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Modelling BSE trend over time in Europe, a risk assessment perspective

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Abstract BSE is a zoonotic disease that caused the emergence of variant Creuzfeldt-Jakob disease in the mid 1990s. The trend of the BSE epidemic in seven European countries was assessed and compared, using Age-Period-Cohort and Reproduction Ratio modelling applied to surveillance data 2001–2007. A strong decline in BSE risk was observed for all countries that applied control measures during the 1990s, starting at different points in time in the different countries. Results were compared with the type and date of the BSE control measures implemented between 1990 and 2001 in each country. Results show that a ban on the feeding of meat and bone meal (MBM) to cattle alone was not sufficient to eliminate BSE. The fading out of the epidemic started shortly after the complementary measures targeted at controlling the risk in MBM. Given the long incubation period, it is still too early to estimate the additional effect of the ban on the feeding of animal protein to all farm animals that started in 2001. These results provide new insights in the risk assessment of BSE for cattle and Humans, which will especially be useful in the context of possible relaxing BSE surveillance and control measures.

Keywords Age period cohort model · Basic reproduction number · Bovine spongiform encephalopathy · Epidemiology · European Union · Risk assessment · Prevention and control

Abbreviations

APC	Age period cohort model
BSE	Bovine spongiform encephalopathy
EU	European Union
MBM	Meat and bone meal
OIE	Office International des Epizooties
OR	Odds ratio
R_0	Basic reproduction number
SRM	Specified risk material

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UK United Kingdom
vCJD variant Creuzfeldt-Jakob disease

Introduction

The first cases of Bovine spongiform encephalopathy (BSE) were observed in 1985 in the United Kingdom (UK), and evidence of the zoonotic impact of the disease was found in 1996 [1], as the source of variant Creuzfeldt-Jakob disease (vCJD); since then, 216 cases of vCJD were detected in Humans (http://www.cjd.ed.ac.uk/vcjdworld.htm; consulted June 29, 2008). Epidemiological studies on BSE indicated that meat and bone meal (MBM) played a major role in disease transmission [2, 3]. This led to a ban on the feeding of MBM to ruminants, implemented in 1988 in the UK and subsequently throughout the European Union (EU). Although the ban significantly decreased exposure [4], by itself it proved insufficient to eliminate disease. Further measures were taken in the mid 1990s by some countries (controls on cross contamination, SRM removal) to eliminate the residual risk posed by MBM. In 2001 the European Union imposed a ban on the feeding of animal protein to all farmed animal species with limited exceptions (so called total feed ban) (http://ec.europa.eu/food/food/biosafety/bse/chronological_list2008_en.pdf; consulted October 20, 2008). As the various control measures, prior to the total EU ban in 2001 were implemented at different times in different EU Member States, it is expected to see variations in the trend of the BSE epidemic by country connected with the date and type of control measures introduced in each of them.

As the incidence of disease declines, there is a huge pressure from different stakeholders to lift certain BSE control measures. In the TSE roadmap published in 2005 (http://ec.europa.eu/food/food/biosafety/bse/roadmap_en.pdf; consulted 20 October 2008), the European Commission planned a relaxation of aspects of the total feed ban provided certain conditions were met. In part these relaxations are based on risk assessments. For this reason, analyses of the trend of the epidemic and the effect of control measures is of major concern for risk assessments and risk management in the coming years.

A comprehensive surveillance system for BSE has been in place in the EU since 2001. The surveillance system is based on clinical surveillance as well as on systematic rapid testing of risk animals (emergency slaughter and animals that die on farm) over 24 months of age and healthy slaughtered cattle over 30 months of age. Data generated by this surveillance programme has been analyzed in the past and has provided insight into the trend of the epidemic in different countries (Netherlands [5], UK [6], Italy [7], France [8, 9], Switzerland [10]. The length and variability of the incubation period for BSE [11] means that a large percentage of the infected animals are already dead or slaughtered before infection can be detected. This must be taken into account when analyzing the epidemic. Over the years different approaches have been used [12] varying from relatively simple approaches based on the age of cases at detection [13, 14] to more complicated approaches such as back calculation modelling [6, 15] and birth cohort modelling with extrapolation based on the reproduction ratio (called R_0 in the text) [5, 16, 17]. Regression integrating birth cohort and year of test [8], and Age-Period-Cohort (APC) [18] models have also been used to model disease trends.

The goal of this study was to compare the trend of the BSE epidemic in several European countries using two different standardized methods and the surveillance data collected between 2001 and 2007. In addition the study examined whether the overall trend was towards eradication and if so at what point in time did this decline start. The results were discussed in comparison with the date and type of control measures introduced. This up to date analysis provides precise risk estimates for birth cohorts born in the second half of the 1990s; it gives new insight into the effect of measures introduced before the total feed ban in 2001, and provides key aspects in a risk assessment perspective for Human Health in the context of relaxing BSE surveillance and control measures.

Materials and methods

Data

Seven EU Member States (Table 1) were involved in the study. BSE cases identified between 2001 and 2007 in all three BSE surveillance streams (clinical surveillance, risk animals and healthy slaughter animals) were used. All positives were confirmed at the Member States' National Reference Laboratories using validated tests (OIE Manual of Diagnostic Tests and Vaccines for Terrestrial Animals Chapter 2.4.6) [19, 20]. Data from the three surveillance streams were merged to facilitate comparison between countries based on the assumption that the surveillance streams varied little among countries (with the exception of the UK with mainly clinical surveillance) and that rapid tests for BSE are detecting infected animals close to onset of clinical disease.

As animals below 2 years of age are not required to be tested under European legislation, these animals were excluded from the study (http://ec.europa.eu/food/food/biosafety/bse/chronological_list2008_en.pdf, consulted 20

Table 1 Data per country included for APC analysis and R_0 estimation

	APC modelling		R_0 estimation		Period of interest
	Nb BSE cases	Nb tested animals	Nb BSE cases	Adult cattle population (million heads 2005)	
France	647	17,248,284[a]	716	10.4	2001–2007
Germany	317[b]	13,879,451[c]	400	5.9	2001–2007
Ireland	657[d]	3,594,378[e]	972	3.1	2001–2007
Italy	135[e]	4,506,951[e]	137	2.9	2001–2007
Poland	56[g]	2,968,541[h]	57	3.0	2002–2007
The Netherlands	70[i]	2,815,671[i]	74	1.7	2001–2007
United Kingdom	1795[j]	2,964,963[k]	3326	4.9	2001–2007

[a] Only indigenous animals over 30 months and tested since July 1st, 2001 were included

[b] About 89 cases detected before 2001 and four BSE cases with incomplete or incorrect data were removed from the analysis

[c] 3282 animals tested before 2001 were excluded

[d] About 17 cases born before 1990 and 67 cases without date of birth were excluded

[e] Number of tested animals derived from the Department of Agriculture, Fisheries and Food Computerised Monitoring and Movement system. Animals born before 1990 were not considered

[f] Animals 13 years old and over (whose three cases) were removed from the analysis because only pooling data for these animals was available (class: "+12 years")

[g] One case excluded because secondary and two more cases excluded because the number of tested animals for the same age and period was not estimable

[h] Estimate

[i] Animals 9 years old and over were removed from the analysis because only pooling data for these animals was available (class: "+9 years")

[j] Nine cases for which the date of birth was unknown were removed from the analysis

[k] Animals for which the date of birth was unknown and/or under 2 years old were excluded from the analysis

October 2008). Moreover, imported cases were excluded when such information was available. Atypical cases were included although they have different epidemiological characteristics as not all countries are capable of identifying them and they represented only a small proportion of all BSE cases [21]. From each participating country, raw surveillance data has been obtained: in particular data on tested animals, broken down by year of birth (or age in years), year of diagnosis and testing result (negative animals vs positive confirmed cases) were available for statistical analysis and allowed computing stratum (i.e., age, birth cohort and period) specific prevalence rates.

For the calculation of the R_0 an estimation of the adult cattle population of each country was used as the background population. The APC model used the number of animals tested in all three surveillance streams. BSE cases and the tested population were classified by age and by birth cohort. The age was calculated in complete years by subtracting the date of birth from the date of diagnosis. The birth cohort was defined as the calendar year of birth. In the R_0 method, the year of detection was the calendar year of detection while in the APC method the year of detection, called the period, was calculated from the age and birth cohort.

The country specific type and year of implementation of the main BSE control measures prior to 2001 for each country included in the study are detailed in Fig. 1 and summarized in Fig. 2. Initially, the primary BSE control measure was a ban on the feeding of MBM to cattle (or ruminants in some countries). This was followed by complementary measures involving the removal of specified risk material (SRM), controls on cross contamination and the sterilization of MBM at 133° under 3 bar pressure and for 20 min (with size particles less than 5 cm). In January 2001, a total ban on the feeding of animal protein to all farmed animal species with certain limited exceptions has been enforced. Finally in May 2001, control measures were harmonized throughout the EU with the introduction of a comprehensive TSE Regulation (Regulation (EC) 999/2001).

Methods

Two complementary methods were used to analyze the data.

Age period cohort analysis (APC)

A logistic regression model was used to model the respective effects, expressed as odds ratios, of the age at diagnosis (age), birth cohort (cohort) and period of detection (period) on BSE prevalence, expressed as cases per

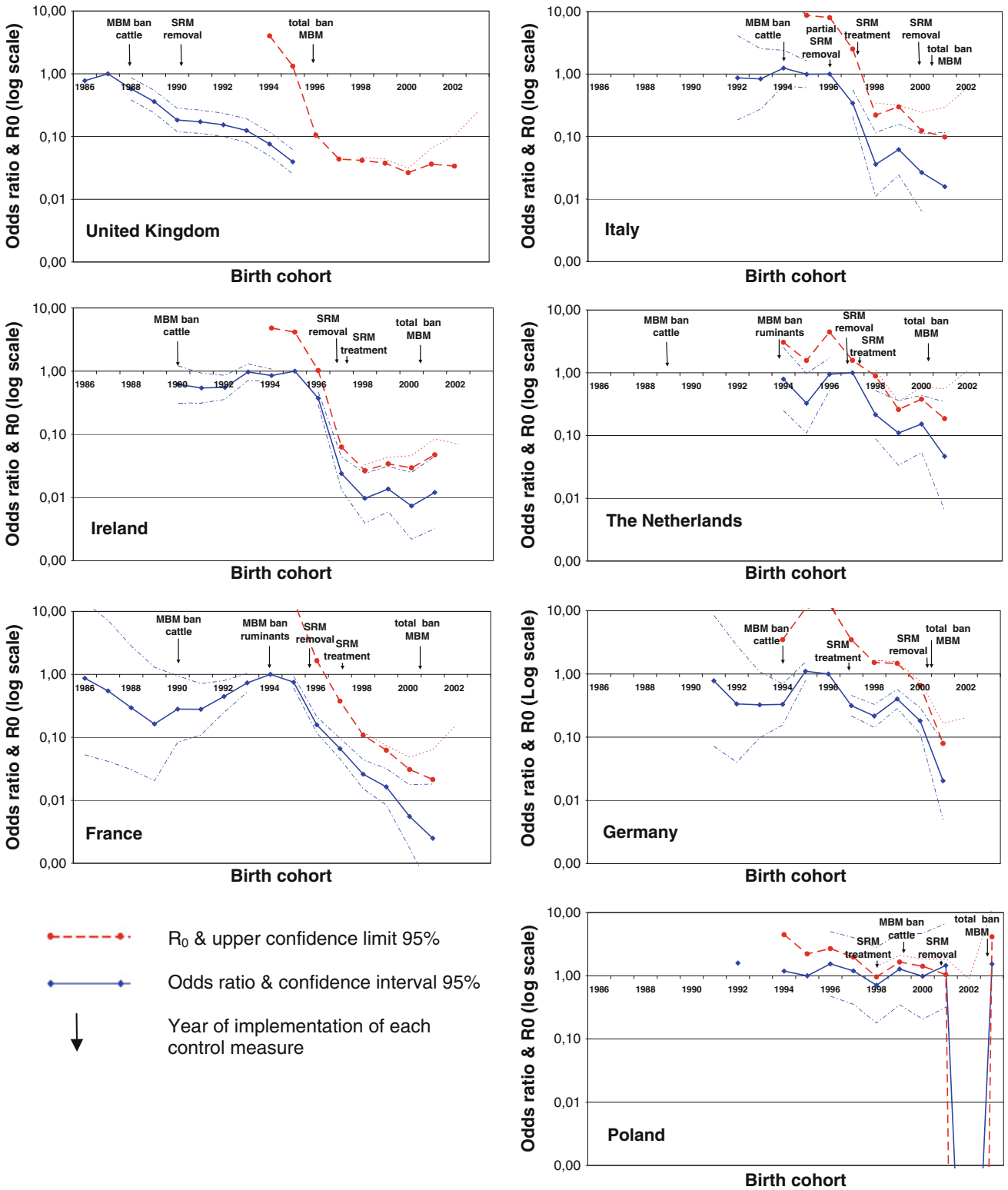


Fig. 1 Plot (log scale) of the reproduction ratio (R_0) and Odds ratio (compared to a reference cohort defined per country (OR = 1)), per birth cohort per country; type and year of control measures are indicated for each country (in the UK, dedicated line for rendering SRM in 1995; in Italy, partial SRM ban from countries with BSE in 1996)

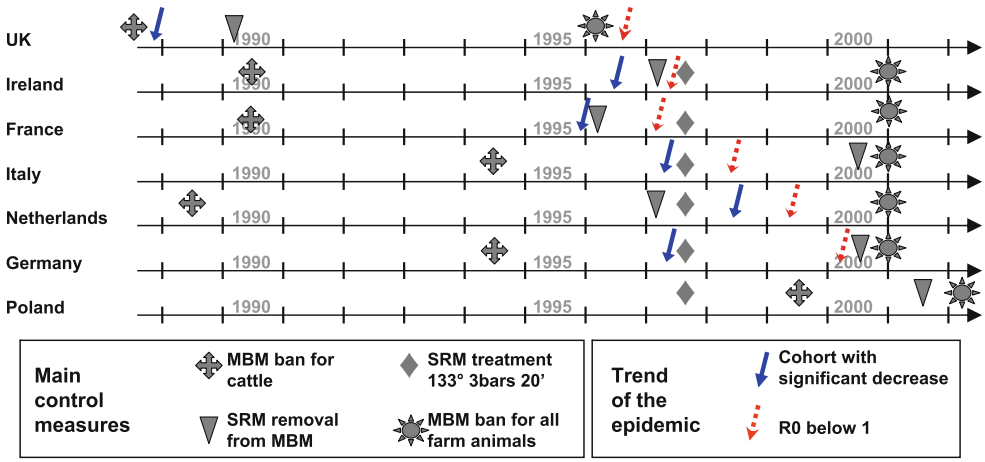


Fig. 2 Schematic time schedule of the main control measures and trend of the BSE epidemic per country

10,000 cows tested. For the cohort, the reference group chosen in each country was the birth cohort in which the highest crude prevalence was observed.

For each country, before fitting the full age-period-cohort (APC) model, we used a stepwise procedure recommended by Clayton and Schiffler [22], and run successively four sub models, including, respectively age, age and drift, age and period, age and cohort. The drift is the global trend, due to the undistinguished linear effects of the period and cohort, that we tested (model 2) before adding the non-linear components of the period (model 3) or cohort (model 4) effects. The drift cannot be attributed specifically to cohort or period, because of the inter-relation between age, period and cohort. Identifying the complete APC model required a minimal additional constraint; this was done by equalizing the effect of two successive periods as we expected little, if any, period effect due to the stability in the surveillance systems during the studied period of time [23, 24]. The significance of each variable was assessed by a log-likelihood ratio test. Goodness of fit was evaluated by the examination of the residual deviance of the models, which approximates a Chi-square distribution [25] (Table 2).

Calculation of the reproduction ratio R_0 per cohort

The reproduction ratio (R_0) [5] provides an estimate of the expected number of newly infected animals resulting from an initial infection. When R_0 is above 1, more than one new infection is expected from each infectious animal, so the epidemic increases; similarly, a R_0 smaller than 1 is linked to a decreasing epidemic. A cohort model with yearly increments was applied on the BSE case data that were categorized by age (2–12 years) and year of birth (1991–2002). The method is described in [17, 26]. We determined the test window of age for each birth cohort which had been tested between January 2001 and December 2007. Next we calculated the expected number of BSE cases in the full cohort using a distribution for the age at onset, derived from the EU15 data [17]; it was applied to all the evaluated countries without further adjustment to the national age distribution of

Table 2 Best APC model per country, effect of adding each variable to the model and goodness of fit

	Effect of the variables (*P*-value*)			Best model	Goodness of fit of the best model		
	Age	Cohort	Period		Residual deviance	Df[b]	*P*-value**
France	0.00	0.00	0.06	Age-cohort	77.57	167	1.00
Germany	0.00	0.00	0.19	Age-cohort	45.81	70	0.99
Ireland[a]	0.00	0.00	0.88	Age-cohort	49.75	46	0.33
Italy	0.00	0.00	0.02	Age-period-cohort	48.61	64	0.98
Poland[a]	0.00	0.45	0.03	Age-period	52.41	50	0.38
The Netherlands	0.00	0.00	0.12	Age-cohort	29.95	30	0.47
UK	0.00	0.00	0.13	Age-cohort	113.39	152	1.00

[a] For Poland and Ireland, because the structure of the tested population by age and cohort was not available, the period was defined as the calendar year of detection and the birth cohort was calculated by subtracting the age from the year of detection

[b] Df degree of freedom

* Log likelihood ratio test ($\alpha = 5\%$); a *P*-value < 0.05 corresponds to a significant effect of the variable

** Goodness of fit test. A *P*-value > 0.05 indicates a good fit

the standing cattle population. From these initial steps, we obtained the estimated number of BSE cases in all age groups and for every cohort from 1991 to 2003, including the age groups that were culled before 2001 and the ones still alive in 2008. From these estimates we calculated the expected number of cases in each age group by test year. The reproduction ratio was calculated as the ratio of the expected number of cases estimated to appear in a birth cohort and the expected number of cases in that test year. For estimates before 1997, this required an estimate of the number of cases found in cohorts born before 1991, which was not available in the data. We assumed that no BSE case was found in animals born before 1991; this led to an increasing overestimation of the R_0, the further we go back from 1997. Confidence intervals (95%) for the reproduction ratio were computed using the method described in [26]. The model was based on three major assumptions. Firstly, all infections occurred at a young age (first year of life); secondly, all imports of infectious animals or material are ignored; and thirdly the age at clinical onset distribution was assumed to be the same for all countries, without further adjustment to the country cattle age distribution or the different exposure pattern because of the difficulty in obtaining country specific information.

Results

The results of APC models and R_0 estimates are presented in Table 2 and Fig. 1. The cohort effect from the APC model was expressed as an Odds Ratio (OR) and plotted on a log scale. As BSE is a disease with a low prevalence the OR can be assumed to be equivalent to the Relative Risk (RR); it provides the risk of an animal of a specific cohort to be detected as a BSE case compared to the risk for an animal of the reference cohort at the same age and observation period. The results of the APC model showed that in the UK, the BSE risk decreased significantly from the 1988 birth cohort onwards. In the other countries a significant decrease started later; from the 1995 cohort onwards in France, from the 1996 cohort onwards in Ireland, from the 1997 cohort onwards in Italy and Germany and the from the 1998 cohort onwards in the Netherlands. Birth cohort was not a significant variable in the Polish model pointing to the lack of a specific temporal trend in BSE risk in Poland in the late nineties. A small increase in risk was observed in Germany, Italy and Ireland in 1999 and in the Netherlands in 2000.

Estimates of R_0 and the upper confidence limit showed that the epidemic was consistently fading out (i.e., estimated upper confidence limit of R_0 below 1) in all countries except Poland. This trend could be observed from the 1996 cohort onwards in the UK, from the 1997 cohort onwards for France and Ireland, from the 1998 cohort onwards for Italy, from the 1999 cohort onwards for the Netherlands and from the 2000 cohort onwards for Germany. In the case of Poland although R_0 was consistently very close to 1, it did not show a clear tendency to decrease below that level. A decline in the Polish BSE epidemic would need to be confirmed using later cohort data that is not yet available.

Figure 2 summarizes conjointly the results of the models and the date of the implementation of control measures per country.

Discussion

Temporal trend of BSE

An important result of the study is the clearly observable decline of the BSE epidemic in all studied countries except Poland. This represents a true decline as the study focused on the period 2001–2007, a period during which intensive and exhaustive surveillance with little bias or uncertainty was carried out for BSE in the EU. In addition both methods (APC and R_0) produced similar results and indicated similar trends. The decrease of the number of cases detected between 2001 and 2007 already gave the idea of a decline of the epidemic. However, our models accounted for the main factors influencing the prevalence, in particular the length and variability of the incubation time, the age at which the animals are tested, and they provided an adjusted estimate of the year when the decrease started and the slope of it.

The study focused on birth cohorts as previous analyses of data from the UK BSE epidemic have shown that the age at infection is mostly likely to be early in life [6], with more than 90% of case animals infected before 12 months of age. Both methods were used in a complementary way. APC modelling was based on an analysis of tested animals and provides an exact calculation of the evolution of BSE risk over successive birth cohorts. R0 modelling provides an estimate of the prevalence per birth cohort, similar to the evolution of risk derived from the APC model, but in addition can provide a measure for the transmission of infection. An assessment of the efficacy of the various control measures can be derived from the results of both models. Unlike the APC model, which looks for statistical correlations in the data, the R_0 model is mechanistic. It assumes that there is a cohort effect because cattle become infected at a young age. It also assumes that there is no period effect, which is likely because there was no change to surveillance requirements during the period of interest. Both of these assumptions are supported by the results of the APC modelling.

The difference in time (a few years) between the first cohort to exhibit decreased risk and the year where R_0 first declined below 1 can be explained by the wave effect [17]. The first cohort with decreased risk results from a combination of exposure (i.e., infection pressure in the past) and transmission level (i.e., R_0). If there was a steeply increasing epidemic in the past, then even if R_0 remains above 1, a temporary decrease in risk for the cohort may be observed. If there are no further changes in the control measures, this would then be followed by an increase in successive birth cohorts, because the exposure from the past is still increasing although the transmission level remains the same. This pattern is typically observed in epidemics when the transmission level (R_0) declines more slowly than the exposure level increases. The theoretical background for this is discussed in [16], although the development of second waves is not specifically addressed there.

The results produced by the APC model and the R_0 model are in agreement with the evolution of the average age of the cases, as suggested previously by Saegerman et al. [13, 14]. Although not reported in this paper an increase in the mean age of the cases was detected for the period 2001–2007 coinciding with a strong decline in cohort risk and R_0 [12, 17].

Finally, it can be observed from results of the APC model (Fig. 1) that the shape of the decline in risk between cohorts differed between countries varying from sharp for Ireland through moderate for Germany. This shape results from the combined effect of the force of the epidemic in the years preceding the decline and the effectiveness of control measures introduced. Furthermore, this decline started at different times in different countries; R_0 was already below 1 in the UK in 1996 though it only declined below 1 in the year 2000 in Germany. It is interesting to note the small increase in risk for animals born in 1999 and 2000 in the case of Germany, Ireland, Italy and the Netherlands. This finding has also been observed in other countries such as Japan, Canada and countries that joined EU recently (Poland, Czech Republic, Slovak Republic, Republic of Slovenia) (Ru, personal communication). It would be worth investigating this further to determine whether there is an identifiable source of these miniature increases in prevalence or whether they are just statistical fluctuations caused by low prevalence.

Control measures

The risk of infecting cattle with the BSE agent is for a given birth cohort influenced by three main parameters. The first one is the level of infectivity in cattle in fallen stock and abattoir in that period; it is the direct consequence of the infection rate about 5–7 years earlier due to incubation period and can be viewed as a wave effect [17]. The second parameter is of course the existence and quality of control measures, which restricts recycling of the BSE agent. The last one is the risk of BSE in other countries in case of imports of feed or living animals. In our study we were interested in analyzing the pattern of the BSE trend in connection with the control measures. This attempt at interpreting the evolution of the BSE trend in terms of efficiency of control measures is possible if we make the assumption that the two other aspects did not have a great impact on the time differences in BSE trend between countries. In fact, the wave effect was almost synchronized between countries, due to the major impact of the UK BSE epidemic on all European countries, with the main peak in 1988 [6] and the closest peak wave on birth cohort 1995 for France [15]. The analysis by reproduction ratio can distinguish this effect from the control measures although this ignores imports of live animals and feed. The third aspect, infections from imported feed might only attenuate the differences in the observed trend of BSE between countries, and might be marginal in most countries with an endemic BSE. For these reasons, we were confident that we can interpret the trend of BSE in relationship with control measures.

Some points arose from analysing the trend of BSE in comparison with the type and date of the introduction of control measures. The first point is that the ban of MBM for cattle alone was not sufficient to control the risk, at least in the Netherlands, France, Italy and Ireland, since it was not followed by a strong decrease of the epidemic and the R_0 remained above 1. This does not mean that in theory the feed ban is not sufficient to control the risk of BSE; it only means that the way it was implemented in various countries did not fully or immediately stop the transmission process. This resulted from the effect of cross-contaminations between feed for monogastrics and feed for cattle, which were observed in different countries and analyzed in detail in different epidemiological studies [12]. The second point of interest is that in almost all the countries studied, such as Ireland, Italy, France and the Netherlands, we observed that the risk decreased significantly and the R0 was below 1 shortly after removal of SRM from MBM and treatment of MBM at 133°/3bars/20'/particles < 5 cm were applied. These two measures were often introduced within a short period of time and it is therefore difficult to separate their respective effects. Also, in some countries such as France [15], the wave effect could have coincided with the effect of a given control measure such as SRM removal, these two effects being difficult to disentangle. It could be argued that since these complementary measures were implemented shortly after the announcement on March 1996 of the zoonotic consequences of BSE, this announcement might have prompted countries and feed industries to step

up compliance with previous regulation measures, such as the ban of MBM for cattle. This could have resulted in an overlap between implementation of complementary actions and increased compliance with previous measures. We believe strongly that the announcement of the zoonotic feature of BSE cannot explain alone the decrease trend observed because the starting date of the decrease varied largely between countries, from birth cohort 1995 to birth cohort 1998. We definitely believe that the complementary measures had a significant impact on the observed decrease, specifically because we observed similar timing between the time of implementation of the complementary measures and the time of decrease in the countries studied (Fig. 2).

The third point of interest is that in all studied countries apart from Germany and Poland, the R_0 was already below 1 (progressive fading out of the epidemic) before the implementation of the ban on the feeding of animal protein to all farm animals in 2001. This does not mean that this total feed ban did not have any effect. In the case of a disease with long incubation time, the fading out of the epidemic can be very slow even with the R_0 below 1. However, it is still a bit too early to quantify the precise effect of this total feed ban in these countries.

In this study, we analyzed the data separately for each country. However, the situation of BSE in a given country is linked to other countries because of the high level of trade; without trade, most of these countries would not have had a BSE epidemic in the first place. Therefore, the control measures decided at the EU level (http://ec.europa.eu/food/food/biosafety/bse/chronological_list2008_en.pdf; consulted October 20, 2008) such as ban on the use of proteins derived from mammalian tissues for feeding ruminants in 1994, pressure cooking system for processing mammalian waste into MBM in 1996, prohibition of the use of SRM in 2000 (application of decision 96/534 was postponed until October 2000 with Decision 2000/412), total ban on the feeding of MBM to all farm animals in 2001, might have had a stronger impact on the international BSE situation than those taken at the country level. However, implementation of these measures was not always at the same time so we specifically looked at the real date of implementation of the measures in our analysis (Figs. 1, 2).

Conclusion

The modelling of the BSE epidemic in seven EU countries using two different methods has shown very coherent results concerning the effect of various types of control measures as they were applied in these countries. We observed a strong decline of the risk of BSE for countries that applied control measures in the nineties. The results show that the implementation of the ban on feeding MBM to cattle alone was not followed by a decrease of the epidemic, which can be linked with the quality of implementation of this measure in the field. We did observe fading out of the epidemic following the introduction of complementary measures which were targeted at controlling the risk in MBM (SRM removal and MBM treatment). It is still too early to quantify the additional effect of the total feed ban of MBM for farm animals implemented in 2001. These comparative results add a new insight in the risk assessment of BSE for cattle and Humans, which will especially be useful in the context of the feasibility to possible lifting control measures in the future.

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