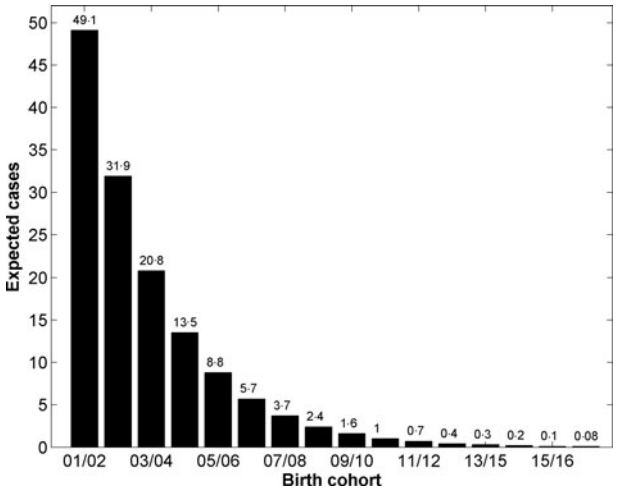

Fig. 3. The expected number of infected cattle in each UK birth cohort between 2001/02 and 2016/17 (birth cohorts are 1 July to 30 June).

with epidemiological investigations into recent cases in IE, UK and France unable to provide conclusive reasons for such cases. One possibility is residual contamination of BSE within the feed/feed production system or farm environment. It is not merely the use of old feed that is a potential cause of recent exposure, but it is possible that contamination remains in feed storage silos and in other parts of the feed production process, e.g. feed mills. We believe this residual contamination is subject to slow decay, thereby giving rise to fewer and fewer cases each year since the feed ban. This mode of transmission may be aided by the slow decay rate of the prion protein and the potential for very low-dose exposure [17]. The hypothesis of residual contamination is consistent with the findings of previous BSE case–control studies in the UK and in IE [7, 18] in concluding that a feedborne source is responsible for continued BSE occurrence, but it suggests that a domestic source of the contamination is more likely, rather than it being imported via legitimate trade in feed products.

Other potential exposure routes such as the spreading of contaminated abattoir wastes on pasture or contaminated manure spreading cannot categorically be ruled out. The possibility of prion contamination in the farm environment has been examined in case–control studies [7], where it was found that having previous BSE cases was not a significant risk factor for having BARBS; suggesting the farm environment is not a key exposure route. Additionally, unlike classical scrapie and chronic wasting disease, there is little evidence of release of classical BSE prions being shed into the environment from infected cattle [19]. Other pathways of contaminating the farm environment have been proposed and risk assessments completed investigating the risk posed by application of abattoir wastewater and soil fertilisers [20, 21]. These risk assessments have indicated an extremely low but non-zero risk of giving rise to additional classical BSE cases. Therefore, while the potential for BARB cases through the environmental contamination route cannot be ruled out, it is believed to be very low or negligible.

Maternal transmission has also been suggested as a potential source of BSE cases, as maternal transmission occurs in other transmissible spongiform encephalopathies, such as scrapie and chronic wasting disease [22, 23]. However, modelling studies have indicated that if it does occur, it does so at a very low level [24] and an epidemiological study of BARB cases in GB found no evidence of maternal transmission [4], so it does not appear to be responsible for the continued occurrence of BSE cases.

There was no evidence in the data for spontaneous classical BSE being the main cause of BARB BSE cases, although the possibility that the occasional case occurs for this reason cannot be excluded, particularly if the rate of spontaneous disease occurrence is below the level of detection of the surveillance system. However, if spontaneous occurrence was a major source of cases, then one would expect case numbers in each MS to be correlated with the size of the cattle population regardless of the occurrence of classical BSE. However, the countries that have most cases are those that have had the greatest number of classical

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BSE cases historically. The statistical approach can help to underline this conclusion, although it is acknowledged that there is limited statistical power to determine a low prevalence of spontaneous cases.

The model suggests that cases in the UK could continue, although highly unlikely, until 2026, assuming that the rate of decline observed up until the present study continues. Since the UK has a higher prevalence of BSE compared with other MSs, as well as one of the largest cattle populations, it will continue to have the highest probability of observing cases out of all the EU MSs. The observed pattern of occurrence in the EU has shown that it is not unusual for MSs to experience several years with no observed cases, and then have a re-occurrence of a single case; e.g. the 2016 case in France. The modelling results suggest that this is likely for the UK, although as time passes it will be increasingly less likely for a further case to be found.

This study has used previously developed models to estimate the trend of BSE, and is reliant on previous assumptions of these models. With regard to the age of onset distribution, it is possible that this has changed over time, especially as the incubation period is dose-dependent [17] and so if the effective dose has changed over time as BSE has decayed from the farm or feed production environment, then this would result in a longer incubation period. This would influence the estimation of trends, although it is likely to affect each EU MS group in the present study equally. A previous study did show no evidence of any change in the age at onset for BARBs and cattle born prior to 1 August 1996 in GB [4], although the power of such studies is inevitably limited by the relatively small sample sizes of the BARB cases.

In conclusion, this study suggests that there is no difference in the rate of decline of classical BSE cases between EU MSs, and so continued occurrence of BSE is due to residual contamination of the farm or feed production system, which is subject to an exponential decay, rather than through contamination of imported feed/feed ingredients (as previously suggested [8]). It also concludes that spontaneous occurrence is not likely to be a major source of classical BSE cases, and therefore, in Europe, we are likely to be in the closing stages of eradication.

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