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CREUTZFELDT-JAKOB DISEASE SURVEILLANCE IN THE UK

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SUMMARY

The national surveillance programme for Creutzfeldt-Jakob disease (CJD) in the UK was initiated in May 1990. In 1999, the National CJD Surveillance Unit (NCJDSU) became a WHO Collaborative Centre for Reference and Research on the surveillance and epidemiology of human transmissible spongiform encephalopathies (TSEs). In September 2001 the National Care Team was formed, which currently comprises two care coordinators and a secretary. It is based within the NCJDSU and was formed in response to concerns regarding the care of CJD patients.

For the first time, the Unit has prepared a Scientific Report, which is available on the Unit's website (www.cjd.ed.ac.uk). The aim of the Scientific Report is to inform interested parties of details of the current and planned future, wide-ranging scientific research being undertaken by staff at the NCJDSU, in the context of the Unit's previous research and its on-going core background surveillance. The Scientific Report complements this Annual Report, which provides a description of the clinicopathological epidemiology of CJD in the previous 12 months, reflecting the Unit's core surveillance work. The NCJDSU Business Plan provides financial, structural and organisational information.

The information provided in this Sixteenth Annual Report continues to indicate that the number of sporadic cases remains relatively stable (the data for 2007 may still be incomplete). Detailed clinical and epidemiological information has been obtained for the great majority of patients. There has been a lower number of referrals since 2003 but analysis suggests that much, if not all, of the decline is due to changes in the number of referrals who turn out not to be CJD cases. Although the post mortem rate for patients with suspected CJD has declined, in line with general autopsy rates in the UK, it remains high (around 60%). The number of brain specimens examined in the neuropathology laboratory for sporadic CJD declined from 32 in 2006 to 23 in 2007.

In 1990-2007 mortality rates from sporadic CJD in England, Wales, Scotland and Northern Ireland were, respectively, 0.90, 1.01, 0.97 and 0.57/million/year. The differences between these rates are not statistically significant ($p>0.5$). The mortality rates from sporadic CJD in the UK are comparable to those observed in most other European countries and elsewhere in the world, including countries that are free of BSE. The highest and lowest mortality rates from sporadic CJD were observed in the South West (SMR=132) and Northern Ireland (SMR=76) respectively. The variation in the observed mortality rates between the different regions within the UK is not statistically significant ($p>0.1$).

Up to 31 December 2007, there were 163 deaths from definite or probable variant CJD (vCJD) in the UK. Of these, 115 were confirmed by neuropathology. A further 3 probable cases were alive on 31st December 2007. The clinical, neuropathological and epidemiological features of these cases of vCJD are remarkably uniform and consistent with our previous descriptions. Risk factors for the development of vCJD include age, residence in the UK and methionine homozygosity at codon 129 of the prion protein gene - all 146 clinically affected cases of vCJD with available genetic analysis have been methionine homozygotes. The incidence of vCJD is higher in the north of the UK than in the south.

Analysis of the incidence of vCJD onsets and deaths from January 1994 to December 2007 indicates that a peak has passed. While this is an encouraging finding, the incidence of vCJD may increase again, particularly if different genetic subgroups with longer incubation periods exist. The identification of disease-related PrP in the spleen of a clinically unaffected blood recipient of PRNP-129 MV genotype is not inconsistent with such an hypothesis. This case, along with the report of the prevalence of abnormal PrP in the large study of appendix and tonsil tissues, suggests the possibility of a greater number of preclinical or subclinical cases in the population than might be indicated by the present numbers of confirmed clinical cases.

The only statistically significant geographic cluster of vCJD cases in the UK was in Leicestershire. All geographically associated cases of vCJD are considered for investigation according to a protocol which involves the NCJDSU, colleagues at the HPA, HPS and local public health physicians.

The activities of the NCJDSU are strengthened by collaboration with other surveillance projects, including the Transfusion Medicine Epidemiology Review and the study of Progressive Intellectual and Neurological Deterioration in Children. The collaboration of our colleagues in these projects is greatly appreciated; the effectiveness of this collaboration allowed the identification in 2003 of a case of vCJD associated with blood transfusion and the identification in 2004 of PrP^{res} in the spleen of a recipient of blood donated by someone incubating vCJD. In 2006 a further two cases of vCJD associated with blood transfusion were identified.

The success of the National CJD Surveillance Unit continues to depend on the extraordinary level of co-operation from the neuroscience community and other medical and paramedical staff throughout the UK. Ongoing support is provided by the Infectious Diseases Epidemiology Unit, London School of Hygiene and Tropical Medicine. We are also particularly grateful to the relatives of patients for their collaboration.

Section

2

CLINICAL SURVEILLANCE

The national surveillance of CJD in the UK was initiated in May 1990 in response to a recommendation in the Report of the Working Party on Bovine Spongiform Encephalopathy (Southwood Committee). The surveillance is funded by the Department of Health and by the Scottish Executive Health Department. The initial aim of the NCJDSU was to identify any change in the pattern of CJD that might be attributable to human infection with the agent responsible for the emergence of bovine spongiform encephalopathy (BSE) in cattle. Such a change was recognised in 1996 when vCJD was first described. The NCJDSU now aims to monitor characteristics of CJD, specifically sporadic CJD and vCJD, to identify trends in incidence rates and to study risk factors for the development of disease. This report documents the findings in relation to UK cases of sporadic, familial, iatrogenic and vCJD referred up to 31st December 2007 (with data ascertained up to 20th March 2008). Mortality data from England and Wales include retrospective data from 1970; for Scotland and Northern Ireland, retrospective mortality data are available from 1985.

2.1 Referrals to NCJDSU

The NCJDSU receives referrals of suspect cases of CJD and a proportion of these will turn out not to have CJD. Referrals of suspect cases increased over the years after the present surveillance system began in 1990, particularly following the description of vCJD in 1996. Over the 1999-2003 period, the annual referral number varied little, between 162 and 179. In 2004, however, there were only 114 referrals, the lowest level since 1996, and they remained around this level over 2005-2007.

This reduction in the number of referrals to NCJDSU has been examined in detail and described in previous NCJDSU Annual Reports (2004, 2005). In summary, it would appear that various factors may be responsible. Part of the decline can be explained by the decline in vCJD cases over that period. Figure 1a shows the number of referrals to NCJDSU split between age groups < 30 and ≥ 30. The number of referrals aged less than 30 has declined from a peak of 29 referrals in 2000 to 3-5 referrals per year in 2004-2007.

However, the decline in referral of those aged 30 years and older is less likely to be explained by a reduction in the number of vCJD cases, because this age group contains more sporadic cases. Finding the reason for the decline is complex, however, over the period 2000-2007 the largest drop in referrals occurred in those whom eventually turned out not to be cases of CJD (Figure 1b).

This suggests that the changes in numbers of referrals in the past couple of years is, at least in part, due to changes in the numbers of non-cases recorded as referrals. In addition, there have been variations in what is recorded as a suspect case of CJD by staff within the Unit over time, particularly since the introduction of 14-3-3 as a routine test in 1999.

Figure 1a Referrals to NCJDSU : 1 May 1990 – 31st December 2007: Age < 30 and age ≥ 30

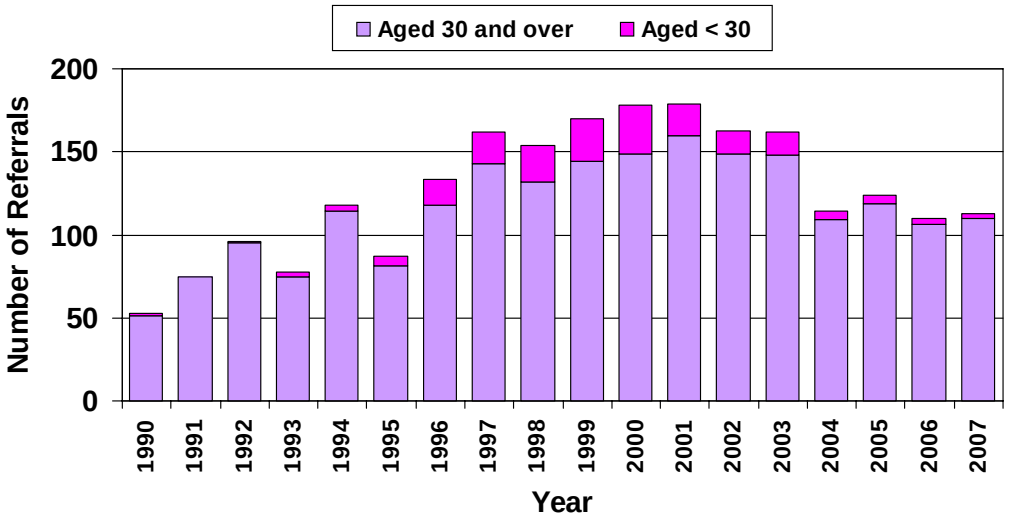
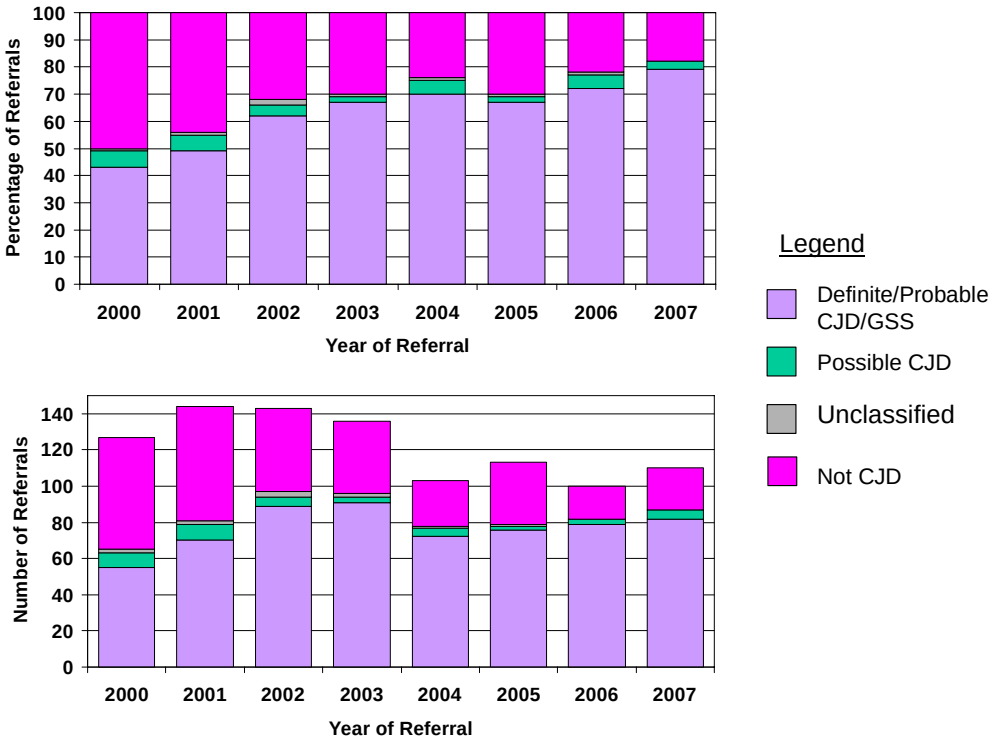


Figure 1b Diagnostic classification of referrals: 2000-2007*
(shown as percentages and absolute numbers)



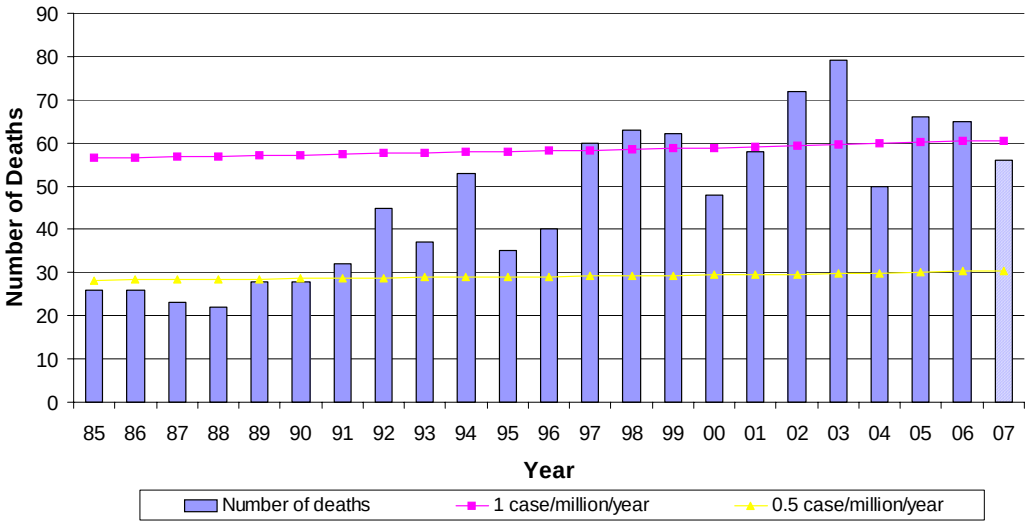
*excludes suspect vCJD referrals and vCJD cases

2.2 *Sporadic Creutzfeldt-Jakob Disease*

Between 1st January 1970 and 31st December 2007, 1361 cases of sporadic CJD were identified in the UK, of which 19 cases were alive on 31st December 2007. Two further cases were identified in Jersey but they are not included in the following UK analyses. Of these UK cases, 1008 (74%) were classified as definite cases with the remainder classed as probable. Figure 2a shows the number of deaths each year from sporadic CJD for the UK between 1985 and 2007, Figure 2b shows similar data for England and Wales between 1970 and 2007 and Figure 2c shows the number of deaths from sporadic CJD in Scotland and Northern Ireland between 1985 and 2007. Over the period 1990-2007 the average crude annual mortality rates from sporadic CJD per million population were 0.90 in England, 1.01 in Wales, 0.97 in Scotland and 0.57 in Northern Ireland (Table 1). When account is taken of age and sex, the variation in recorded mortality between the different countries is not statistically significant ($p > 0.5$).

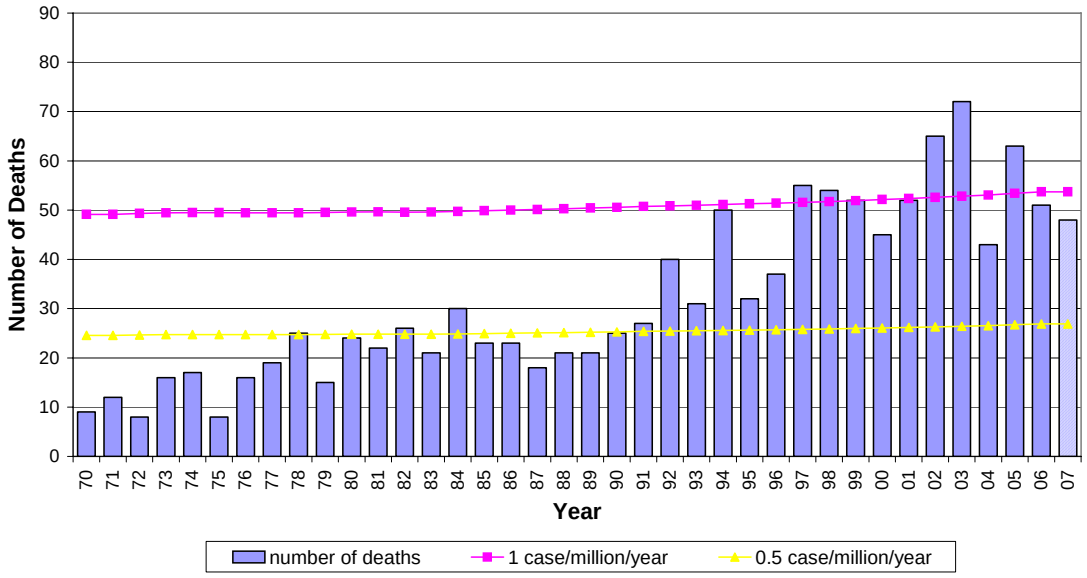
Table 2 shows data on cases of CJD (deaths and cases still alive as of 31st December 2007) according to age. In England and Wales the number of deaths identified each year increased from an average of about 10 per year at the beginning of the 1970s, to about 30 to 50 per year in the 1990s. A similar phenomenon has been observed in other European countries and this probably largely reflects improved case ascertainment. Over the shorter time period for which data are available for Scotland and Northern Ireland there is no clear secular trend.

Figure 2a Deaths from sporadic CJD, UK, 1985-2007



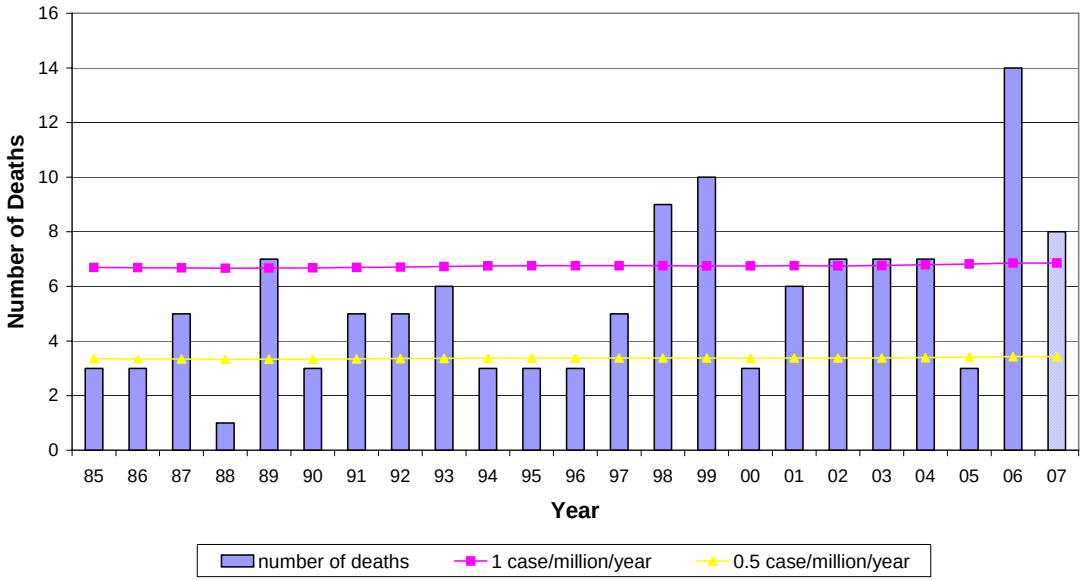
Note: The horizontal lines indicate the number of deaths equivalent to crude mortality rates of 0.5 and 1 case per million per year. Data for 2007 may be incomplete.

Figure 2b Deaths from sporadic CJD, England and Wales, 1970-2007



Note: The horizontal lines indicate the number of deaths equivalent to crude mortality rates of 0.5 and 1 case per million per year. Data for 2007 may be incomplete.

Figure 2c Deaths from sporadic CJD, Scotland and Northern Ireland 1985-2007 (please note different scale from Figs 1a and 1b)



Note: The horizontal lines indicate the number of deaths equivalent to crude mortality rates of 0.5 and 1 case per million per year. Data for 2007 may be incomplete.

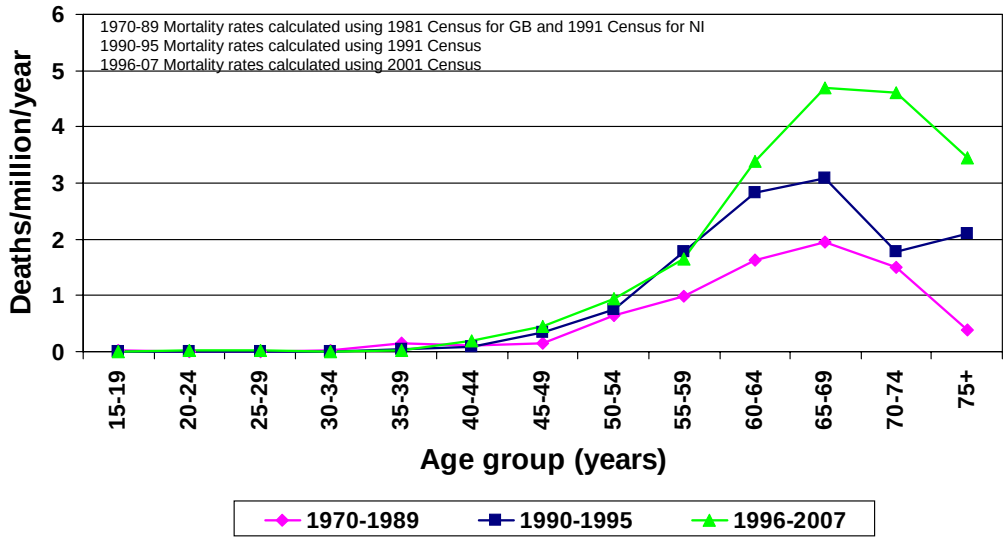
Table 1 Deaths from definite and probable sporadic CJD by region and county of death: 1st January 1990 to 31st December 2007

		No of cases	Total no (mortality rate/million/ annum)*		No of cases	Total no (mortality rate/million/ annum)*
ENGLAND				**ENGLAND**		
North				Yorkshire & Humberside		
Cleveland		7		Humberside	10	
Cumbria		13		NorthYorkshire	15	
Durham		6	48 (0.86)	South Yorkshire	26	82 (0.91)
Northumberland		6		West Yorkshire	31	
Tyne & Wear		16				
				East Anglia		
East Midlands				Cambridgeshire	6	
Derbyshire		11		Norfolk	16	36 (0.95)
Leicestershire		16		Suffolk	14	
Lincolnshire		11	58 (0.79)			
Northamptonshire		2		South West		
Nottinghamshire		18		Avon	22	
				Cornwall	15	
South East				Devon	21	
Bedfordshire		8		Dorset	17	111 (1.29)
Berkshire		12		Gloucestershire	12	
Buckinghamshire		6		Somerset	14	
East Sussex		11		Wiltshire	10	
Essex		36				
Greater London		89	277 (0.86)	West Midlands		
Hampshire		26		Hereford & Worcs.	9	
Hertfordshire		14		Shropshire	4	
Isle of Wight		3		Staffordshire	20	74 (0.78)
Kent		21		Warwickshire	5	
Oxfordshire		13		West Mids (Met)	36	
Surrey		17				
West Sussex		21				
North West						
Cheshire		16				
Greater Manchester		33	103 (0.89)	**TOTAL FOR ENGLAND**		**789 (0.90)**
Lancashire		29				
Merseyside		25				
WALES				**SCOTLAND**		
Clwyd		7		Borders	3	
Dyfed		4		Central	6	
Gwent		7		Dumfries & Galloway	2	
Gwynedd		11		Fife	5	
Mid Glamorgan		11		Grampian	12	
Powys		4		Highland	1	
South Glamorgan		6		Lothian	21	
West Glamorgan		3		Strathclyde	32	
				Tayside	5	
TOTAL FOR WALES			**53 (1.01)**	Islands (Shetland)	3	
				Islands (Orkney)	0	
NORTHERN IRELAND		17	**17 (0.57)**	Islands (Western Isles)	0	
				TOTAL FOR SCOTLAND		**90 (0.97)**

* based on 1994 population by region (as published in ONS Regional Trends, 1996 edition) over the 18-year period of the study.

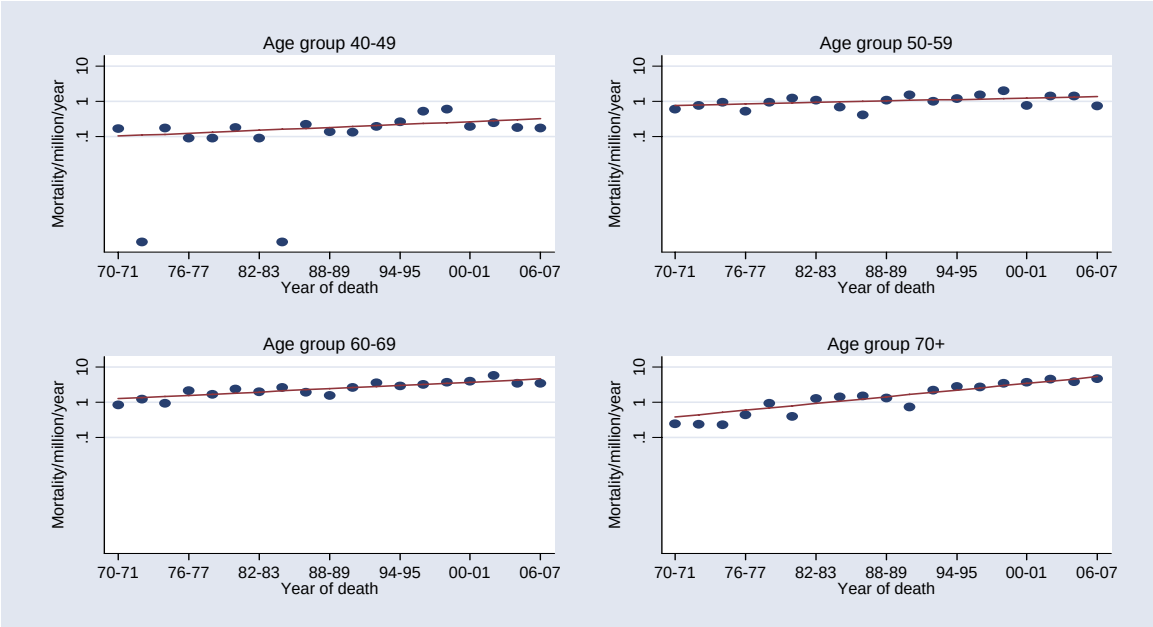
Figure 3 shows average annual age-specific mortality rates over the time periods 1970-89, 1990-95 and 1996-07. The median ages of cases at death during these time periods were 64, 66 and 68 years, respectively. In all three time periods, the mortality rates below 40 years of age were extremely low (< 0.2/million/year). Thereafter, in all three periods, the mortality rates increased up to ages 60-74 years and then declined. This decline might be explained by an under-ascertainment in the most elderly.

Figure 3 Age-specific mortality rates from sporadic CJD in the UK 1970-2007



An analysis of age specific trends from 1970 to 2007 (Figure 4) shows there has been an increase in recorded mortality over time in all age groups, but that the greatest relative increase has occurred in those aged 70 years and above. The mortality rate in this age group is similar to that in the age group 60-69 years from the early 1990s when the NCJDSU was first established. The temporal increases in mortality are statistically significant in all age groups ($p=0.019$, $p=0.006$, $p<0.001$, $p<0.001$ for age groups 40-49, 50-59, 60-69 and ≥70 years respectively). These observations are consistent with improved case ascertainment in all ages, but with the greatest increase occurring in the elderly.

Figure 4 Trends in mortality from sporadic CJD by age: 1970-2007



Mortality rates calculated using annual population estimates.
Source: Population Estimates Unit, ONS: Crown Copyright.

Table 2 presents, by 2-year period, the numbers of deaths underlying these trends. These data emphasise the very small numbers of cases of sporadic CJD occurring in individuals aged <50 years. They show clearly the substantial increase in the numbers of deaths identified among those aged 70 years and above, from around one per year in England and Wales in the early 1970s to around 25 per year in the UK in recent years.

Table 2 Cases of sporadic CJD in England and Wales (from 1970) and the UK (from 1985) by two year period

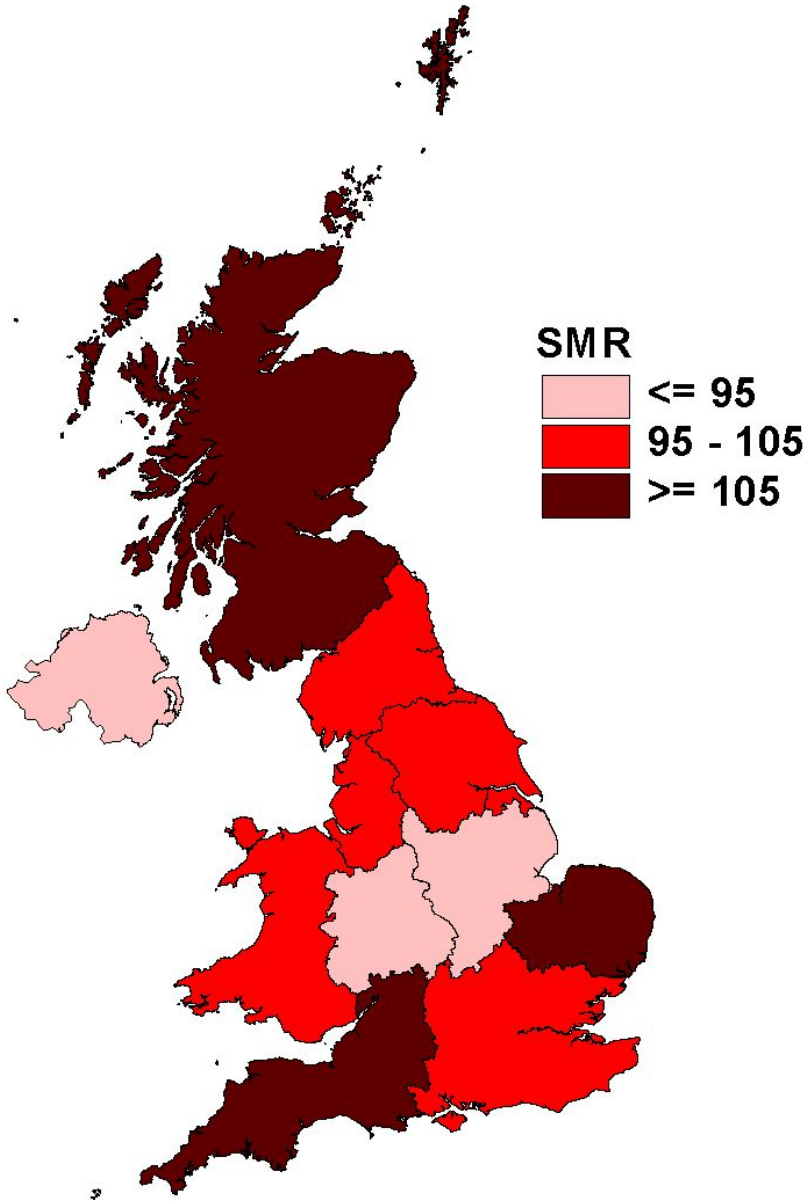
Age at death (yrs)	Year of death																			
	70-71	72-73	74-75	76-77	78-79	80-81	82-83	84-85[1]	86-87	88-89	90-91	92-93	94-95	96-97	98-99	00-01	02-03	04-05	06-07[2]	**Total**[2,3]
10-19	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	**1**
20-29	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	**2**
30-39	1	0	0	2	2	1	1	4	1	0	1	0	0	0	1	0	0	0	0 (1)	**14 (1)**
40-49	2	0	2	1	1	2	1	0	3	2	2	3	4	8	9	3	4	3	3 (0)	**53 (0)**
50-59	7	9	11	6	11	14	12	8	5	13	18	12	15	20	28	11	21	21	11 (6)	**253 (6)**
60-69	9	13	10	22	17	24	20	28	22	18	30	39	32	35	40	43	65	39	41 (8)	**547 (8)**
70-79	2	2	2	4	9	4	11	16	18	15	7	21	34	30	35	38	51	38	52 (4)	**389 (4)**
80-89	0	0	0	0	0	0	2	0	0	2	2	7	3	6	10	11	9	15	14	**81**
90+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	0	0	**2**
Total	**21**	**24**	**25**	**35**	**40**	**46**	**47**	**56**	**49**	**50**	**60**	**82**	**88**	**100**	**125**	**106**	**151**	**116**	**121 (19)**	**1342(19)**

[1] Up to 1984, cases from England and Wales only. From 1985 onwards, cases from Scotland and Northern Ireland are included.

[2] Deaths up to 31st December 2007. Numbers in parentheses indicate additional cases alive on 31st December 2007. Data for 2007 not yet complete.

Age- and sex- standardised mortality ratios (SMRs) for the 11 standard regions of the UK for the period 1st January 1990 to 31st December 2007 were calculated (Figure 5). An SMR of 100 equates to average mortality rate. After adjusting for the age/sex distribution of the population, the variation in mortality rates between the different regions is not statistically significant ($p>0.1$). Regions of relatively high mortality are South West (SMR=132), East Anglia (SMR=107) and Scotland (SMR=106). Low mortality rates were observed in Northern Ireland (SMR=76), East Midlands (SMR=83) and West Midlands (SMR=85). The highest SMR (132 in South West) arose from 107 cases observed compared with 81 expected, an excess of about 1.5 cases every year compared to the national average. For Scotland and East Anglia the total numbers of excess cases was approximately 5 and 2 respectively.

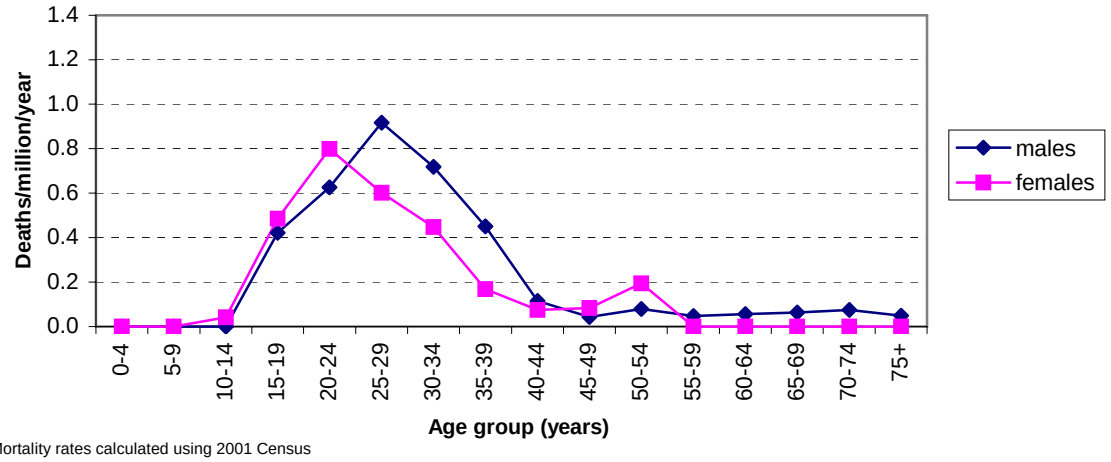
Figure 5 Standardised mortality ratios (SMRs) by standard region, UK 1 January 1990 - 31 December 2007



2.3 Variant Creutzfeldt-Jakob Disease

Up to 31st December 2007, 166 cases of definite or probable vCJD had been identified in the UK (115 definite, 48 probable who did not undergo post mortem and 3 probable cases still alive). Seventy-three (44%) of the 166 cases were women. The median age at onset of disease was 26 years and the median age at death 28 years (compared with 67 years for the median age at onset and 67 years for the median age at death for sporadic CJD). The youngest case was aged 12 years at onset while the oldest case was aged 74 years. To date, no case of vCJD has been identified in the UK in individuals born after 1989. The age- and sex-specific mortality rates for vCJD over the time period 1 May 1995 to 31 December 2007 are shown in Figure 6. The median duration of illness from the onset of first symptoms to death was 14 months (range 6-40). The median duration of illness for cases of sporadic CJD was 4 months (range 1 to 74) during the period 1990-2007.

Figure 6 Age- and sex-specific mortality rates from vCJD in the UK 1 May 1995 - 31st December 2007



Mortality rates calculated using 2001 Census

Incidence of vCJD onsets and deaths from January 1994 - December 2007

Each quarter data on diagnosed cases of vCJD in the UK are reviewed in order to investigate trends in the underlying rate at which disease onsets and deaths are occurring. The following analysis reviews the data to the end of December 2007.

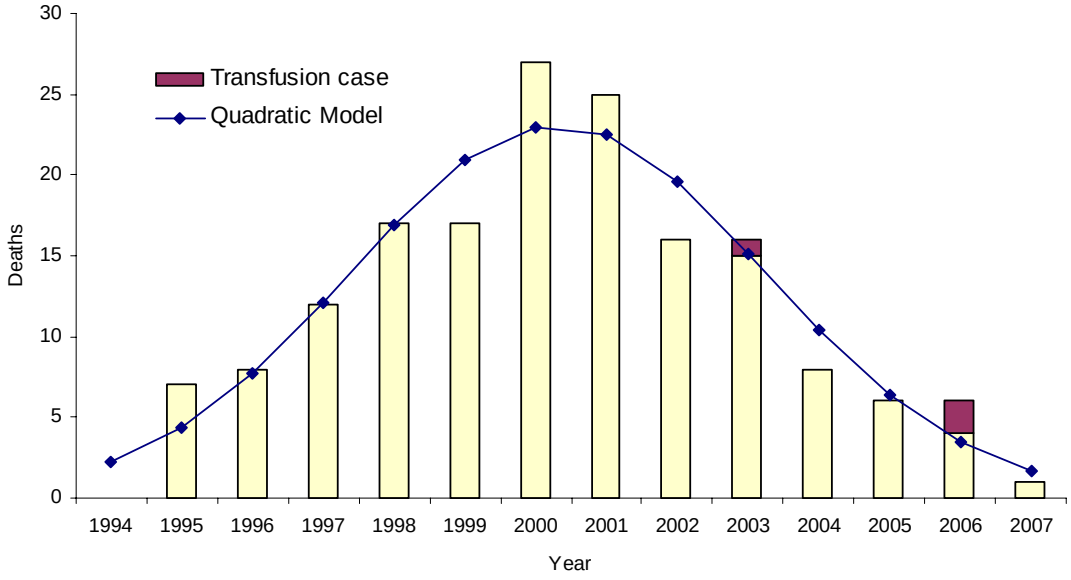
Methods

The incidence of deaths and diagnoses was modelled by Poisson regression using polynomials. Most deaths and diagnoses are reported quickly so an adjustment for reporting delay is not necessary. With the exception of some increase in 2005 the age at death has not increased as might have been expected if exposure to BSE ceased by the early 1990s. In order to examine this further the cases were stratified by year of death and birth cohort (pre1970, 1970s and 1980s). Trends in deaths over time were compared between these cohorts.

Results for Diagnoses

The quadratic trend model provided the best fit to the data. A model with a cubic term was also fitted but did not provide an improved fit (p=0.75). The fitted trend is shown in Figure 7 and estimates that the current annual incidence of diagnoses is 1.7. The peak is estimated to have occurred in mid 2000.

Figure 7: Quadratic-exponential model for vCJD diagnoses incidence trend



Prediction for diagnoses in 2008

Extrapolation of the model with the quadratic term predicts a total of just one diagnosis in the next 12 months with a 95% prediction interval of 0 to 3. The cubic model also gives an estimate of one diagnosis with 95% CI of 0 to 3.

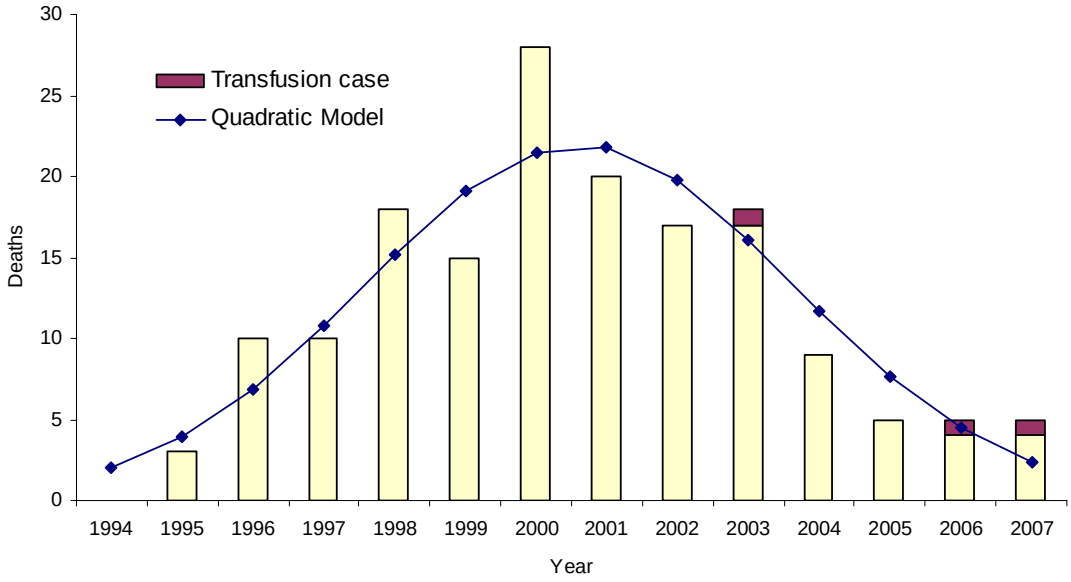
Assessment of Predictions made at the end of December 2006

The quadratic model gave a prediction of one diagnosis (95% prediction interval 0 to 3) compared to 3 (95% prediction interval 0 to 6) from the cubic model. The observed number of one agrees with the quadratic model.

Results for Deaths

The quadratic trend model provided the best fit to the data. A model with a cubic term was also fitted but did not provide an improved fit (p=0.06). The fitted trend is shown in Figure 8 and estimates that the current annual incidence of deaths is 2.4. The peak is estimated to have occurred in mid 2000.

Figure 8 Quadratic-exponential model for vCJD deaths incidence trend



Predictions for deaths in 2008

Extrapolation of the model with the quadratic term predicts a total of just one death in the next 12 months with a 95% prediction interval of 0 to 4. The cubic model gives an estimate of 2.5 deaths with 95% CI of 0 to 6.

Assessment of Predictions made at the end of December 2006

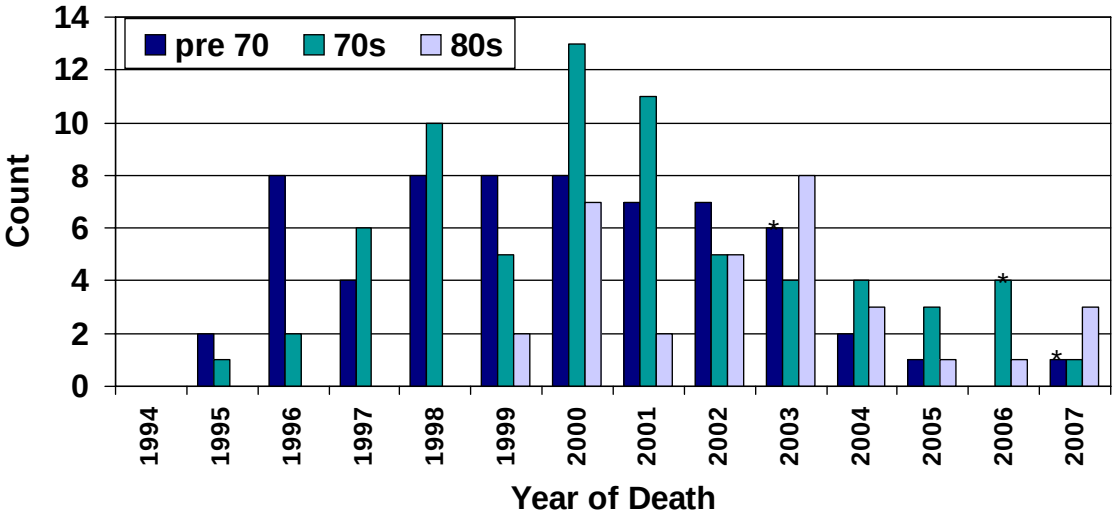
The quadratic model gave a prediction of one death with a 95% prediction interval of 0 to 3. The cubic model gave a prediction of 3 deaths with a 96% prediction interval of 0 to 6. The actual observed number was 5, which is not consistent with the quadratic model but is with the cubic model. Although this, along with the p-value of 0.06 for the cubic verse quadratic model, may be considered as some evidence that the exponential decline is not continuing, the fact that the analysis by diagnoses showed no such evidence and that one of the cases in 2007 was a transfusion case would indicate that the quadratic model is still more plausible. The difference between the analysis by deaths and diagnosis may be due to the fact that some more recent cases have survived longer since diagnosis.

Deaths by cohort

The age at death has so far remained stable, contrary to what might be expected given that most exposure to BSE is presumed to have ceased in the early 1990s. To examine this in more detail the epidemic curves (quadratic model) are compared in those born before 1970 with two other groups: those born in the 1970s and the 1980s. This analysis showed significant differences by cohort in the shape of the fitted curves ($p<0.001$). The main difference is due to the fact that in the 1980s cohort no deaths were seen prior to 1999 (Figure 9). This finding is consistent with those born in the 1980s being infected towards the end of the BSE epidemic when they were older rather than at the beginning. This requires a lower exposure/susceptibility in the very young, which is reasonable because no cases have been seen to date in individuals born in the 1990s. An alternative explanation of the stable age distribution could be shorter incubation periods in those exposed as teenagers/young adults than those exposed as young

children. Note that these explanations would only be expected to yield a temporary stable age distribution.

Figure 9 Deaths by year and birth cohort



*count includes a transfusion transmission case

Summary

Results from modelling the underlying incidence of diagnoses and deaths indicate that the epidemic reached a peak in the year 2000 when there were 27 diagnoses and 28 deaths and has since declined to a current incidence of about 2 diagnoses/deaths per year. Extrapolating the best fitting model (the quadratic model) gives an estimate of one death in the next 12 months (95% prediction interval 0 to 4).

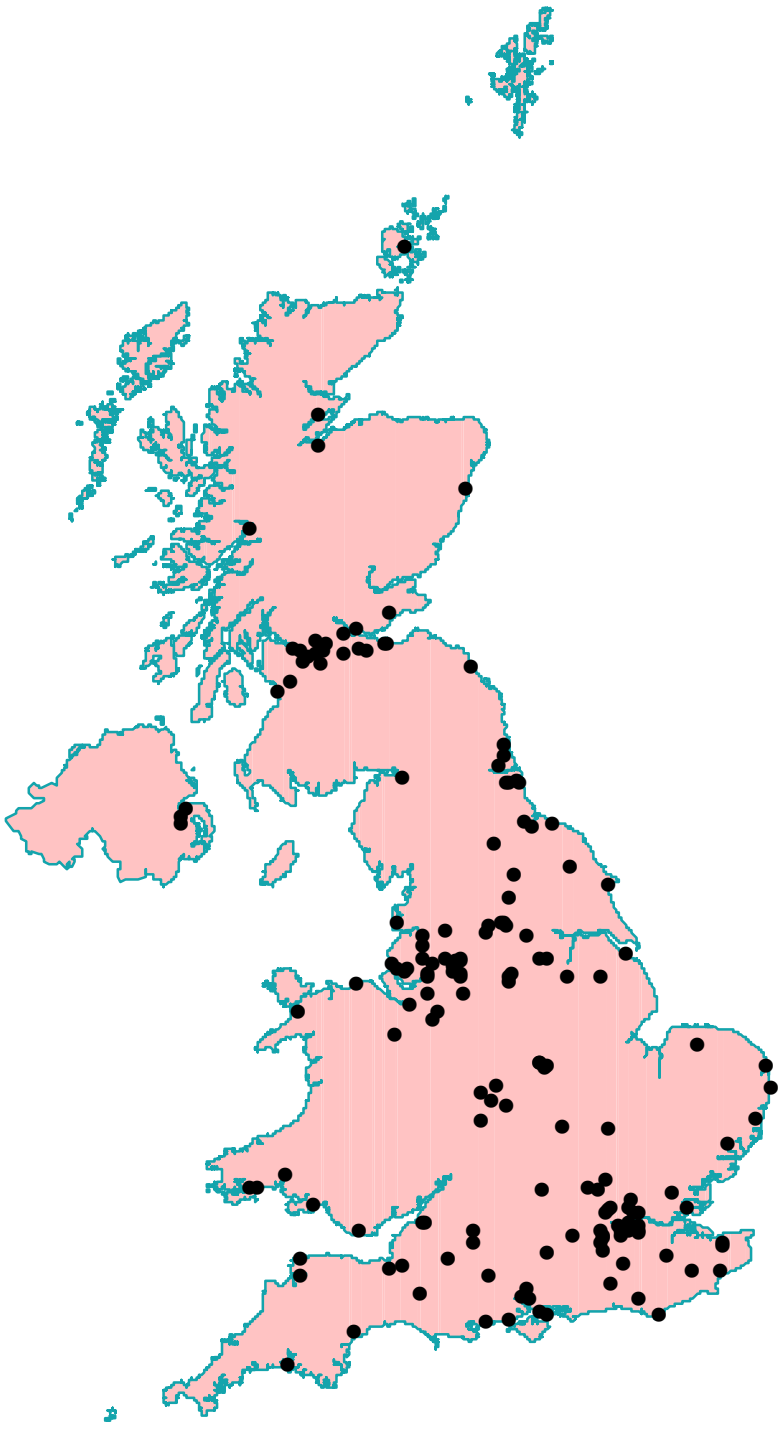
An analysis that looked at deaths by birth cohort (pre 1970, 1970s, 1980s) showed that the shape of the epidemic differs between cohorts, mainly due to the fact that deaths of individuals born in the 1980s were only seen from 1999 onwards.

It is important to note that although a peak has been passed, it is possible that there will be future peaks, possibly in other genetic groups. There is also the possibility of ongoing person to person spread as seen with four instances of transfusion association vCJD infection to date, who received blood from earlier cases. Three of these individuals developed vCJD (one diagnosed in 2003 and two in 2006), whilst the fourth died from causes unrelated to vCJD, but was found on post mortem examination to have abnormal prion protein present in the spleen and a lymph node.

Geographical distribution of vCJD

Figure 10 shows the geographical distribution, by place of residence at onset, of 165 cases of vCJD in the UK. For one additional case the address at onset is known only at county level. Cases have been widely spread throughout the UK. Table 3 presents data on the geographical distribution by county of residence at onset (for all 166 vCJD cases) and residence at death (for 160 vCJD cases who had died by 31st December 2007 and were resident in the UK at death), along with the crude mortality rate per million population per annum of each standard region.

Figure 10 Geographical distribution of places of residence at onset of symptoms of vCJD (n=165*)



* in one case only county of residence was known and could not be plotted.

Table 3 Cases of definite and probable vCJD shown by region and county of onset (n=166†) and region and county of death (n=160‡)

	No of cases resident at onset	No of cases resident at death (mortality rate*)
ENGLAND		
North		
Cleveland	3	3
Cumbria	1	1
Durham	1	2
Northumberland	3	4
Tyne & Wear	4	2
Total	**12**	**12 (0.31)**
East Midlands		
Derbyshire	0	1
Leicestershire	4	5
Lincolnshire	2	2
Northamptonshire	1	1
Nottinghamshire	0	0
Total	**7**	**9 (0.17)**
South East		
Bedfordshire	0	0
Berkshire	1	2
Buckinghamshire	0	0
East Sussex	2	2
Essex	2	2
Greater London	16	14
Hampshire	7	4
Hertfordshire	3	3
Isle of Wight	0	1
Kent	5	5
Oxfordshire	1	1
Surrey	6	4
West Sussex	1	1
Total	**44**	**39 (0.19)**
North West		
Cheshire	7	8
Greater Manchester	10	9
Lancashire	4	4
Merseyside	4	4
Total	**25**	**25 (0.31)**
WALES		
Clwyd	1	0
Dyfed	3	3
Gwent	0	0
Gwynedd	1	1
Mid Glamorgan	0	0
Powys	0	0
South Glamorgan	1	1
West Glamorgan	1	0
WALES TOTAL	**7**	**5 (0.14)**
NORTHERN IRELAND TOTAL	**3**	**2 (0.10)**

	No of cases resident at onset	No of cases resident at death (mortality rate*)
ENGLAND		
Yorkshire & Humbs		
Humberside	2	2
NorthYorkshire	4	3
South Yorkshire	5	5
West Yorkshire	6	7
Total	**17**	**17 (0.27)**
East Anglia		
Cambridgeshire	1	1
Norfolk	2	3
Suffolk	3	2
Total	**6**	**6 (0.23)**
South West		
Avon	2	1
Cornwall	2	1
Devon	3	4
Dorset	1	1
Gloucestershire	0	0
Somerset	4	5
Wiltshire	3	1
Total	**15**	**13 (0.21)**
West Midlands		
Hereford & Worcs.	0	1
Shropshire	1	1
Staffordshire	0	0
Warwickshire	1	2
West Mids (Met)	4	6
Total	**6**	**10 (0.15)**
ENGLAND TOTAL	**132**	**131 (0.23)**
SCOTLAND		
Borders	0	0
Central	1	1
Dumfries & Galloway	0	0
Fife	2	2
Grampian	1	1
Highland	3	2
Lothian	4	4
Strathclyde	12	12
Tayside	0	0
Islands (Shetland)	0	0
Islands (Orkney)	1	0
Islands (Western Isles)	0	0
SCOTLAND TOTAL	**24**	**22 (0.34)**

* mortality rate/million/annum based on 1994 population by region (as published in ONS Regional Trends, 1996 edition) over the period 1st May 1995 to 31st December 2007.

† includes cases still alive at 31st December 2007.

‡ excludes 3 cases who died abroad.

Table 4 shows cumulative regional rates of vCJD based on cases' place of residence in 1991, rather than at onset, and the population aged 10 years and above resident at that time.

Age- and sex- standardised incidence ratios (SIRs) based on cases' place of residence in 1991 are shown in Figure 11 for the 11 standard regions of the UK.

Table 4 Distribution of 166 vCJD cases by standard region of residence on 1st January 1991

Standard region (in order of latitude of the centre of the region)	Population aged 10 years and above at the 1991 census	Number (cumulative incidence/million) of vCJD cases by place of residence in 1991
Scotland	4,363,684	19 (4.35)
North	2,635,785	11 (4.17)
Yorkshire & Humberside	4,202,051	18 (4.28)
North-West	5,326,333	25 (4.69)
East Midlands	3,444,391	12 (3.48)
West Midlands	4,464,592	10 (2.24)
East Anglia	1,775,687	6 (3.38)
Wales	2,466,669	5 (2.03)
South-East	15,010,650	44 (2.93)
South-West	4,055,268	13 (3.21)
Northern Ireland	1,320,430	3 (2.27)
Total	49,065,540	166 (3.38)

Figure 11 Standardised incidence ratios (SIRs) up to 31st December 2007 of vCJD by standard region on 1st January 1991

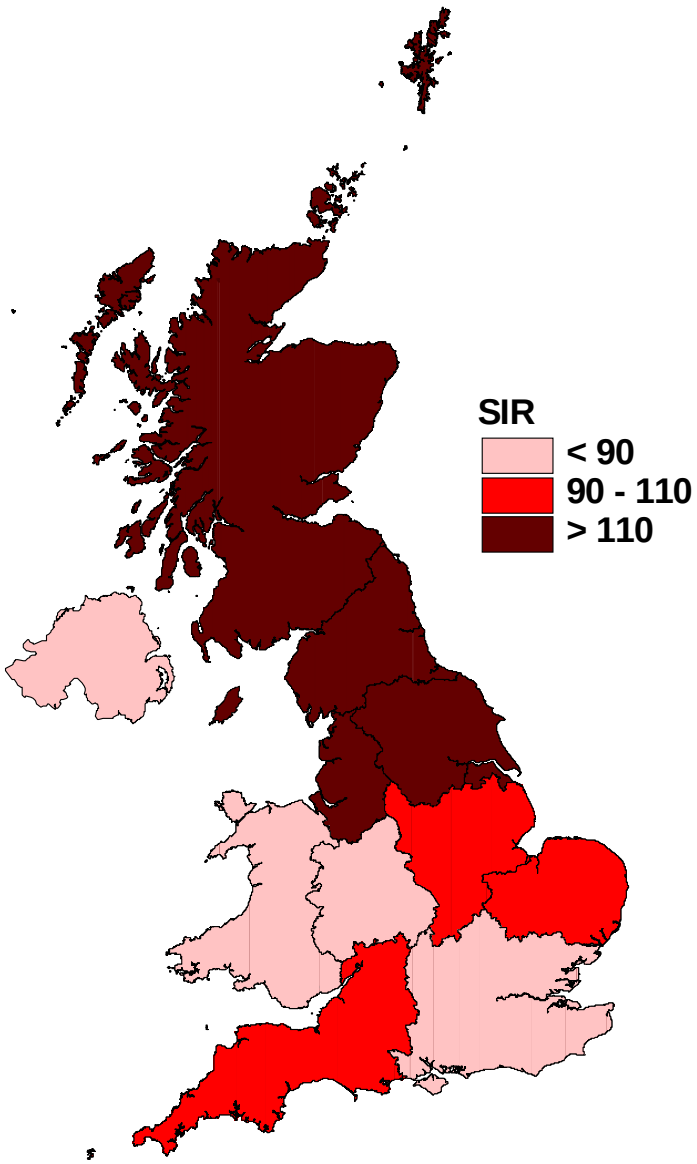


Table 5 shows the distribution of cases between the "North" and the "South" according to place of residence in 1991. We originally performed an analysis of the first 51 cases, distinguishing two areas. The "North" comprised four standard regions: Scotland, North, Yorkshire and Humberside, North West. The "South" comprised the remaining 6 regions: Wales, West Midlands, East Midlands, East Anglia, South West, South East. The excess of cases previously identified in the "North" (rate ratio controlling for age and sex = 1.94; 95% c.i. 1.12, 3.36) has declined somewhat as further cases have accrued, but remains statistically significant. The rate ratio controlling for age and sex is 1.54 (95% c.i., 1.13, 2.09), i.e. individuals living in the "North" in 1991 are about one and a half times more likely to have developed vCJD than individuals who were living in the "South" in 1991[1]. This relatively high incidence of cases of

[1] Cousens S, Smith PG, Ward H, Everington D, Knight RSG, Zeidler M, Stewart G, Smith-Bathgate EAB, Macleod MA, Mackenize J, Will RG. Geographical distribution of variant Creutzfeldt-Jakob disease in Great Britain, 1994-2000. Lancet 2001; 357: 1002-1007.

CJD in the north of the UK compared with the south will continue to be monitored in the event of future cases of vCJD.

Table 5 Comparison of cumulative incidence in the "North" of the UK (excluding Northern Ireland) with that in the "South"

Region	Population aged 10 years and above at the 1991 census	Number (rate/million) of vCJD cases by place of residence at 1st January 1991	
		First 51 cases	Total
"North" (North West, Yorks & Humbs, Northern, Scotland)	16.6 million	26 (1.57)	73 (4.42)
"South" (South West, South East, Wales, West Midlands, East Midlands, East Anglia)	31.2 million	25 (0.80)	90 (2.88)
Total (rate ratio*)	47.8 million	51 (1.94)	163 (1.54)

*North versus South, adjusted for age and sex

Northern cases were slightly older at onset than southern cases (median of 27 years versus 25.5 years; p=0.7), a similar proportion were male (55% of northern and 56% of southern cases).

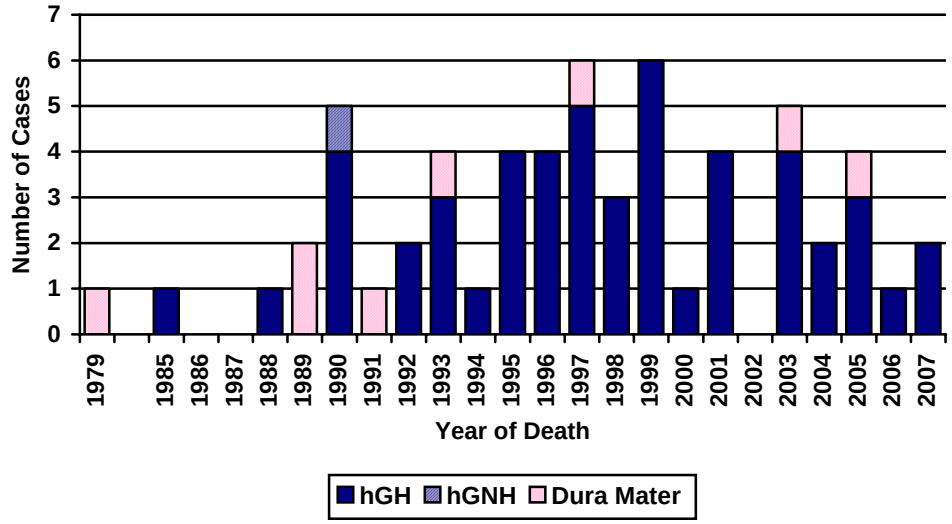
Geographically Associated Cases of vCJD

Geographically associated cases of vCJD are defined to be two or more cases of probable or definite vCJD with a geographical association, either through proximity of residence or through another link with the same location (occupational, educational or social/recreational). A total of thirteen investigations into geographically associated cases of vCJD have been conducted in the UK. None have been undertaken in the past year, because of the low number of new cases. The Leicestershire cluster of five cases remains the only statistically significant cluster of cases to date. None of the concluded investigations have revealed any suggestion of possible iatrogenic transmission. No evidence emerged from these investigations in any of the areas apart from Leicestershire of bovine heads being split or brains removed by local butchers in their shops during the relevant time period.

2.4 Iatrogenic Creutzfeldt-Jakob disease

Since 1970, up to 31st December 2007, 65 cases of CJD attributable to iatrogenic exposure have been identified, 8 in individuals receiving dura mater implants, 56 in individuals who had received human-derived growth hormone (hGH) and one in a recipient of human gonadotrophin (hGN). Sixty of these individuals have died (Figure 12) and 5 were still alive as at 31st December 2007.

Figure 12 Deaths from iatrogenic CJD, 1979-2007



The mean age at death of the hGH/hGN group was 31 years (with a range of 20-46 years) and for the dura mater cases 46½ years (range 27-78 years).

The first identified iatrogenic case was a dura mater recipient who died in 1979. The first hGH-related death occurred in 1985. Since 1985 in the UK, human pituitary-derived hormones have been replaced by synthetic preparations. Details of the UK human pituitary-derived hormone cases, with a discussion of the incubation periods, have been published in 2003.[2]

A study of the accumulated UK experience with dura mater-related CJD, including incubation periods, was undertaken and the results published in 2006.[3]

2.5 Transfusion Medicine Epidemiology Review

The Transfusion Medicine Epidemiology Review (TMER) is a collaborative project between the UK NCJDSU and UK Blood Services (UKBS). The main purpose is to investigate whether there is any evidence that CJD or vCJD may have been transmitted via the blood supply. The following report is based on vCJD cases who donated or received blood and does not include data from the ongoing study of sporadic CJD.

Methods

vCJD cases (definite and probables) are notified to the UKBS by NCJDSU; a search establishes whether any have acted as donors. Donation records are checked and all components traced through hospital records. Details of all identified recipients are forwarded to NCJDSU for subsequent checking.

In the reverse procedure, patients with vCJD reported to have received blood transfusions are identified by NCJDSU and notified to UKBS. Details of transfusions are traced through hospital records and relevant blood donors identified. The identity of donors is notified to NCJDSU for subsequent checking.

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[2] Swerdlow AJ, Higgins CD, Adlard P, Jones ME, Preece MA. Creutzfeldt-Jakob disease in United Kingdom patients treated with human pituitary growth hormone. Neurology 2003; 61: 783-91.

[3] Heath CA, Barker RA, Esmonde TFG, Harvey P, Trend P, Head MW, Smith C, Bell JE, Ironside JW, Will RG, Knight RSG. Dura mater-associated Creutzfeldt-Jakob disease: experience from surveillance in the UK. JNNP 2006; 77: 880-2.

Results

Thirty-one vCJD cases were reported to have been blood donors. Four additional cases who were not reported to have been blood donors were found to be registered with UKBTS. One of these cases was found to have been a blood donor while the other three cases were registered as a donor but never made any donations. Twenty-four of the cases have been traced at blood centres, including the four additional cases mentioned above. Components derived from donations made by 18 of these individuals were actually issued to hospitals. It has been established that 66 components were transfused to identified recipients.

Four instances of probable transfusion transmitted infection have been identified. The first recipient (Case 1) developed symptoms of vCJD 6½ years after receiving a transfusion of red cells donated 3½ years before the donor (Donor 1) developed symptoms of vCJD[4]. The second recipient (Case 2) died from a non-neurological disorder 5 years after receiving blood from a donor (Donor 2) who subsequently developed vCJD[5]; protease-resistant prion protein (PrP^{res}) was detected in the spleen but not in the brain. This is the first recorded case in the UK of autopsy detection of presumed pre- or sub-clinical vCJD infection. The third recipient (Case 3) developed symptoms of vCJD 7 years, 10 months after receiving a transfusion of red cells donated about 21 months before the donor (Donor 3) developed symptoms of vCJD[6]. The fourth recipient (Case 4) who also received a transfusion from the same donor as Case 3, developed symptoms of vCJD 8 years, 4 months after receiving a transfusion of red cells donated about 17 months before this donor (Donor 3) developed symptoms of vCJD[7].

In the reverse study, 14 vCJD cases were reported to have received blood transfusions in the past. A further case received a blood transfusion after onset of illness and is excluded from further discussion. Checks revealed that of these 14 cases, one was not transfused, 4 had transfusions which pre-dated available records (pre-1980), and 9 had records of transfusion which could be traced. These 9 individuals had received 207 donor exposures (with one patient given 103 components), which have been traced to 190 named donors (two of whom had vCJD as described above). No additional links between donors and recipients have been identified by the reverse study.

Conclusion

The identification of 3 cases of vCJD in the small cohort of known recipients of blood from persons incubating vCJD, together with the fact that 2 of the cases were associated with a common blood donor, establishes beyond reasonable doubt that blood transfusion is a transmission route for vCJD.

(Collaborators on this project: Dr P.E. Hewitt, Dr C.A. Llewelyn, Ms M Malfroy).

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[4] Llewelyn CA, Hewitt PA, Knight RSG, Amar K, Cousens S, Mackenzie J, Will RG. Possible transmission of variant Creutzfeldt-Jakob disease by blood transfusion. Lancet 2004; 363: 417-421.

[5] Peden AH, Head MW, Ritchie DL, Bell JE, Ironside JW. Preclinical vCJD after blood transfusion in a PRNP codon 129 heterozygous patient. Lancet 2004 364: 527-529.

[6] Wroe SJ, Pal S, Siddique D, Hyare H, Macfarlane R, Joiner S, Linehan JM, Brandner S, Wadsworth JD, Hewitt P, Collinge J. Clinical presentation and pre-mortem diagnosis of variant Creutzfeldt-Jakob disease associated with blood transfusion: a case report. Lancet 2006; 368: 2061-2067.

[7] Health Protection Agency. Fourth case of transfusion-associated variant-CJD. Health Protection Report 2007;1(3):

2.6 Study of Progressive Intellectual & Neurological Deterioration (PIND)

The aim of this project is to use the mechanism of the British Paediatric Surveillance Unit to identify all cases of progressive intellectual and neurological deterioration in children in the UK, particularly those with features suggestive of vCJD. All cases are discussed by an Expert Neurological Advisory Group of seven paediatric neurologists which allocates the cases to a diagnostic category [8-9].

As of 31st December 2007, after nearly 11 years surveillance, 2383 patients with suspected PIND have been reported. The Expert Group has discussed 1666 cases, of which 995 have a confirmed underlying cause other than vCJD, being categorised into 115 known neurodegenerative diseases. Among them were six cases of vCJD; four definite and two probable. Three were reported in 1999, one in 2000 and 2 in mid-2001. One girl was aged 12 at onset - the youngest case of vCJD identified to date.

(Collaborators: Dr C. Verity, Prof A. Nicoll, Ms L. Stellitano, Ms AM Winstone)

[8] Verity CM, Nicoll A, Will RG, Devereux G, Stellitano L. Variant Creutzfeldt-Jakob disease in UK children: a national surveillance study. Lancet 2000; 356: 1224-1227.

[9] Devereux G, Stellitano L, Verity CM, Nicoll A, Will RG, Rogers P. Variations in neurodegenerative disease across the UK: findings from the national study of Progressive Intellectual and Neurological Deterioration (PIND). Arch Dis Child 2004; 89: 8-12.

Section

3

CASE-CONTROL STUDY

Since May 1990 a case-control study of CJD has been carried out in the UK to investigate potential risk factors for variant and sporadic CJD. Patients themselves are usually too unwell to answer questions when they are seen by members of the Unit. Therefore, relatives of patients with suspected CJD are approached and, with informed consent, interviewed about the patient using a standard questionnaire relating to possible risk factors for CJD, including residential, occupational, dietary and medical histories. To maximise the study's validity, this interview takes place as early as possible after a person is suspected of having CJD. We are indebted to the families of those with suspected CJD, who agree to be interviewed at what is an extremely difficult time in their lives.

The choice of the source of controls, with which to compare the information for cases, is extremely important in a case-control study. There are a number of possible choices each of which has its own advantages and disadvantages in terms of suitability as controls, practicalities of recruitment and cost. Since 1990 there have been some variations in control recruitment for the CJD risk factor study:

1990-1997

Hospital controls: For each suspect case, an age- and sex-matched patient with a non-neurological disease at the same hospital was identified as a control. Eighty hospital controls have been recruited for vCJD cases (between August 1995 to July 2006) and 227 for sporadic CJD cases (between May 1990 and June 1998).

1998-2002

Community (General practice) controls: With the diagnosis of the first cases of vCJD, it was decided that in addition to hospital controls for variant cases, and instead of hospital controls for sporadic cases, sex and age-matched community controls would be recruited through general medical practices. In general, community controls are more suitable than hospital controls for the investigation of potential medical risk factors. However, major difficulties were encountered arising from the complex process of recruitment that we were required to follow for general practice based controls, resulting in a very low response rate. Therefore, a revised strategy for control recruitment was devised and recruitment of controls through general medical practices ceased in 2002.

2003-2006

Friend nominated controls: From 2003 to 2006, a group of controls comprising friends nominated by relatives of cases was recruited. Relatives of cases were asked to nominate a friend who would agree to be interviewed about a relative of theirs (the control), who was age- and sex-matched to the case. The degree of relative between control and friend was matched to that between the case and their relative. Consent of the control was sought before the friend was

interviewed. The recruitment of this control group was complex, involving relatives of cases at a difficult point in their lives, and was, therefore, discontinued towards the end of 2006.

As was detailed in Table 6 of last year's Annual Report,[10] we interviewed 15 friends, out of 41 relatives of cases of vCJD approached, and 85 friends, of 250 relatives of sCJD cases approached.

Community (General population) controls: During 2002/03 a one-off recruitment of approximately 900 general population controls throughout Great Britain was carried out on our behalf by the National Centre for Social Research, which is the largest independent social research institute in Britain. These controls were selected across a wide age range so that their data could be compared with that from both variant and sporadic CJD cases. This control group has proved the most successful in terms of numbers recruited and response rate. It has, therefore, been used in two analyses, to date, comparing risk factors of the control group with cases of vCJD and sCJD (for details of the findings please see below). The methodology of the recruitment of this control group can be found in Ward et al, 2006 Annals of Neurology[12].

Results from the case-control study of risk factors for variant and sporadic CJD

Variant CJD

In 2004 we undertook the first comprehensive analysis of data from variant cases compared with general population controls[11]. In this study we included all "definite" or "probable" vCJD cases identified in Great Britain between May 1995 and November 2003 and 922 controls recruited between 2002 and 2003. Reported frequent consumption of beef and beef products thought likely to contain mechanically recovered and/or head meat, including burgers and meat pies, was associated with increased risk of vCJD, as was reported frequent chicken consumption. The reported histories of surgical operations were generally similar for cases and controls, with the exception of a small group of minor operations, possibly attributable to under-reporting in controls. Cases and controls had similar reported occupational histories and exposure to animals. These findings are consistent with dietary exposure to contaminated beef products being the main route of infection of vCJD, but recall bias cannot be excluded as an explanation for the findings regarding diet. There was no convincing evidence of increased risk through medical, surgical or occupational exposure, or exposure to animals.

We aim to commence an analysis of medical risk factor data obtained directly from primary care records in late 2008/early 2009 (see below, section "2007 onwards" for more details).

Sporadic CJD

A recent publication describes the analysis of medical risk factors among 431 sCJD cases referred to the unit between 1998 and 2006 compared with 454 population controls. We also investigated possible geographical and temporal links between neurological and gynaecological operations in 857 sCJD cases referred to the unit between1990 and 2006 [12]. A reported history of ever having undergone surgery was associated with increased risk of sCJD (OR 2.0; 95% CIs 1.3, 2.1; p=0.003). Increased risk was not associated with surgical categories chosen a priori, but was confined to the residual category "other surgery", covering a wide range of procedures from minor stitching of wounds to major cardiovascular procedures. Within the "other" category the increase in risk appeared most marked for 3 subcategories; skin stitches, nose/throat operations and removal of growths/cysts/moles. No convincing evidence was found of links (same hospital, within 2 years) between cases undergoing neurosurgery or gynaecological surgery. The conclusion of the paper was that it was unlikely that a high proportion of UK sCJD cases

[10] National CJD Surveillance Unit 15th Annual Report, 2006. National CJD Surveillance Unit, Edinburgh, 2007.
[11] Ward HJT et al. Risk factors for variant Creutzfeldt-Jakob disease: a case-control study. Ann Neurol 2006; 59: 111-120.
[12] Ward HJT et al. Risk factors for sporadic Creutzfeldt-Jakob disease. Ann Neurol 2008; 63: 347- 354.

are the result of transmission during surgery, but we cannot exclude the possibility that such transmission occurs occasionally. To determine whether the increased risk associated with reported surgical history reflects a causal association or recall bias, a study based on accurate surgical histories obtained from medical records is required.

As with variant CJD, we are in the process of obtaining medical risk factor data directly from primary care records (see below, section "2007 onwards" for more details).

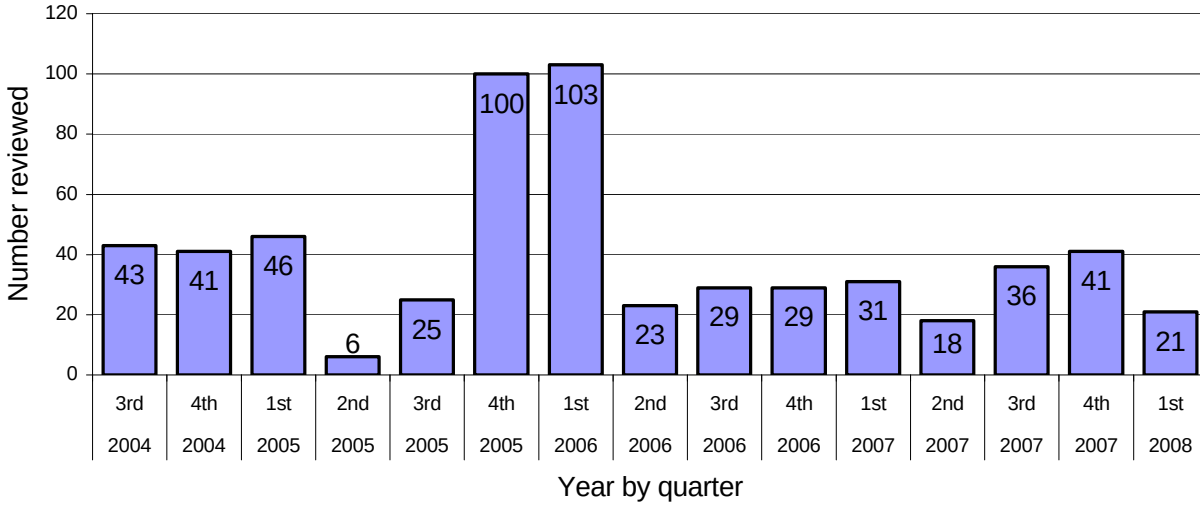
2007 onwards

In the light of the declining numbers of cases of vCJD observed between 2000 and 2006, it was decided that on-going control recruitment would cease at the end of 2006. However, risk factor information continues to be collected for cases of CJD. In addition, because of the interest in the possibility of onward transmission of CJD through medical procedures, it was decided that efforts should be concentrated on collecting medical records of both cases and general population controls in order to investigate the possibility of secondary transmission of CJD. The data acquired from primary care records are likely to be more accurate and detailed than that obtained from relatives and are not subject to recall bias.

For cases, records are obtained prospectively as they are identified. For the general population controls, we have written consent from three-quarters (approximately 670) to access their primary care medical records. To assemble this information is a huge task and involves visiting practices throughout the UK. This work is near completion for primary care medical records and we have obtained records for 594 individuals to date. Figure 13 shows this by time. As we near completion of the task, as shown in the figure below, the last few records are more time consuming to obtain mainly because of people moving practices or insufficient/ inaccurate details recorded.

Once this is complete, we aim to compare the frequency of medical risk factors for cases of variant and sporadic CJD, separately, with the 'general population control' group, described above. We aim to have the data entered towards the end of 2008 and begin analysis in early 2009.

Figure 13 Number of GP records reviewed for NatCen Controls



It should be noted that during 4th quarter of 2005 and 1st quarter of 2006, there was a second research nurse employed who was dedicated to this task only. For the remainder of the time there was only one research nurse with a number of other duties in addition to obtaining primary care records.

Dentistry

For public health purposes, it is important to assess whether dental treatment is a potential source of iatrogenic transmission of vCJD in the UK. A risk assessment by the Department of Health (2006) concluded that, given the existence of a carrier state, a self- sustaining epidemic of vCJD via dentistry was feasible. In addition, preliminary findings from a mouse model (HPA) has lead SEAC to conclude that the potential risk of transmission of vCJD via a range of dental procedures may be greater than previously anticipated.

However, to date there has been no evidence in humans of transmission of CJD by dental treatment. This study aims to investigate dental treatment as a possible risk factor for vCJD by examining the records of cases of vCJD and general population controls.

A previous study found no significant associations between dental treatment and vCJD[13]. However, the study was limited to data reported from relatives, which may be unreliable. Therefore, there is a need to examine dental records of cases (and controls) directly to obtain more accurate information. A pilot study (funded by the Department of Health) has demonstrated the feasibility of collating information from dental records.

Dental records will be traced with the assistance of the Dental Practice Boards for vCJD cases (n=161) and general population controls (up to 700) resident in England, Wales and Scotland. Details of dental treatment will be collected onto a standardised data collection form by a dental professional. Partial or unavailable dental histories will be investigated through NHS Dental payment schemes.

Data will be examined to determine if two or more cases had dental treatment at the same practice within a similar time-frame. Statistical analysis will also be undertaken to determine if there is evidence of an association between dental treatment and vCJD. We aim to have completed gathering dental records by early 2009 and to have analysed the data by spring/ summer 2009.

The future of the case control study

The case control study has been funded since 1998 by three consecutive research grants (Department of Health and Scottish Government). The funding for the case- control study will cease as of May 2008. With the decrease in the number of incident (new) cases of vCJD, further funding was not awarded.

However, the Unit will continue to collect risk factor information of all suspect cases referred to the Unit as part of its core work. In addition, analysis will be undertaken on data gathered already, such as the examination of medical risk factor data obtained directly from medical records. Ad hoc studies, for example, examining the risk of dental treatment, that may require extra funding, will also be undertaken as necessary. If in the future it is thought necessary, funding could be sought to recruit further controls.

[13] Everington D et al. Dental treatment and risk of variant CJD. British Dental Journal 2007; 202: E19. [doi 10.1038/bdj.2007.126

Section

4

LABORATORY ACTIVITIES

Laboratory investigations are part of the internationally-agreed diagnostic criteria for CJD, both during life (CSF protein analysis, PrP genetic studies, brain biopsy neuropathology and prion protein studies) and post-mortem (autopsy neuropathology and prion protein studies). The NCJDSU has facilities to perform all of these investigations, which aid the timely and accurate diagnosis of all forms of CJD and are essential for surveillance purposes.

4.1 Neuropathology – Statement of Progress and Surveillance Activities

The neuropathology laboratory in the NCJDSU continues to maintain its diagnostic and research activities, including the work of the protein laboratory. The laboratory maintains close links with other neuropathology centres across the UK and overseas with scientific, medical, technical and student visitors over the past year for specialist training purposes. The laboratory has continued to maintain an active research programme both in-house and by collaboration with other research centres in UK, Europe and across the world. The laboratory is part of the NeuroPrion and BrainNet II networks of centres of excellence across Europe.

Since 2001 the autopsy rates for sCJD and vCJD have declined, in keeping with national trends. This is reflected in the number of cases examined in 2007, with fewer cases of sCJD and no cases of vCJD from the UK. In addition to the UK CJD surveillance work, the neuropathology laboratory is involved in vCJD screening studies in 3 groups of patients identified as being at increased risk of vCJD through exposure to blood products (Table 6). As in 2006, as a result of the Department of Health's guidelines for the examination of brain biopsy specimens, the increased number of cerebral biopsies referred to NCJDSU has continued. These samples require intensive investigation by conventional histology, immunocytochemistry, PET blot and western blot analysis. Many of these biopsy samples do not show any specific histological abnormalities, and so a conclusive diagnosis cannot always be reached, although a descriptive report is issued for each case. In 2007, the commonest alternative diagnosis to CJD was cerebrovascular disease, with no cases of Alzheimer's disease and Lewy body disease, each of which have been the commonest alternative diagnoses in the past.

The laboratory and its staff continue to participate in a range of EQA activities related to both technical and diagnostic neuropathology. As before, the laboratory continues to act as a source of information to a wide range of professionals involved in health and safety issues relating to CJD. We are most grateful to all neuropathologists, general pathologists and their technical, secretarial and autopsy room staff for their continuing support of the NCJDSU. We are also grateful to the relatives of patients with CJD for allowing us to study this group of devastating disorders.

Table 6 Breakdown of Laboratory Activities:
Period 1st January 2007– 31st December 2007

	CURRENT YEAR	PREVIOUS YEAR
REFERRED CASES (UK)		
Sporadic CJD	23	32
Familial CJD	0	2
Variant CJD (vCJD)	0	1
Iatrogenic CJD (Growth Hormone)	3	1
Iatrogenic CJD (Lyodura)	0	0
Gerstmann-Straussler-Scheinker Syndrome	0	2
Fatal Familial Insomnia	0	0
No evidence of CJD (no alternative pathological diagnosis)	12	23
Alzheimer's disease	0	2
Dementia with Lewy Bodies	0	2
Motor neurone disease	1	0
Other forms of brain disease†	6	7
REFERRED CASES (EU)		
Sporadic CJD	5	2
Familial CJD	0	1
Variant CJD	1	0
GSS	0	0
Other forms of brain disease	4	5
REFERRED CASES (ROW)		
Sporadic CJD	1	0
Variant CJD	0	0
Familial CJD	0	0
Other forms of brain disease	1	1
UK vCJD SCREENING STUDIES		
Haemophilia cases	6	
Primary immunodeficiency cases	10	
Blood product recipient cases	2	
TOTAL NUMBER OF CASES	**75**	**81**

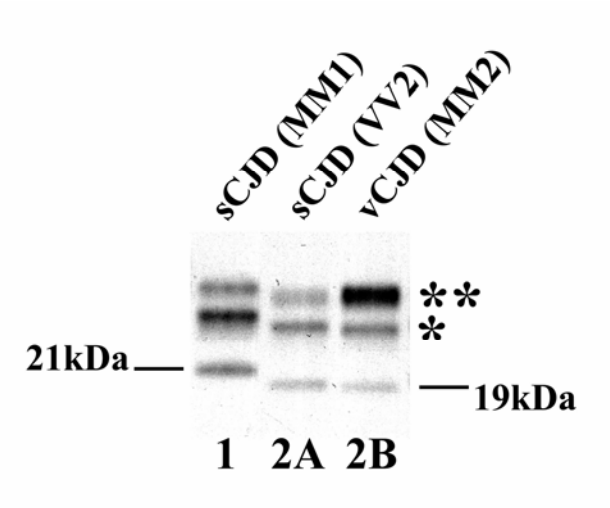
† Other forms of brain disease**:** arteriosclerosis and infarction (2); spinocerebellar ataxia (1); malignant lymphoma (1); cerebral diffuse astrocytoma (1); cerebral amyloid angiopathy (1).

Abbreviations:
EU European Union
ROW Rest of World

4.2 Prion Protein Laboratory

Prion protein typing is carried out as a routine diagnostic test on all suspected cases of CJD where frozen brain tissue is received by the NCJDSU. Small quantities of cerebral cortex are homogenized, treated with proteases and the size and relative abundance of the three PrP^{res} glycoforms determined by Western blot analysis. The prion protein type is classified as type 1 if the nonglycosylated form has a molecular weight of ~21kDa or type 2 if the nonglycosylated form has a molecular weight of ~19kDa. The suffix B is used to denote a PrP^{res} isotype where the diglycosylated band predominates. The remaining type 2 cases where the diglycosylated band does not predominate are termed type 2A. The type 2B isotype has previously found to be characteristic of vCJD. A typical result is shown in Figure 14.

Figure 14: PrP^{res} types in sporadic and variant CJD



Western blot analysis of protease-resistant prion protein (PrP^{res}) in two cases of sporadic CJD (sCJD) of the MM1 and VV2 subtypes and in a case of vCJD (vCJD (MM2)). The size of the nonglycosylated (bottom band) is either 21kDa (termed type 1) or 19kDa (termed type 2). Diglycosylated PrP^{res} (**) predominates in the vCJD and the pattern is termed type 2B to distinguish it from type 2 cases in which the monoglycosylated form (*) predominates (type 2A).

In cases from which only peripheral tissues are available (such as those in which diagnostic tonsil biopsy is performed), or in cases in which the patient is thought to have been at risk of developing CJD due to potential iatrogenic exposure and is enrolled in a UK prion screening study, a modified Western blot procedure is used which employs centrifugal concentration or sodium phosphotungstic acid precipitation to enrich for PrP^{res} and increase the sensitivity of the test.

UK Referrals

A total of 38 UK cases with frozen tissue were received and analysed in 2007, representing a small decrease in the number of cases with frozen tissue referred to the NCJDSU for analysis compared with the previous year. The results of the analysis were as follows:

Table 7 Breakdown of cases analysed in 2007

Diagnosis	**Type**	**PrP^{res} +ve CNS**
CJD (n=21)	Sporadic	18/18[1]
	Iatrogenic	3/3
Alternative final diagnosis or not determined		0/17[2]

[1] includes one case of the panencephalopathic variant of sporadic CJD.

[2] includes central and/or peripheral tissues from six individuals involved in prion screening studies, one tonsil biopsy and one autopsy tonsil specimen, analysed by high sensitivity Western blotting methods.

Further sub-classification by PrP^{res} type and *PRNP* genotype yields the following results:

Table 8 PrP^{res} type / *PRNP* genotype breakdown of CJD cases analysed in 2007

Diagnosis	*PRNP* genotype	Type 1	Type 2A
Sporadic CJD	M/M	12[1]	
	M/V	-	2
	V/V	1	3
Iatrogenic CJD (GHT)	M/M	1	-
	M/V	1	1[2]
	V/V	-	-

[1]includes one case of the panencephalopathic variant of sporadic CJD.
[2]Shows a doublet of non-glycosylated PrP^{res} as has been reported in M/V sporadic CJD cases.

Non-UK referrals

Five requests for Western blot analysis were received from non-UK (EU) referrals: One Swedish case was found to be PrP^{res} negative, whereas another Swedish case was found to have type 1 PrP^{res} (MM1 sporadic CJD). Two Dutch cases of the panecephalopathic variant of sporadic CJD were found to be MM1 and M/V1+2. A Portuguese case of variant CJD was found to have type 2B PrP^{res}, as expected from prior examination of a tonsil biopsy specimen from this same individual reported in 2005.

4.3 Brain banking activities

The bank of fixed and frozen tissues in the surveillance unit was used extensively in 2007 for diagnostic and collaborative research purposes with colleagues in the UK and overseas. Funding from MRC was obtained in January 2007 to support the activities of the Bank for 2 years, under the direction of the Steering Group for the MRC Edinburgh Brain Banks. The local management of the bank has been modified accordingly and a revised request form is available for all potential users. The activities of the Bank comply with current guidelines from MRC and the Royal College of Pathologists, and the Human Tissue (Scotland) Act and the Human Tissue Act.

4.4 Molecular Genetics

Familial CJD

Ninety-one cases of familial CJD (excluding cases of GSS) have been identified since 1970 by the NCJDSU (these data are incomplete as formal investigation of familial CJD in the UK is undertaken by the National Prion Clinic in London). Of the 91 cases, 82 were resident in England, 7 were resident in Wales and 2 were resident in Northern Ireland. Eighteen cases were still alive as at 31st December 2007. Forty-seven of the cases had insertions in the coding region of the PrP gene, 23 carried the mutation at codon 200 (Glu-Lys), 5 at codon 178 (Asp-Asn, with methionine at codon 129, ie FFI), 2 at codon 178 (MV), 2 at codon 210 (Val-Ile), one at codon D167G and one at codon V163STOP. The remaining 10

were identified as familial on the basis of relatives known to have had CJD. The mean age at death was 55 years (range 31-77 years).

Codon 129 distribution in sporadic CJD

The distribution of codon 129 genotypes in sporadic CJD has been analysed since the inception of the Unit in 1990. The overall distribution of codon 129 genotypes in sporadic CJD is 64% MM, 18% MV, 18% VV (see Table 9). There appears to be evidence (p=0.010) of a change in the codon 129 distribution in sporadic CJD between the periods 1990-1995 and 1996-2007. The explanation for this remains unclear and is being investigated further. It should be noted that not all cases are genotyped (data available on 64%) and, therefore, changes in codon 129 distribution may reflect changes in the way in which cases are selected for analysis.

Table 9 Codon 129 genotypes of cases of sporadic CJD in the UK, 1990-2007

Deaths from sporadic CJD	**MM(%)**	**MV(%)**	**VV(%)**
Deaths from 1 May 1990 – 31 December 1995	97 (75)	15 (12)	17 (13)
Deaths from 1 January 1996 – 31 December 2007	283 (61)	93 (20)	89 (19)
Total	380 (64)	108 (18)	106 (18)
Genotype distribution for the normal population Pooling data from five studies	(39)	(50)	(11)

Codon 129 distribution in vCJD

All clinical cases for whom genetic data are available (n=146, 88%) were methionine homozygotes at codon 129 of the PrP gene.

The genetic laboratory undertakes genetic analysis on a national and international basis.

4.5 CSF 14-3-3 and other brain specific proteins

The laboratory received 361 cerebrospinal fluid (CSF) samples from January 2007 – December 2007. Of these, 295 were from patients residing in the United Kingdom (UK), 66 were from patients from non-UK countries. Thirteen samples were blood-stained and as such unsuitable for analysis. The origin and numbers of these samples are given in Table 10.

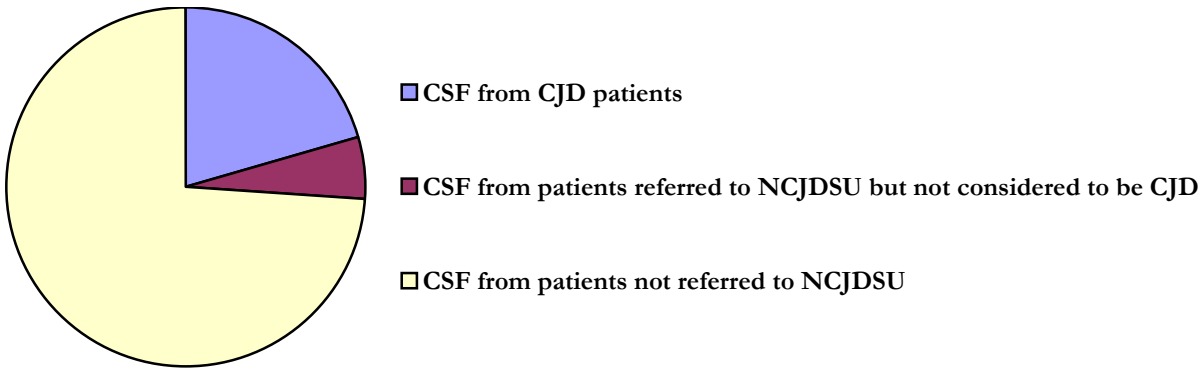
Table 10 Origin of CSF samples sent to the National CJD Surveillance unit (NCJDSU) for CSF 14-3-3 analysis from January 2007 – December 2007

Origin of CSF samples	**Total number CSF samples (%)**
CSF from UK patients	295 (82%)*
CSF from non-UK countries	66 (18%)
Total number	361 (100%)

* Thirteen CSF samples were blood-stained and as such unsuitable for analysis.

Of the 282 analysable CSF samples received from patients within the United Kingdom, 58 were finally diagnosed with CJD, another 16 were referred to the unit as suspect cases of CJD but did not satisfy the diagnostic criteria to be considered as a case of CJD and 208 patients did not have clinical features to merit formal referral as a suspect case of CJD (Figure 15).

Figure 15 Source of CSF samples received from UK for CSF 14-3-3 analysis



Of those patients diagnosed with CJD, 20 had neuropathologically confirmed sCJD, 28 were classified as probable sCJD, 3 were classified as probable vCJD, 3 were classified as probable iatrogenic CJD secondary to growth hormone therapy and 4 were classified as probable genetic CJD. Two of the CSF samples from vCJD patients came from a single vCJD patient undergoing therapeutic intervention. Of the four patients with genetic mutations, two patients had E200K mutations, one patient had a V210I mutation and one patient had a D178N mutation. The D178N mutation was located on the allele containing valine at codon 129 of the PRNP gene. The CSF 14-3-3 results in these patients are given in Table 11.

Table 11 The CSF 14-3-3 results in patients diagnosed with CJD.

Diagnosis	Number of cases	Number of positive CSF 14-3-3
Definite sporadic CJD	20	19
Probable sporadic CJD	28	28
Probable variant CJD	3	2
Probable genetic CJD	4	4
Probable iatrogenic CJD	3	3

Of the patients with probable sporadic CJD, 17 died with no post-mortem, 4 have died and neuropathological confirmation of sCJD is awaited. The remaining 7 patients are still alive. Of the 17 patients who died without post-mortem examination, two had EEG traces that were considered typical for sporadic CJD whilst 15 had either EEG traces that were not considered typical or an EEG was not performed. NB: this is based on locally reported EEGs as most have not been seen by the NCJDSU. Therefore, 15 of the 17 patients with probable sCJD who died without neuropathological confirmation have been classified as probable on the basis of the 14-3-3 result without independent EEG support.

Of the 208 CSF samples sent from patients who did not have enough signs and symptoms of CJD to merit formal referral to the NCJDSU, 34 had a positive CSF 14-3-3. In 24 of these patients an alternative diagnosis was identified and these are given in Table 12. The diagnosis in the remaining 10 cases is unknown. Of the 174 patients with negative CSF 14-3-3 none were subsequently referred to the NCJDSU as a suspect case of CJD. It is improbable that this group contains unidentified cases of CJD but formal follow-up of all these patients would be required to confirm this.

Table 12 Diagnosis in those patients with a positive CSF 14-3-3 who were diagnosed with an alternative diagnosis.

Diagnosis in CSF only referral cases with positive CSF 14-3-3	Number of cases
Improved	5
Paraneoplastic syndrome	3
Seizures	4
Stroke	1
Herpes Simplex encephalitis/encephalitis	2
Lewy Body dementia	2
Awaiting PM result	2
Weirnicke's encephalitis	1
Intracerebral malignancy	1
Alzheimer's disease	1
Motor Neurone Disease	1
Multi-infarct dementia	1

Section

5

NATIONAL CJD CARE TEAM

The National CJD Care Team is based within the National CJD Surveillance Unit and was formed in response to concerns regarding the care of patients suffering from CJD. An initial national care coordinator post was established in February 2000 and in September 2001 the National CJD Care Team was formed. The present team consists of 2 care coordinators and an administrator with clinical neurological support from within the unit.

When a referral has been made to the NCJDSU and a diagnosis of probable or possible CJD is made, the coordinator makes direct contact with the family and offers the opportunity to meet and to assist with care intervention. Referrals are also made to the Care Team from the National Prion Unit in London and Leah Davidson, who coordinates the care of iatrogenic CJD cases. Once contact is made, the coordinator can meet with the patient and family on a regular basis, depending on need, to provide support and to assist with coordination of local health and social care professions. Now that there are 2 care coordinators, more families are having the benefit of contact with a care coordinator. This does not always involve a personal visit. Contact by telephone is just as important and can be the preferred method by families and other professionals involved. Post bereavement support is offered to the family after the patient dies and assistance given with accessing more specialised counselling.

The National CJD Care Team works in close liaison with the Department of Health and provides access to the CJD Care Package, which is a sum of money available to assist local authorities with the care of patients suffering from all forms of CJD. The Care Fund is available to supplement local care provision for all types of CJD rather than replace it – health and social services are still required to provide the necessary elements of an individual patient's care package. Care packages for individual patients will vary according to their individual need and it is not possible to be prescriptive about what each care package should contain. What is needed is a package that will provide the appropriate level of care at home both for the patient and for their family.

As well as working with national organisations in the UK, the Care Team also works internationally with the Australian and American CJD Support Groups.

From the establishment of the first National Care Coordinator post in 2000 until 31st December 2007, the care team have been in contact with, and/or provided access to care funds, to 87 variant cases, 119 sporadic cases, 46 familial cases and 13 iatrogenic cases.

The National Care Coordinators undertook 200 patient visits and case conferences during 2007 (Table 13). In addition, 25 teaching sessions were provided to professionals involved in the provision of care to CJD patients.

Table 13 Patient Visits and Case Conferences
1st January to 31st December 2007

Month	Cases Alive	Cases in contact with	Case Conferences/Visits/ Teaching Sessions
January	33	18	20
February	34	18	22
March	35	20	15
April	32	21	21
May	32	20	12
June	34	18	18
July	36	22	9
August	41	27	15
September	49	37	23
October	48	36	21
November	49	37	26
December	45	35	23

Expenditure from the National CJD Care Fund during 2007 was £345,118.03, bringing the overall expenditure of the Care Fund since 2000 to £2,017,988.85. A breakdown of expenditure during 2007 is shown in Table 14.

Table 14 Care Fund Payments
1st January to 31st December 2007

Adaptations	64,334.28
Alternative Therapy	5,509.00
Car Hire	73,310.12
Counselling	1,050.00
Equipment	44,702.06
Nursing	133,024.36
Physiotherapy	6,526.50
Social Care	12,872.37
Transport	3,789.34
TOTAL	**345,118.03**

Section

6

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Section

7

Staff based at the National CJD Surveillance Unit, Western General Hospital, Edinburgh in 2007

Dr RSG Knight	Director, NCJDSU
Professor RG Will	Consultant Neurologist
Professor JW Ironside	Consultant Neuropathologist
Dr H Ward	Consultant Epidemiologist, Deputy Director
Professor JE Bell, Dr C Smith	Honorary Consultants in Neuropathology
Dr M Gillies, Dr G Chohan, Dr C Pennington	Clinical Research Fellows
Mrs B Smith-Bathgate	Nurse Practitioner
Ms M Leitch	National Care Co-ordinator
Dr MW Head	Senior Research Fellow
Dr A Green	Senior Clinical Scientist
Mr M Bishop	Molecular Biologist
Ms J Mackenzie	Study Coordinator
Mr A Hunter	Business Manager
Ms D Everington	Statistician
Mr N Attwood	Database Manager
Ms D Ritchie	Research Assistant
Mrs L McCardle	Chief Biomedical Scientist
Mrs M Le Grice, Ms S Lowrie, Mrs M Nicol	Senior Biomedical Scientists
Ms C-A Mackenzie	Tissue Bank Manager
Ms H Yull	Research Technician
Mr D Wight	Research Technician
Ms Y McCord	Research Technician
Ms Elaine Lord	Administrative Co-ordinator
Ms K Forrest, Ms A Honeyman	Secretariat – Neuropathology
Ms G Stone	Secretariat - Clinical
Mrs S Macdonald	Secretariat - Care Team
Ms K Anderson	Secretariat - Case-control study

<u>Staff funded by Other Sources</u>

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Professor PG Smith	Epidemiologist, Infectious Diseases Epidemiology Unit
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