Temporal aspects of the epidemic of bovine spongiform encephalopathy in Great Britain: holding-associated risk factors for the disease

J. W. WILESMITH, J. B. M. RYAN, M. A. STEVENSON, R. S. MORRIS, D. U. PFEIFFER, D. LIN, R. JACKSON, R. L. SANSON

The objectives of this study were first to describe the pattern of the epidemic of bovine spongiform encephalopathy (BSE) in Great Britain in terms of the temporal change in the proportion of all cattle holdings that had experienced at least one confirmed case of BSE to June 30, 1997, and secondly to identify risk factors that influenced the date of onset of a holding's first confirmed BSE case. The analyses were based on the population of British cattle at risk, derived from agricultural census data collected between 1986 and 1996, and the BSE case data collected up to June 30, 1997. The unit of interest was the cattle holding and included all those recorded at least once on annual agricultural censuses conducted between June 30, 1986, and June 30, 1996. The outcome of interest was the date on which clinical signs were recorded in a holding's first confirmed case of BSE, termed the BSE onset date. Univariate and multivariate survival analysis techniques were used to describe the temporal pattern of the epidemic. The BSE epidemic in Great Britain started in November 1986, with the majority of affected holdings having their BSE onset date after February 1992. After adjusting for the effect of the size and type of holding, holdings in the south of England (specifically those in the Eastern, South east and South west regions) had 2·22 to 2·43 (95 per cent confidence interval [CI] 2·07 to 2·58) times as great a monthly hazard of having a BSE index case as holdings in Scotland. After adjusting for the effect of region and type of holding, holdings with more than 53 adult cattle had 5·91 (95 per cent CI 5·62 to 6·21) times as great a monthly hazard of having a BSE index case as holdings with seven to 21 adult cattle. Dairy holdings had 3·06 (95 per cent CI 2·96 to 3·16) times as great a monthly hazard of having a BSE index case as beef suckler holdings. These analyses show that there were different rates of onset in different regions and in holdings of different sizes and types, that the epidemic was propagated most strongly in the south of the country, and that the growth of the epidemic followed essentially the same pattern in each region of the country, with modest temporal lags between them. The control measures imposed in 1988 and 1990 brought the expansion of the epidemic under control, although the rate of progress was slowed by those regions where the effectiveness of the control methods took some time to take full effect.

Veterinary Record (2000) **147,** 319-325

J. W. Wilesmith, BVSc, MRCVS, HonMFPHM,
J. B. M. Ryan, BEd, MIBiol, Epidemiology Department, Veterinary Laboratories Agency – Weybridge, New Haw, Addlestone, Surrey KT15 3NB
M. A. Stevenson, MVSc, MACVSc,
R. S. Morris, MVSc, PhD, FACVSc,
D. U. Pfeiffer, DrMedVet, PhD, DiplTropVetMed, MACVSc,
D. Lin, BSc,
R. Jackson, BVSc, PhD, EpiCentre, Institute of Veterinary, Animal and Biomedical Sciences, Massey University, Private Bag 11-222 Palmerston North, New Zealand
R. L. Sanson, BVSc, PhD, MACVSc, AgriQuality New Zealand, PO Box 1654, Palmerston North, New Zealand

Professor Pfeiffer's present address is Department of Farm Animal and Equine Medicine and Surgery, Royal Veterinary College, Hawkshead Lane, North Mymms, Hertfordshire AL9 7TA

BOVINE spongiform encephalopathy (BSE) was first recognised as a pathological entity in November 1986 (Wells and others 1987) and soon afterwards cases began to be recognised throughout Great Britain. There have been marked variations in incidence, with the largest number of cases being diagnosed in the southern counties of England and the smallest in Scotland. It has been suggested that this geographical pattern of incidence might have been a result of variations in the risk of exposure to the BSE-contaminated meat and bone meal included in ruminant feedstuffs (Wilesmith and others 1991). It has also been suggested in epidemiological analysis by Wilesmith (1994, 1998) that holding-associated risk factors such as enterprise type (dairy, beef suckler or mixed) and size might have contributed to the pattern, but these factors have not been quantified against a spatially and temporally precise population at risk, and the important issue of confounding between them has not been adequately examined. The BSE epidemic in Great Britain is now clearly in decline, and it is timely that the accumulated epidemiological data should be used to provide detailed analyses of the entire epidemic and obtain a better understanding of its temporal and spatial features.

In this paper the temporal pattern of the BSE epidemic is analysed against the population of cattle holdings recorded on the annual agricultural censuses conducted in England, Scotland and Wales between 1986 and 1996. Case holdings were those that experienced at least one confirmed case of BSE up to June 30, 1997. After this date, the targeted slaughter of at-risk cattle has created biases which make it inappropriate to include later cases in an epidemiological analysis. Survival analysis techniques were used to describe the temporal pattern of occurrence of the first confirmed BSE case on affected holdings, in relation to the population of holdings at risk. Cox proportional hazards regression was used to identify holding-associated risk factors that influenced the date of onset of the clinical signs of a holding's first confirmed BSE case.

MATERIALS AND METHODS

Study population

The unit of interest was the cattle holding, including all those which had details recorded on the annual agricultural censuses conducted by the Ministry of Agriculture, Fisheries and Food (MAFF) in England and Wales and by the Scottish Office, Agriculture, Environment and Fisheries Department (SOAEFD), Scotland between June 30, 1986, and June 30, 1996. Census data for each holding included a unique identifier and the number of adult dairy and beef suckler animals present on June 30 of each census year. For holdings in England and Wales, census data were collected for all holdings employing at least one labour unit and a random sample of holdings employing less than one labour unit. In Scotland, census data were collected for all holdings.

On the basis of the census data recorded over the entire study period, each holding was assigned a type classification according to the following rule. The total number of cattle recorded on each holding at each census was summed and if the number of dairy cattle exceeded 80 per cent of the total, the holding was classified as dairy, and if the number of suckler cattle exceeded 80 per cent of the total, the holding was classified as beef suckler, and holdings fitting neither category were classified as mixed. A summary data set was constructed recording the region in which the holding was located, the date of the holding's first recorded census, the date of the last observation (assumed to be 12 months after the last recorded census date), the mean size of the holding (referred to subsequently as 'holding size') and the type of holding.

The BSE database (Wilesmith and others 1992b, Sanson and Ryan 1997) provided details of the outcome of interest, that is, the date of onset of clinical signs in the first confirmed case of BSE recorded on a holding. The term 'BSE-positive' is used to describe holdings that had at least one BSE case confirmed by histopathology (Wells and others 1989) and 'BSE-negative' is used to describe holdings that either never reported a suspect BSE case or reported suspect cases but had none confirmed. The term 'BSE index case' is used to describe the first confirmed BSE case recorded on a holding and 'BSE onset date' identifies the date on which clinical signs were first observed in a BSE index case.

BSE-positive holdings which could not be matched with data on either the MAFF or SOAEFD census rolls were presumed to be holdings employing less than one labour unit (for those located in England and Wales) or holdings where there was a discrepancy in the unique identifier recorded in the census database and the BSE database. For these BSE-positive holdings, the BSE database was used to provide details of the size and type, and for these holdings it was assumed that the first census date was June 30, 1986.

Because BSE is thought to have occurred principally as a result of exposure to the causative agent early in life (as a result of consuming meat and bone meal supplement in the period between birth and first calving) (Wilesmith and others 1992a, b) cases recorded as purchased were included with data for the natal holding, if it was known. The BSE database provided details of the natal holding either via a separate variable specifically to record the natal holding for purchased cases or via the herdmark descriptor of the animal's ear tag. Purchased cases for which the natal holding could not be identified were included with the data for the holding where they were diagnosed.

FIG 1: Map of Great Britain showing the regions described: EA Eastern, MW Mid and West, NO Northern, SC Scotland, SE South east, SW South west, WA Wales

Statistical analyses

Univariate and multivariate survival analysis techniques were used to identify factors influencing BSE onset date. Data for the holdings were left-truncated up until their first recorded census date. Holdings that never experienced a case of BSE were right-censored 12 months after the date of their last recorded census. The influence of three holding-associated risk factors on BSE onset date were investigated. First, the geographical region in which the holding was located (Eastern, Mid and West, Northern, Scotland, South east, South west and Wales, as defined in Fig 1), secondly, the size of the holding (mean adult cattle numbers) and, thirdly, the type of holding (dairy, mixed or beef suckler). Region and type of holding were analysed as categorical variables and holding size was classified into quartiles and analysed as a categorical variable. The effect of each stratum of each hypothesised risk factor on BSE onset date was assessed by using the Kaplan-Meier technique in the LIFETEST procedure in SAS (SAS System for

TABLE 1: Numbers of holdings in the seven regions of Great Britain between June 30, 1986, and June 30, 1997, and estimates of each region's area (in hectares) and the numbers of holdings per 100 hectares

Region	Total holdings included	Area (hectares x 10^6)	Holdings per 100 hectares
Eastern	5978	2·4	0·25
Mid and West	23,116	2·6	0·89
Northern	16,393	2·8	0·59
Scotland	19,285	7·8	0·25
South east	7779	1·5	0·52
South west	24,661	2·4	1·03
Wales	20,845	2·0	1·04
Total	118,057	22	0·54

TABLE 2: Numbers of BSE-positive holdings confirmed up to June 30, 1997, and numbers of BSE-negative holdings to June 30, 1997, and the total numbers of cattle holdings recorded on MAFF and SOAEFD censuses between June 30, 1986, and June 30, 1996, in the seven regions of Great Britain. BSE-positive holdings have been classified according to whether the natal holding of the index case was known

		Number (%) of total holdings		
		BSE-positive		
Region	Total holdings	Natal holding of index case known	Natal holding of index case unknown	BSE-negative
Eastern	5978	862 (14)	329 (6)	4787 (80)
Mid and West	23,116	5293 (23)	1606 (7)	16,217 (70)
Northern	16,393	3268 (20)	1126 (7)	11,999 (73)
Scotland	19,285	1648 (9)	1002 (5)	16,635 (86)
South east	7779	1610 (21)	479 (6)	5690 (73)
South west	24,661	6528 (26)	1940 (8)	16,193 (66)
Wales	20,845	3090 (15)	1261 (6)	16,494 (79)
Total	118,057	22,299 (19)	7743 (7)	88,015 (75)

TABLE 3: Descriptive statistics of the size of the BSE-positive and BSE-negative holdings in the seven regions of Great Britain. The table is based on MAFF and SOAEFD census data recorded between June 30, 1986, and June 30, 1996, and data derived from the BSE database up to June 30, 1997

Region	BSE-positive holdings Number	Mean (sd)	Median	Q1, Q3*	BSE-negative holdings Number	Mean (sd)	Median	Q1, Q3
Eastern	1191	79 (66)	67	33, 104	4787	18 (28)	8	2, 21
Mid and West	6899	81 (59)	69	44, 102	16,217	24 (30)	12	4, 32
Northern	4394	72 (51)	61	40, 92	11,999	26 (30)	16	5, 35
Scotland	2650	93 (62)	84	52, 120	16,635	36 (43)	20	5, 52
South east	2089	94 (72)	80	44, 124	5690	19 (29)	9	3, 23
South west	8468	81 (63)	68	43, 102	16,193	21 (31)	10	3, 28
Wales	4351	61 (46)	51	32, 78	16,494	20 (23)	12	4, 28
Total	30,042	79 (59)	67	41, 101	88,015	25 (33)	13	4, 33

* Q1 25th percentile, Q3 75th percentile

TABLE 4: Numbers of BSE-positive and BSE-negative holdings of the three types in the seven regions of Great Britain. The table is based on MAFF and SOAEFD census data recorded between June 30, 1986, and June 30, 1996, and data derived from the BSE database up to June 30, 1997

Region	BSE-positive holdings Dairy	Mixed	Beef suckler	Unknown*	BSE-negative holdings Dairy	Mixed	Beef suckler	Total
Eastern	669	71	397	54	553	338	3896	5978
Mid and West	5498	427	828	146	4666	1531	10,020	23,116
Northern	2893	407	984	110	2472	1173	8354	16,393
Scotland	1190	242	1195	23	1736	912	13,987	19,285
South east	1378	139	495	77	830	459	4401	7779
South west	6677	580	1079	132	3888	1617	10,688	24,661
Wales	2886	355	1074	36	3240	1704	11,550	20,845
Total	21,191	2221	6052	578	17,385	7734	62,896	118,057

* Holdings not present on MAFF or SOAEFD census rolls for which no type description was given in the BSE database

Windows, Release 6.12; SAS Institute). Kaplan-Meier survival curves for each stratum of a hypothesised risk factor were plotted and the homogeneity of the curves between strata was tested by using the Log Rank statistic. Risk factors that showed an association with BSE onset date (that is, a difference in the Kaplan-Meier survival curves that was significant at $P<0·20$) were selected for inclusion in the multivariate analysis.

Regression coefficients for the Cox proportional hazards regression model were determined by using a forward-stepping approach using the PHREG procedure in SAS Release 6.12. The Efron approximation was used to handle tied event times (Efron 1977). The significance of the addition of explanatory variables into the model was tested by using a likelihood ratio test, and explanatory variables that were significant at $P<0·05$ remained in the model. To verify that the proportional hazards assumption for the Cox model was valid for each prognostic variable, the survivorship function, S(t), for each stratum was determined and a plot of log[–log S(t)] against time was constructed for each stratum (Collett 1994). Covariate-adjusted survival curves, based on the results of the Cox proportional hazards regression model, were computed by using the modified estimated risk score approach described by Hosmer and Lemeshow (1999).

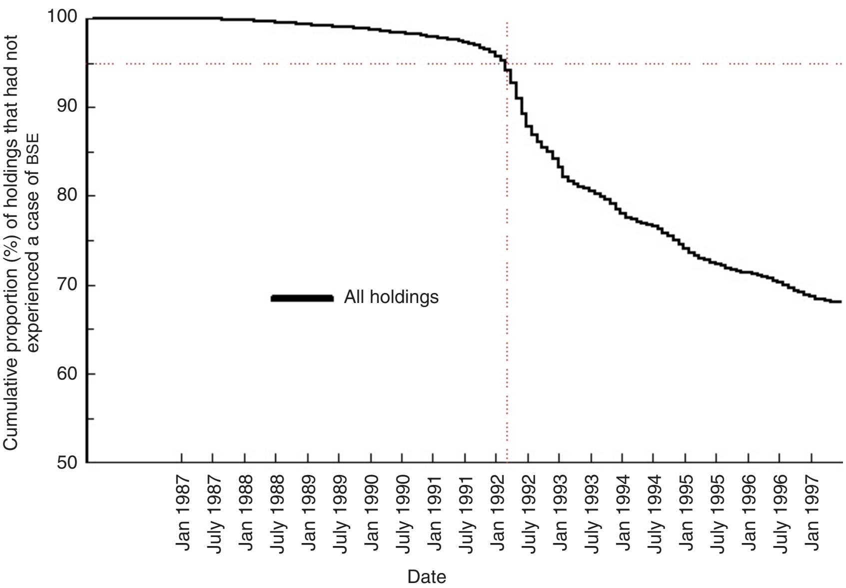

FIG 2: Kaplan-Meier survival curve showing the cumulative proportion of cattle holdings that had not experienced a BSE index case. The reference line indicates when 5 per cent of all cattle holdings in Great Britain were confirmed with BSE (February 1992). The curve has been calculated from the population of cattle holdings estimated to have been present in Great Britain from June 30, 1986, to June 30, 1997

RESULTS

Table 1 shows the total numbers of holdings, and the numbers of holdings per 100 hectares in each region. Table 2 shows the numbers of BSE-positive and BSE-negative holdings up to June 30, 1997, in each region. In total 22,299 (74 per cent) of the 30,042 BSE index cases could be located to their natal holding. The proportion of BSE index cases that could not be located to their natal holding differed significantly between regions ($P<0·01$) (Table 2).

Descriptive statistics of the size of BSE-positive and BSE-negative holdings in each region are shown in Table 3. In all the regions the median size of the BSE-positive holdings was greater (by inspection) than the median size of the BSE-negative holdings. Table 4 shows the numbers of BSE-positive and BSE-negative holdings of each type in each region.

Fig 2 shows the cumulative proportion of all the cattle holdings that had not experienced a BSE index case, as a function of time, and Fig 3 shows the cumulative proportion of the cattle holdings in each region that had not experienced a BSE index case. As a result of censoring, the regional proportions of holdings that were BSE-positive by June 30, 1997 (as shown in Fig 3), differ slightly from the results obtained by dividing the number of BSE-positive holdings by the total number of holdings present throughout the study period. In the discussion that follows, the Kaplan-Meier estimate has been used to describe the final proportion of holdings which were BSE-positive by June 30, 1997.

Table 5 gives the results of the Cox proportional hazards regression model for BSE onset date. On the basis of this regression analysis, Fig 4 shows the cumulative proportion of cattle holdings in each region that had not experienced a BSE index case, adjusted to account for the effects of mean holding size and holding type. Fig 5 shows the cumulative proportion of cattle holdings in each category of holding size that had not experienced a BSE index case, adjusted to account for the effect of location and type of holding. Fig 6 shows the cumulative proportion of cattle holdings of the different types that had not experienced a BSE index case, adjusted to account for the effects of location and category of holding size.

After adjusting for the effects of the size and type of holding, holdings in the Eastern, South east and South west regions of England had, respectively, 2·22 (95 per cent CI 2·07 to 2·38), 2·43 (95 per cent CI 2·29 to 2·58) and 2·40 (95 per cent CI 2·29 to 2·51) times as great a monthly hazard of having a BSE index case as holdings in the reference category (those in Scotland). All the other regions had between 1·67 and 1·79 (95 per cent CI 1·59 to 1·88) times as great a monthly hazard of having a BSE index case as holdings located in Scotland.

After adjusting for the effect of region and holding type, holdings with more than 53 adult cattle had 5·91 (95 per cent CI 5·62 to 6·21) times as great a monthly hazard of having a BSE index case as holdings in the reference category (those with seven to 21 adult cattle). Dairy holdings had 3·06 (95 per cent CI 2·96 to 3·16) times as great a monthly hazard of having a BSE index case as beef suckler holdings.

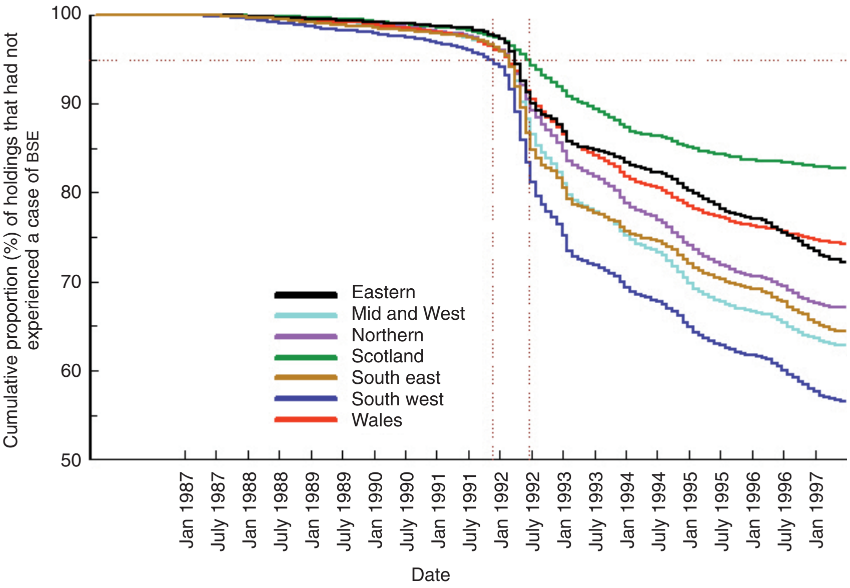

FIG 3: Kaplan-Meier survival curve showing the cumulative proportion of cattle holdings in each region that had not experienced a BSE index case. Dates when 5 per cent of a region's holdings were confirmed with BSE (in order) were: South west (November 1991, indicated by the left reference line), Mid and West (February 1992), Northern (February 1992), South east (February 1992), Wales (February 1992), Eastern (March 1992), and Scotland (June 1992, indicated by the right vertical reference line). These curves have been calculated from the population of cattle holdings estimated to have been present in Great Britain from June 30, 1986, to June 30, 1997

DISCUSSION

The BSE epidemic in Great Britain has been the subject of continuous epidemiological analysis to identify and understand the major risk factors for the disease and to assess the effects of the control measures instituted (Wilesmith and others 1992b, Wilesmith 1996). This is the first of a series of studies in which the accumulated data on the BSE epidemic have been analysed in conjunction with demographic data from the national population at risk.

This study was based on data from 118,057 cattle holdings in England, Scotland and Wales. Of these, 30,042 had at least one confirmed case of BSE diagnosed up to June 30, 1997. Relating the numbers of BSE-affected holdings to the total number of cattle holdings at risk makes it possible to quantify risk factors for the presence of the infective agent in a holding (such as its type and size) and to compare the temporal progression of the epidemic among regions. In this study the unit of interest was the holding (rather than the individual animal), and holdings that experienced a single confirmed case received the same analytical weighting as

TABLE 5: Cox proportional hazards regression model showing the effect of region, holding size and holding type on the monthly hazard of experiencing a BSE index case

Explanatory variable	Number of holdings	Number BSE-positive	Regression coefficient (se)	P	Hazard ratio‡	95% CI of hazard ratio
Region				<0·01*		
Eastern	5924†	1137	0·7981 (0·0359)		2·22	2·07-2·38
Mid and West	22,970	6753	0·5830 (0·0241)		1·79	1·71-1·88
Northern	16,283	4284	0·5632 (0·0254)		1·76	1·67-1·85
Scotland	16,635	2627			1·00	
South east	7702	2012	0·8865 (0·0302)		2·43	2·29-2·58
South west	24,529	8336	0·8746 (0·0234)		2·40	2·29-2·51
Wales	20,809	4315	0·5127 (0·0256)		1·67	1·59-1·76
Holding size				<0·01		
1-6	31,469	644	–0·8344 (0·0468)		0·43	0·40-0·48
7-21	25,142	2021			1·00	
22-53	29,145	8479	1·061 (0·0257)		2·89	2·75-3·04
>53	29,702	18,320	1·776 (0·0254)		5·91	5·62-6·21
Holding type				<0·01		
Dairy	38,576	21,191	1·117 (0·0168)		3·06	2·96-3·16
Mixed	9955	2221	0·5462 (0·0253)		1·73	1·64-1·81
Beef suckler	62,896	6052			1·00	

Likelihood ratio test statistic 35,570; df 11; P<0·01
* The significance of inclusion of the six region variables in the model
† Cases with missing values have been excluded, so counts vary slightly from those shown in Table 4
‡ Interpretation: compared with the reference category (holdings in Scotland), after adjusting for the effect of the size and type of holding, up to June 30, 1997, holdings in the Eastern region of England were at 2·22 (95% CI 2·07 to 2·38) times the monthly hazard of having a BSE index case
CI Confidence interval

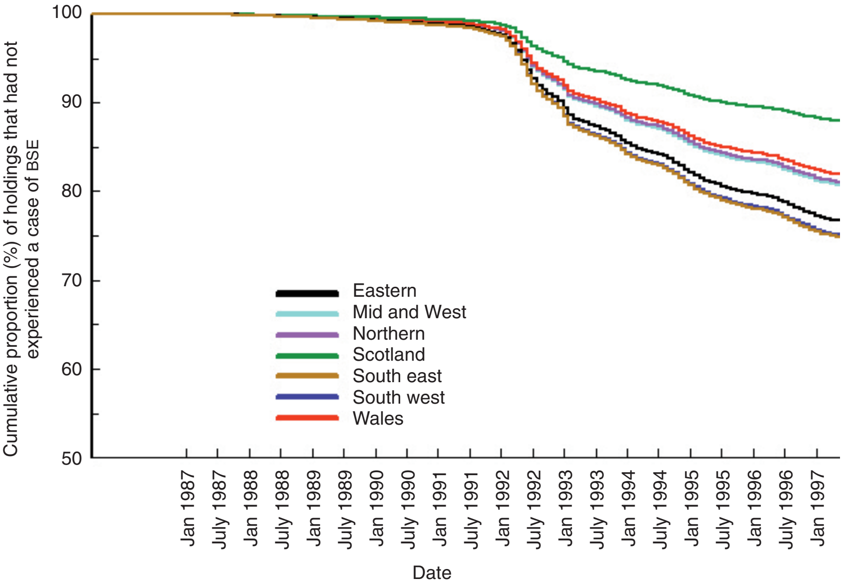

FIG 4: Kaplan-Meier survival curves showing the cumulative proportion of cattle holdings in each region that had not experienced a BSE index case. These curves have been calculated from the population of cattle holdings estimated to have been present in Great Britain from June 30, 1986, to June 30, 1997, and have been adjusted to account for the effect of holding size and holding type, on the basis of the Cox proportional hazards regression model shown in Table 5

holdings that had more than one case. As a result, the consideration of when holdings were first exposed to the BSE agent was uncomplicated by factors which might have influenced whether they had further cases.

The geographical distribution of the earliest recorded cases of BSE revealed a remarkably contemporaneous occurrence throughout Great Britain with no evidence of an obvious initial focus (Wilesmith 1991). However, in the early stages there was a marked geographical heterogeneity in its incidence and this has persisted throughout (Wilesmith and others 1988, Wilesmith 1998). The results of this study indicate that the temporal evolution of the BSE epidemic differed markedly between regions, with the epidemic being propagated at different rates. Five per cent of holdings in the South west region had experienced a BSE index case by November 1991 (Fig 3) and by June 30, 1997, 44 per cent of this region's holdings were BSE-positive, the highest proportion of holdings affected of all the regions. Collectively, the South east, Mid and West and Northern regions showed similar temporal patterns of onset throughout the epidemic, all having 5 per cent of holdings affected by February 1992. Their rates of breakdown were similar to the South west region throughout the epidemic, and by June 30, 1997, 36 per cent, 37 per cent and 33 per cent of holdings in the South east, Mid and West and Northern regions were BSE-positive, respectively. Wales and the Eastern region of England shared similar temporal patterns of onset (Fig 3); 5 per cent of holdings in these regions were BSE-positive by February 1992 and March 1992, respectively, and by June 30, 1997, 26 per cent and 28 per cent of holdings were BSE-positive. In Scotland, 5 per cent of holdings were BSE-positive by June 1992 and by June 30, 1997, 17 per cent of holdings were BSE-positive. The unadjusted Kaplan-Meier survival curves (Fig 3) show consistent differences between the different regions throughout the epidemic, indicating clear differences in their capacity for the propagation of the epidemic, and possibly differences in the initial seeding of the infection. After controlling for the effects of size and type of holding, holdings in the south of England (those in the South west, South east and Eastern regions) had similar (and the highest) monthly hazards of becoming BSE-positive (Table 5, Fig 4). Further analysis is required to clarify whether this south-to-north gradient in the risk of infection of a holding was the result of transmission and amplification mechanisms or more simply due to variations in the scale of the infectious challenge.

After the introduction of the primary control measure, a ban on the feeding of ruminant-derived protein to ruminants in July 1988 (HMSO 1998a, b), the epidemic was monitored closely to assess its effectiveness, and beneficial effects were observed (Wilesmith and Ryan 1992, 1993, Hoinville 1994). Subsequent analyses of the geographical occurrence of cases in animals born after the July 1988 ban revealed that the response to the ban was less marked in the Eastern region of England, an effect which was attributed to ruminant-derived meat and bone meal intended for the pig and poultry industry contaminating cattle feed (Wilesmith 1996). These findings were confirmed by the analysis of finished feedstuffs, using an ELISA to detect species-specific proteins (MAFF, unpublished observations), and Fig 3 shows that there was an increase in the confirmation rate of BSE on holdings in the Eastern region of England in 1996 to 1997, which was probably due to this problem of cross-contamination in feed mills. This finding also indicates the incomplete compliance to the specified bovine offal ban introduced in September 1990 (HMSO 1990) which was intended to prevent the inclusion of meat and bone meal derived from high-risk bovine tissues in pig and poultry feedstuffs. Although individual animal data (rather than holding-level data) would provide more accurate insights into the effectiveness of the control measures applied, Figs 2 and 3 show a decline in the number of holdings affected per unit of time commencing in the middle of 1993, five years after the imposition of the July 1988 feed ban.

The high proportion of BSE index cases that could not be assigned to their natal herd in Scotland (Table 2) is due to the fact that a large proportion of BSE cases in Scotland occurred in purchased animals, many of which were of unknown origin (Wilesmith and others 1992b). Some of them would have been born in Scotland but most would have been born further south. As a result, the proportion of

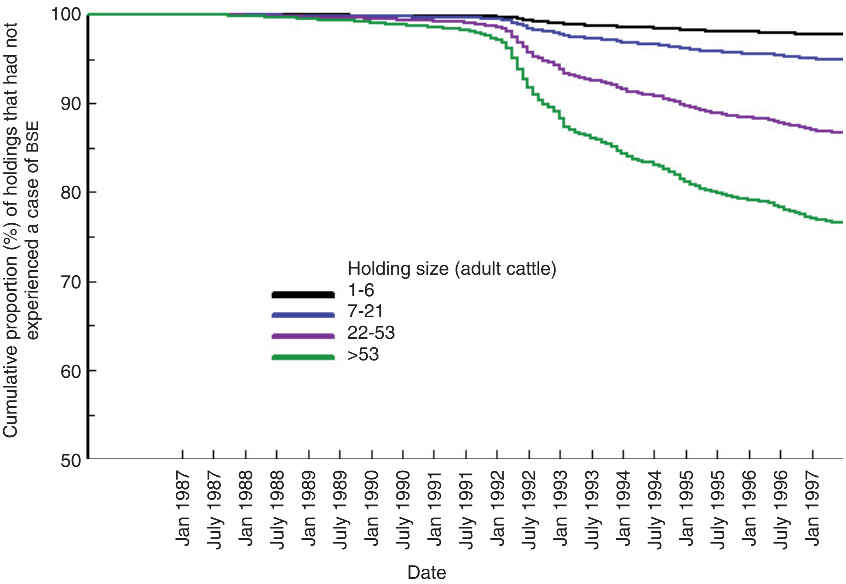

FIG 5: Kaplan-Meier survival curves showing the cumulative proportion of cattle holdings in the four size categories that had not experienced a BSE index case. These curves have been calculated from the population of cattle holdings estimated to have been present in Great Britain from June 30, 1986, to June 30, 1997, and have been adjusted to account for the effect of the holding location and holding type on the basis of the Cox proportional hazards regression model shown in Table 5

BSE-positive holdings reported for Scotland is probably overestimated.

The origin of the exposure of the British cattle population to the agent of a transmissible spongiform encephalopathy (TSE) is not the subject of this paper, but the working hypothesis for the evolution of the epidemic is that the scale of the observed clinical BSE epidemic was the result of the recycling of BSE-infected tissues via meat and bone meal back to cattle (Wilesmith and Wells 1991). On the basis of this hypothesis, the rate of progression of the regional epidemics and the ultimate cumulative proportion of holdings affected is thought to have been determined by three key factors. The first is the relative risk of cattle (particularly those in the late stage of incubation) being rendered and the resultant meat and bone meal being incorporated into cattle feedstuffs. Within a region, the relative contributions that cattle make to the production of meat and bone meal and the size of the cattle population relative to that of other species, such as pigs and poultry, which are fed the product, are therefore important. The second factor is the effect of the rendering system in reducing the infectivity of the meat and bone meal. Laboratory-based studies have indicated that none of the basic rendering systems used in Europe are capable of disinfecting tissues (Taylor and others 1995). However, the solvent extraction process, although it has been only partially simulated in a laboratory study, has been found to be the most effective of the methods examined in reducing the titre of the BSE agent (Taylor and others 1998). The original survey of rendering plants in Great Britain had identified that a reduction in the use of hydrocarbon solvents to maximise the extraction of tallow (fat) might have been a precipitating factor for the sudden exposure of the cattle population to a TSE agent (Wilesmith and others 1991). This survey of rendering plants also provided some explanations for the variation in geographical risk. These were the continued use of hydrocarbon solvents in Scotland, and geographical variations in the proportion of meat and bone meal which had been produced as a result of double treatment, in the reprocessing of greaves. The third factor influencing the rate of progression of the regional epidemics and the ultimate cumulative proportion of holdings affected is the degree of effectiveness of the control measures which were imposed.

Given these factors, the more rapid propagation of the infection among holdings in the south of the country can be explained in part, first, by the high density of cattle in the region relative to other species (infected tissues from cattle were more likely to be converted to meat and bone meal and fed back to cattle in the South west than in the other regions), secondly, by changes in the use of solvent extraction during the amplification phase of the epidemic, and, thirdly, by the relatively small proportion of the meat and bone meal produced in the region which had been subjected to double heat treatment. An alternative, or possibly complementary, explanation is that the epidemic started in the south. The contemporaneous occurrence of BSE cases throughout Great Britain is not, at first sight, consistent with this hypothesis, but this apparent inconsistency will be examined in later papers.

An advantage of a multivariate analysis of this type is that the contributions of the various interacting risk factors for disease can be distinguished and quantified. In agreement with previous analyses (Wilesmith 1998) the hazard of a holding being BSE-positive depended on its type and size. Holdings with more than 53 adult cattle had 5·91 (95 per cent CI 5·62 to 6·21) times as great a monthly hazard of having a BSE index case as holdings with seven to 21 adult cattle (Table 5, Fig 5). Dairy holdings had 3·06 (95 per cent CI 2·96 to 3·16) times as great a monthly hazard of having a BSE index case as beef suckler holdings (Table 5, Fig 6). In the context of the current

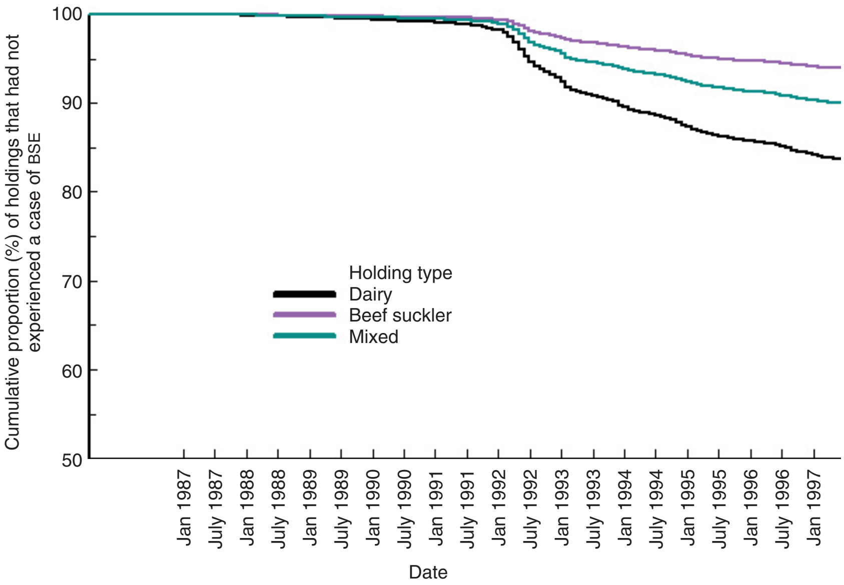

FIG 6: Kaplan-Meier survival curves showing the cumulative proportion of cattle holdings of the three types that had not experienced a BSE index case. These curves have been calculated from the population of cattle holdings estimated to have been present in Great Britain from June 30, 1986, to June 30, 1997, and have been adjusted to account for the effect of holding location and holding size, on the basis of the Cox proportional hazards regression model shown in Table 5

knowledge of the epidemiology and pathogenesis of BSE these findings are logical: larger holdings were more likely to use significant amounts of compound feeds and had, on average, a greater chance of an infected animal surviving long enough for clinical signs to be detected. After controlling for the effect of the location of the holding and its size, dairy holdings had a greater monthly hazard of having their first BSE case confirmed than beef suckler holdings (Table 5, Fig 6), probably as a result of the greater use of compound feeds in dairy holdings, which are more intensively managed than other enterprise types.

Because census data have been used to provide details of the population at risk throughout the epidemic, these analyses have quantified factors that influenced the BSE onset date for cattle holdings in Great Britain up to June 30, 1997. They show that there were different rates of onset in different regions and in holdings of different types and size, and that the epidemic was propagated most strongly in the south of England. They also show that the growth of the epidemic followed essentially the same pattern in each region of the country, with modest temporal lags between them. In the Eastern region there was evidence of a later recycling of the infection, consistent with the known problems of cross-contamination in feed mills, which resulted in a slower response to the imposition of the control measures. The control measures imposed in 1988 and 1990 brought the expansion of the epidemic under control, although the rate of progress was slowed by those regions where the effectiveness of the control measures took some time to take full effect.

ACKNOWLEDGEMENTS

The authors would like to thank the staff of the Central Veterinary Laboratories Agency, Weybridge, for maintaining the BSE database. Sincere thanks are due to James Lee for providing the code to compute the covariate adjusted survival curves, and to Steve Haslett, Jeff Jones and Duncan Hedderley for statistical advice. The authors are grateful for funding from MAFF for this study.

References

COLLETT, D. (1994) Modelling Survival Data in Medical Research. London, Chapman and Hall. pp 192-197

EFRON, B. (1977) The efficiency of Cox's likelihood function for censored data. *Journal of the American Statistical Association* **76,** 312-319

HMSO (1988a) The Bovine Spongiform Encephalopathy Order 1988a. Statutory Instrument 1988a, Number 1039. London, HMSO

HMSO (1988b) The Bovine Spongiform Encephalopathy Amendment Order 1988b. Statutory Instrument 1988b, Number 1345. London, HMSO

HMSO (1990) The Bovine Spongiform Encephalopathy (No 2) Amendment Order 1990. Statutory Instrument 1990, Number 1930. London, HMSO

HOINVILLE, L. J. (1994) Decline in the incidence of BSE in cattle born after the introduction of the 'feed ban'. *Veterinary Record* **134,** 274-275

HOSMER, D. W. & LEMESHOW, S. (1999) Applied Survival Analysis Regression Modeling of Time to Event Data. New York, John Wiley and Sons. pp 137-152

MINISTRY OF AGRICULTURE, FISHERIES AND FOOD (1986-1996) Agricultural Statistics – United Kingdom. London, HMSO

SANSON, R. L. & RYAN, J. B. M. (1997) User manual for the BSE release database. New Haw, Epidemiology Department, Central Veterinary Laboratory

SCOTTISH OFFICE, AGRICULTURE, ENVIRONMENT AND FISHERIES DEPARTMENT (1986-1996) Agricultural statistics – Scotland. Edinburgh, Department of Agriculture, Environment and Fisheries

TAYLOR, D. M., FERNIE, K., McCONNELL, I., FERGUSON, C. E. & STEELE, P. J. (1998) Solvent extraction as an adjunct to rendering: the effect on BSE and scrapie agents of hot solvents followed by dry heat and steam. *Veterinary Record* **143,** 6-9

TAYLOR, D. M., WOODGATE, S. L. & ATKINSON, M. J. (1995) Inactivation of the bovine encephalopathy agent by rendering procedures. *Veterinary Record* **137,** 605-610

WELLS, G. A. H., HANCOCK, R. D., COOLEY, W. A., RICHARDS, M. S., HIGGINS, R. J. & DAVID, G. P. (1989) Bovine spongiform encephalopathy: diagnostic significance of vacuolar changes in selected nuclei of the medulla oblongata. *Veterinary Record* **125,** 521-524

WELLS, G. A. H., SCOTT, A. C., JOHNSON, C. T., GUNNING, R. F., HANCOCK, R. D., JEFFREY, M., DAWSON, M. & BRADLEY, R. (1987) A novel progressive spongiform encephalopathy in cattle. *Veterinary Record* **121,** 419-420

WILESMITH, J. W. (1991) Origins of BSE. *Veterinary Record* **128,** 310

WILESMITH, J. W. (1994) An epidemiologist's view of bovine spongiform encephalopathy. *Philosophical Transactions of the Royal Society of London B, Biological Sciences* **343,** 357-361

WILESMITH, J. W. (1996) Recent observations on the epidemiology of bovine spongiform encephalopathy. In Bovine Spongiform Encephalopathy. The BSE dilemma. New York, Springer-Verlag. pp 45-55

WILESMITH, J. W. (1998) Manual on Bovine Spongiform Encephalopathy. Rome, Food and Agriculture Organization of the United Nations

WILESMITH, J. W. & RYAN, J. B. M. (1992) Bovine spongiform encephalopathy: recent observations on the age-specific incidences. *Veterinary Record* **130,** 491-492

WILESMITH, J. W. & RYAN, J. B. M. (1993) Bovine spongiform encephalopathy: observations on the incidence during 1992. *Veterinary Record* **132,** 300-301

WILESMITH, J. W., RYAN, J. B. M. & ATKINSON, M. J. (1991) Bovine spongiform encephalopathy: epidemiological studies on the origin. *Veterinary Record* **128,** 199-203

WILESMITH, J. W., RYAN, J. B. M. & HUESTON, W. D. (1992a) Bovine spongiform encephalopathy: case control studies of calf feeding practices and meat and bone meal inclusion in proprietary concentrates. *Research in Veterinary Science* **52,** 325-331

WILESMITH, J. W., RYAN, J. B. M., HUESTON, W. D. & HOINVILLE, L. J. (1992b) BSE: epidemiological features 1985 to 1990. *Veterinary Record* **130,** 90-94

WILESMITH, J. W. & WELLS, G. A. H. (1991) Bovine spongiform encephalopathy. In Transmissible Spongiform Encephalopathies. Current Topics in Microbiology and Immunology. Berlin, Springer-Verlag. pp 21-38

WILESMITH, J. W., WELLS, G. A. H., CRANWELL, M. P. & RYAN, J. B. M. (1988) Bovine spongiform encephalopathy: epidemiological studies. *Veterinary Record* **123,** 638-644

Long-term outcome of surgery for dogs with cranial cruciate ligament deficiency

Veterinary Record (2000) **147,** 325-328

J. F. Innes, D. Bacon, C. Lynch, A. Pollard

J. F. Innes, BVSc, PhD, CertVR, CertSAO, MRCVS, Division of Companion Animals, Department of Clinical Veterinary Science, University of Bristol, Langford House, Langford, Bristol BS40 5DU

D. Bacon, BVSc, MRCVS, Brookside, Milton Mills, Milton Abbas, Blandford, Dorset DT11 0BQ

C. Lynch, BVSc, MRCVS, The Old Golfhouse Veterinary Group, Brandon Road, Thetford, Norfolk IP24 3ND

A. Pollard, BVSc, MRCVS, The Cromwell Veterinary Group, 36 St Johns Street, Huntingdon, Cambridgeshire PE18 6DD

Fifty-eight dogs with cranial cruciate ligament deficiency were assessed and treated surgically. At an average of 50 months postoperatively, the functional outcome was assessed by means of an owner-based clinical assessment and a clinical examination. Client-based data were available for 26 dogs and 20 dogs were reassessed after 50 months. The results were compared with the initial values and with data from an assessment 13 months postoperatively. The level of disability at 50 months was judged to be significantly less than initially. However, there were no differences between the initial assessments and those made after 50 months for the perceived 'effect of cold weather' and the dogs' 'ability to jump', despite both measures having improved after 13 months. Age and meniscal injury were identified as poor prognostic indicators for the long-term outcome. The equivalent joint on the contralateral limb deteriorated significantly during the study.

IN dogs, a loss of function of the cranial cruciate ligament is the most common condition to affect the stifle joint. Cranial cruciate ligament deficiency is a broad term which includes the complete rupture or partial tearing of the ligament, whether traumatic or degenerative in aetiology, and which results in the loss of functional stability of the stifle joint. Many studies have shown that the loss of function of the ligament inevitably results in a pattern of pathological change in the joint which is consistent with osteoarthritis (Brandt 1991).

Osteoarthritis is a disease characterised by the aberrant repair and eventual focal loss of articular cartilage, osteophyte formation at the joint margins, changes in subchondral bone architecture and variable synovial inflammation (Johnston 1997). Osteoarthritis may be a cause of pain and disability, particularly the end-stage disease (Bennett 1990). In dogs, the experimental transection of the ligament is a well-established model of osteoarthritis, and short- to medium-term studies (weeks to months) have shown that after the transection of the ligament there is hypertrophy and increased hydration of articular cartilage. The few long-term studies have shown that it takes three to five years before there is full-thickness loss of articular cartilage (Brandt and others 1991).

The treatment of cranial cruciate ligament deficiency may be conservative or surgical, but in dogs weighing over 15 kg it