SEVENTEENTH ANNUAL REPORT 2008

CREUTZFELDT-JAKOB DISEASE SURVEILLANCE IN THE UK

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Table of Contents

Section

1

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.

The information provided in this Seventeenth Annual Report continues to indicate that the number of sporadic cases remains relatively stable (the data for 2008 may still be incomplete). Detailed clinical and epidemiological information has been obtained for the great majority of patients. Referrals, having been fewer between 2004 and 2007, increased in 2008, back towards pre-2004 levels. 2008 has seen the highest mortality rate from sporadic CJD in the UK (1.43 per million per year) since 1985; a rate which is comparable with other European countries. 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 for sporadic CJD in the neuropathology laboratory rose from 23 in 2007 to 28 in 2008 (32 in 2006).

In 1990-2008 average annual mortality rates from sporadic CJD in England, Wales, Scotland and Northern Ireland were, respectively, 0.94, 1.08, 0.96 and 0.58/million/year. The differences between these rates are not statistically significant ($p=0.4$). 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=122) and Northern Ireland (SMR=74) 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 2008, there were 164 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 2008. The clinical, neuropathological and epidemiological features of the cases of vCJD are remarkably uniform and consistent with 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 147 clinically affected cases of vCJD with available genetic analysis have been methionine homozygotes. In 2008 the NCJDSU was referred the first case who met the clinical criteria in life for possible vCJD and was heterozygous (methionine/valine) at codon 129 of the *PRNP* gene (no post-mortem was undertaken). The clinical picture was typical of vCJD seen to date, which is reassuring for surveillance purposes. For further information on this case, see Section 2.3, page 14. Although a single case with only a 'possible' classification, this may have implications for the presentation of further clinical cases in codon 129 heterozygotes in the future and for the estimation of prevalence of sub-clinical infection in the population.

Analysis of vCJD diagnoses and deaths from January 1994 to December 2008 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 an individual of the *PRNP*-129 MV genotype as a possible case of vCJD and, in a separate case, disease-related prion protein in the spleen of a clinically unaffected blood recipient (reported in 2004) is consistent with such a hypothesis. These cases, along with the report of the prevalence of abnormal prion protein 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 incidence of vCJD is higher in the north of Britain than in the south and the only statistically significant geographic cluster of vCJD cases in the UK remains that seen in Leicestershire (5 cases occurring between 1996 and 1999.

The NCJDSU continues to collaborate with the Health Protection Agency Centre for Infections and Health Protection Scotland, in relation to a range of activities, including testing of pathological specimens from the National Anonymous Tonsil Archive study through to input into the development and implementation of public health policy, for example, in relation to the follow up of those identified as at increased risk of CJD. This year, the neuropathology laboratory identified a UK adult haemophiliac patient with PrP^{res} in a restricted distribution in the spleen. This patient had been entered into a joint study with the UK Haemophilia Centre Doctors' Organisation and NCJDSU. The patient had no neurological signs or symptoms, and no neuropathological evidence of vCJD. This case raises the possibility of transmission of vCJD infectivity via plasma products, and is the subject of ongoing investigations.

A case of protease-sensitive prionopathy was identified on neuropathological and biochemical grounds, the first case of this disorder identified in the UK since its description by Gambetti et al in the USA in 2008.

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 disease-related PrP in the spleen of a recipient of blood donated by someone incubating vCJD.

In 2008, for the first time, the Unit 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 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 the 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 success of the National CJD Surveillance Unit continues to depend on the extraordinary level of co-operation from the neurology and neuropathology communities and other medical and paramedical staff throughout the UK. Ongoing support is provided by the Infectious Disease 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 2008 (with data ascertained up to 31st May 2009). Mortality data from England and Wales include retrospective data from 1970; for Scotland and Northern Ireland, retrospective mortality data are available from 1985. Case definitions for the various types of CJD can be found at www.cjd.ed.ac.uk/criteria.htm. Cases classified as definite or probable are included in all analyses.

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 period 1999-2003, the annual number of referrals varied little, between 162 and 179. Between 2004-2007 the referrals dropped to between 114 to 124. However, last year, 2008, saw a rise in referrals to the NCJDSU to 146, closer to previous levels (Figure 1a).

This rise is partly explained by an increase in the number of non-CJD cases, such cases recorded as referrals are now back to pre-2004 levels as shown in Figure 1b. The number of referrals of cases aged greater than 30 who turn out to have definite/probable CJD have also increased to pre-2004 levels (Figure 1b). This would suggest that year on year variation in referral and classification patterns, particularly since the introduction of 14-3-3 as a routine test in 1999, have produced these changes as described in detail in previous NCJDSU Annual Reports (2004-2007) (available at www.cjd.ed.ac.uk).

Figure 1a **Referrals to NCJDSU : 1 May 1990 – 31st December 2008: Age < 30 and age ≥ 30**

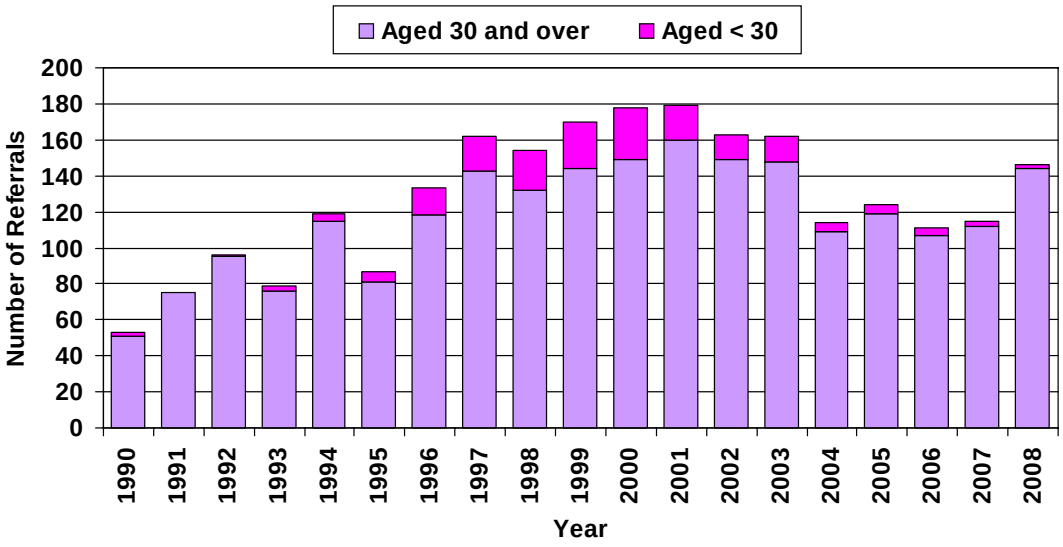
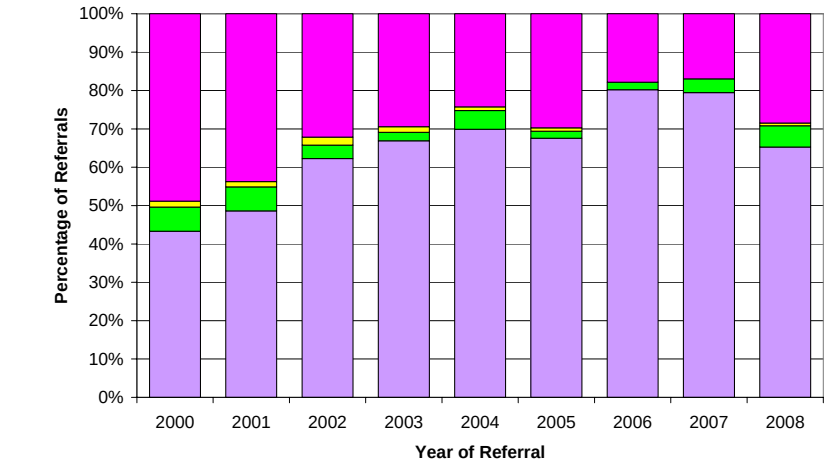
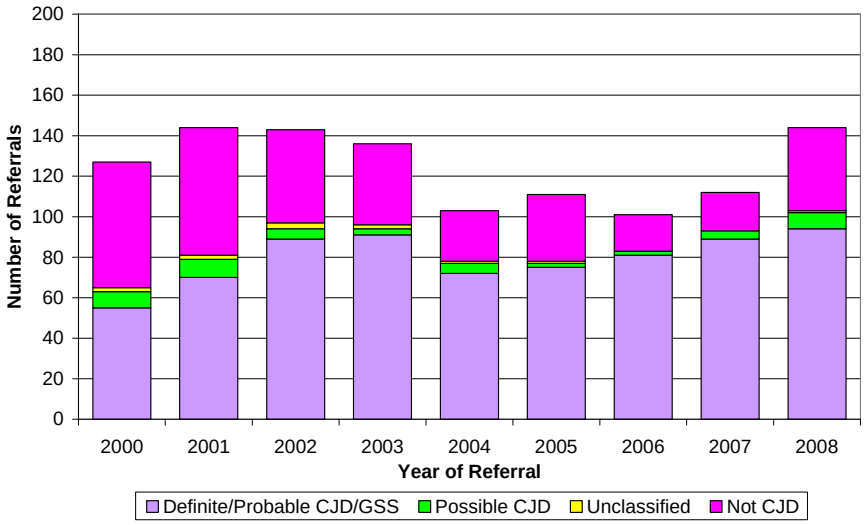


Figure 1b **Diagnostic classification of referrals: 2000-2008***
(shown as percentages and absolute numbers)





*excludes suspect vCJD referrals and vCJD cases

2.2 *Sporadic Creutzfeldt-Jakob Disease*

Between 1st January 1970 and 31st December 2008, 1455 cases of sporadic CJD were identified in the UK, of which 16 cases were alive on 31st December 2008. Two further cases were identified in Jersey but they are not included in the following UK analyses. Of these UK cases, 1072 (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 2008, Figure 2b shows similar data for England and Wales between 1970 and 2008 and Figure 2c shows the number of deaths from sporadic CJD in Scotland and Northern Ireland between 1985 and 2008. 2008 saw the highest UK mortality rate from sporadic CJD since 1985 of 1.43 per million per year (Figure 2a). This rate is comparable with other European countries and probably largely reflects improved case ascertainment, particularly in the elderly (see below***).***

Over the period 1990-2008 the average crude annual mortality rates from sporadic CJD per million population were 0.94 in England, 1.08 in Wales, 0.96 in Scotland and 0.58 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=0.4).

Table 2 presents data on the number cases of sporadic CJD (deaths and cases still alive as of 31st December 2008) according to age in England and Wales. It shows that the number of deaths identified each year has increased substantially since 1970, from an average of 15 per year in the 1970s, to 25 per year in the 1980s, to 45 per year in the 1990s and to 66 per year in the 2000s. A similar phenomenon has been observed in other European countries. These increases may reflect improved case ascertainment, particularly in the those aged over 70 years. The number of deaths identified among those aged 70 years and above has risen from around one per year in England and Wales in the early 1970s to around 30 per year in the UK in recent years. (Table 2 and Figure 4). These data also emphasise the very small numbers of cases of sporadic CJD occurring in individuals aged <50 years. 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, 1985-2008

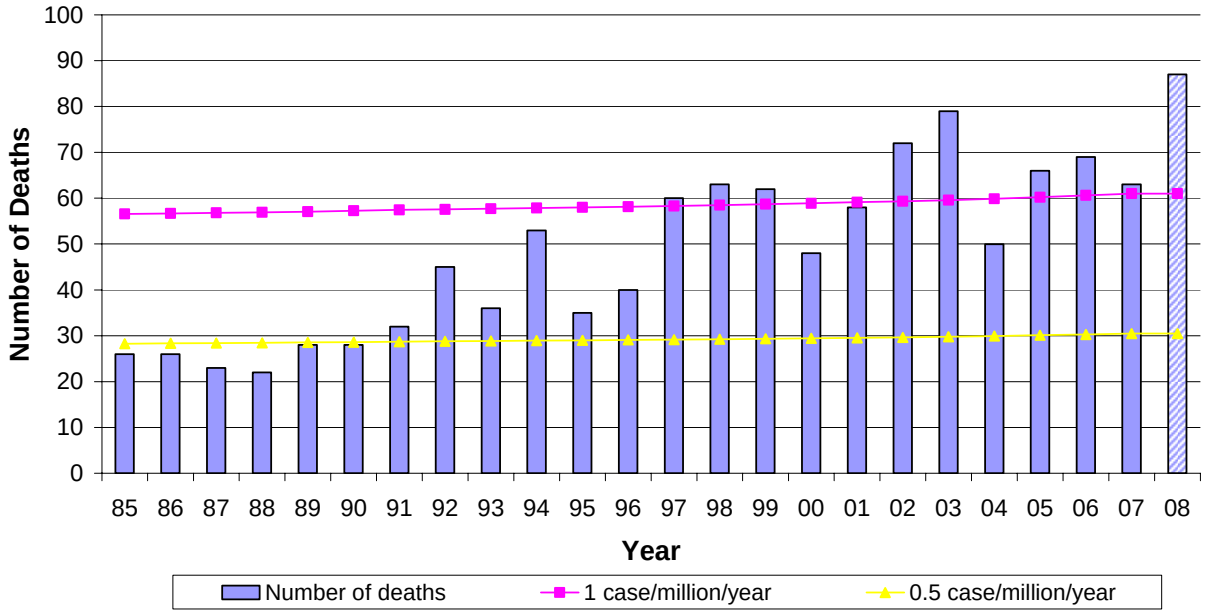


Figure 2b **Deaths from sporadic CJD, England and Wales, 1970-2008**

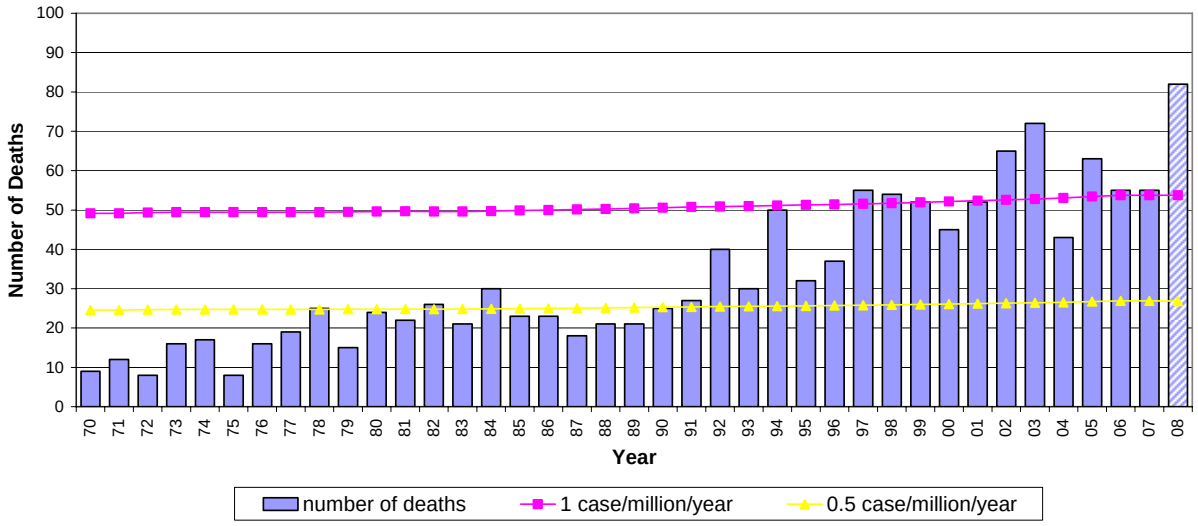


Figure 2c **Deaths from sporadic CJD, Scotland and Northern Ireland 1985-2008 (please note different scale from Figs 1a and 1b)**

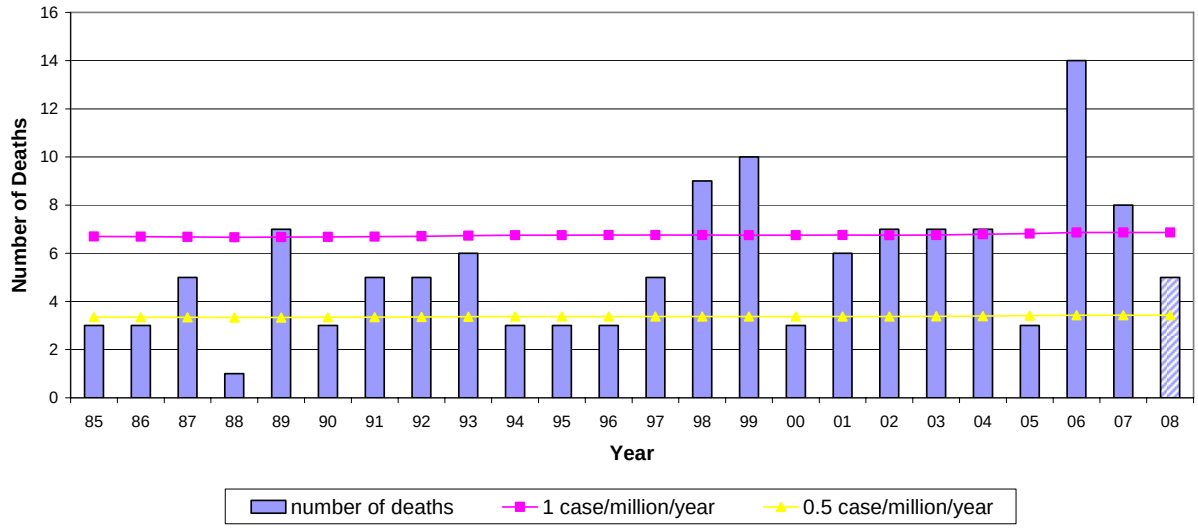


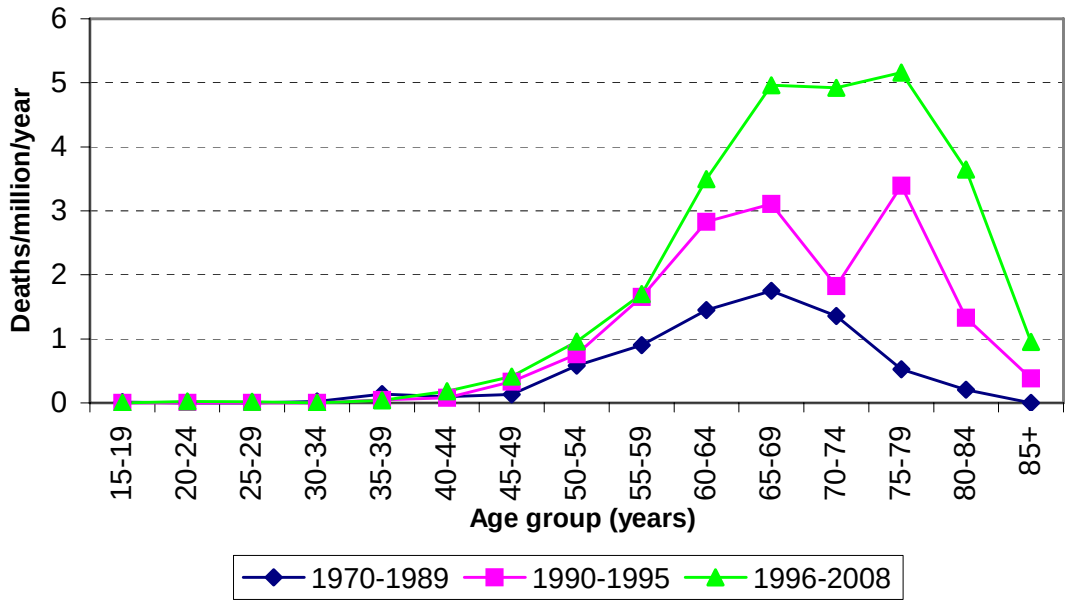
Table 1 Deaths from definite and probable sporadic CJD by region and county of death: 1st January 1990 to 31st December 2008

		No of cases	Total no (mortality rate/million/ annum)*		No of cases	Total no (mortality rate/million/ annum)*
ENGLAND				**ENGLAND**		
North				Yorkshire & Humberside		
Cleveland		9		Humberside	11	
Cumbria		13		NorthYorkshire	18	
Durham		6	52 (0.88)	South Yorkshire	29	92 (0.96)
Northumberland		7		West Yorkshire	34	
Tyne & Wear		17				
				East Anglia		
East Midlands				Cambridgeshire	8	
Derbyshire		14		Norfolk	18	44 (1.10)
Leicestershire		17		Suffolk	18	
Lincolnshire		11	62 (0.80)			
Northamptonshire		2		South West		
Nottinghamshire		18		Avon	23	
				Cornwall	14	
South East				Devon	24	
Bedfordshire		9		Dorset	17	116 (1.27)
Berkshire		14		Gloucestershire	13	
Buckinghamshire		6		Somerset	14	
East Sussex		11		Wiltshire	11	
Essex		40				
Greater London		101	314 (0.92)	West Midlands		
Hampshire		30		Hereford & Worcs.	11	
Hertfordshire		19		Shropshire	4	
Isle of Wight		3		Staffordshire	25	83 (0.83)
Kent		25		Warwickshire	6	
Oxfordshire		14		West Mids (Met)	37	
Surrey		19				
West Sussex		23				
North West						
Cheshire		17				
Greater Manchester		38	111 (0.91)	**TOTAL FOR ENGLAND**		**874 (0.94)**
Lancashire		29				
Merseyside		27				
WALES				**SCOTLAND**		
Clwyd		7		Borders	3	
Dyfed		4		Central	6	
Gwent		10		Dumfries & Galloway	2	
Gwynedd		11		Fife	7	
Mid Glamorgan		12		Grampian	12	
Powys		5		Highland	1	
South Glamorgan		7		Lothian	22	
West Glamorgan		4		Strathclyde	33	
				Tayside	5	
TOTAL FOR WALES			**60 (1.08)**	Islands (Shetland)	3	
				Islands (Orkney)	0	
NORTHERN IRELAND		18	**18 (0.58)**	Islands (Western Isles)	0	
				TOTAL FOR SCOTLAND		**94 (0.96)**

* based on 1994 population by region (as published in ONS Regional Trends, 1996 edition) over the 19-year period of the study.

Figure 3 shows average annual age-specific mortality rates over the time periods 1970-89, 1990-95 and 1996-08. 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 65-79 years and then declined. This decline might be explained by an under-ascertainment in the most elderly.

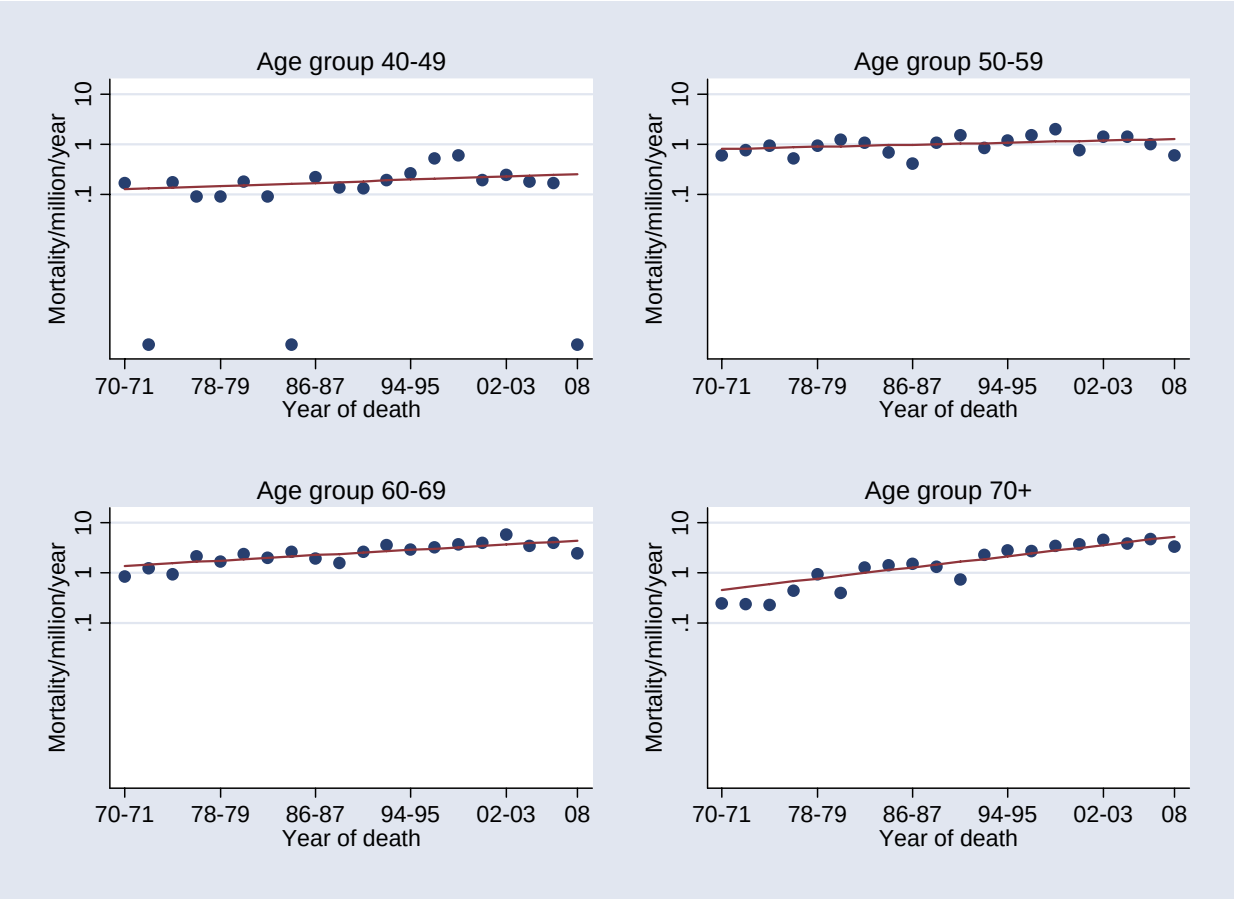
Figure 3 Age-specific mortality rates from sporadic CJD in the UK 1970-2008



1970-89 Mortality rates calculated using mid-1981 UK population estimates based on the 1981 Census
1990-95 Mortality rates calculated using mid-1991 UK population estimates based on the 1991 Census
1996-07 Mortality rates calculated using mid- 2001 UK population estimates based on the 2001 Census

An analysis of age-specific trends from 1970 to 2008 (Figure 4) shows there has been an increase in recorded mortality over time in all age groups over 50 years, but that the greatest relative increase has occurred in those aged 70 years and above. The mortality rate in this age group is now similar to that in the age group 60-69 years. P-values for temporal trends are $p=0.1$, $p=0.024$, $p<0.001$, $p<0.001$ for age groups 40-49, 50-59, 60-69 and $\geq$ 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: 1970-2008



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

Table 2 presents the actual annual numbers of sporadic CJD cases (For England and Wales) by age group underlying these trends.

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

	15-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	90+	Total
1970	0	0	1	1	3	4	0	0	0	9
1971	0	0	0	1	4	5	2	0	0	12
1972	0	0	0	0	3	5	0	0	0	8
1973	0	0	0	0	6	8	2	0	0	16
1974	0	0	0	1	10	6	0	0	0	17
1975	0	0	0	1	1	4	2	0	0	8
1976	0	0	1	0	3	12	0	0	0	16
1977	0	0	1	1	3	10	4	0	0	19
1978	0	0	1	0	7	11	6	0	0	25
1979	0	0	1	1	4	6	3	0	0	15
1980	1	0	0	2	8	11	2	0	0	24
1981	0	0	1	0	6	13	2	0	0	22
1982	0	0	1	0	5	14	5	1	0	26
1983	0	0	0	1	7	6	6	1	0	21
1984	0	0	2	0	3	14	11	0	0	30
1985[1]	0	0	2	0	5	14	5	0	0	26
1986	0	0	0	1	4	12	9	0	0	26
1987	0	0	1	2	1	10	9	0	0	23
1988	0	0	0	1	7	9	5	0	0	22
1989	0	0	0	1	6	9	10	2	0	28
1990	0	0	1	1	9	14	3	0	0	28
1991	0	0	0	1	9	16	4	2	0	32
1992	0	0	0	2	7	21	12	3	0	45
1993	0	0	0	1	3	18	10	4	0	36
1994	0	0	0	4	8	19	19	3	0	53
1995	0	0	0	0	7	13	15	0	0	35
1996	0	0	0	4	6	14	13	3	0	40
1997	0	1	0	4	14	21	17	3	0	60
1998	0	0	1	3	12	21	19	6	1	63
1999	0	1	0	6	16	19	16	4	0	62
2000	0	0	0	3	2	24	16	3	0	48
2001	0	0	0	0	9	19	22	8	0	58
2002	0	0	0	3	11	33	22	3	0	72
2003	0	0	0	1	10	32	29	6	1	79
2004	0	0	0	3	11	17	12	7	0	50
2005	0	0	0	0	10	22	26	8	0	66
2006	0	0	0	2	8	24	25	10	0	69
2007	0	0	0	1	7	23	28	4	0	63
2008[2]	0	0	1	0	9	30	37	10	0	87
Alive[3]	0	0	1	2	4	6	3	0	0	16
Total	1	2	16	55	268	589	431	91	2	1455

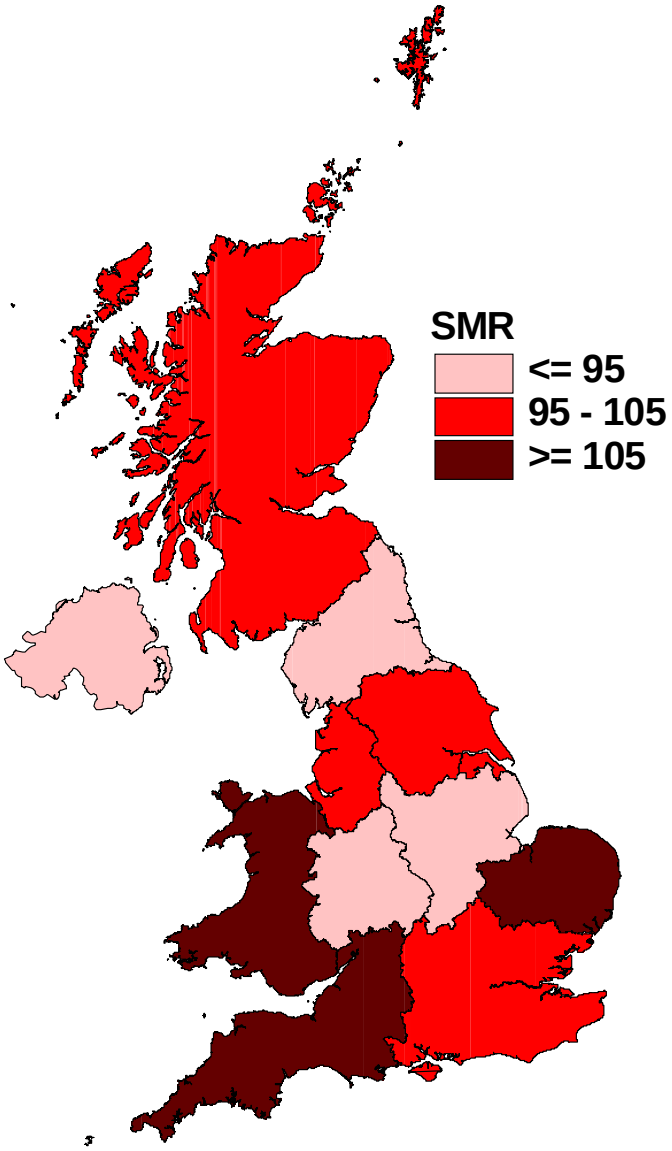
[1] Up to 1984, cases from England and Wales only. From 1985 onwards, cases from Scotland and Northern Ireland are included.

[2] Deaths to 31 December 2008. Data for 2008 not yet complete.

[3] Additional cases alive on 31st December 2008.

Age- and sex- standardised mortality ratios (SMRs) for the 11 standard regions of the UK for the period 1st January 1990 to 31st December 2008 were calculated (Figure 5). An SMR of 100 equates to the national 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=122), East Anglia (SMR=111) and Wales (SMR=107). Low mortality rates were observed in Northern Ireland (SMR=74), East Midlands (SMR=84) and West Midlands (SMR=88). The highest SMR (122 in South West) arose from 117 cases observed compared with 96 expected, an excess of just over one case every year compared to the national average. For East Anglia and Wales, the total numbers of excess cases was approximately 4.

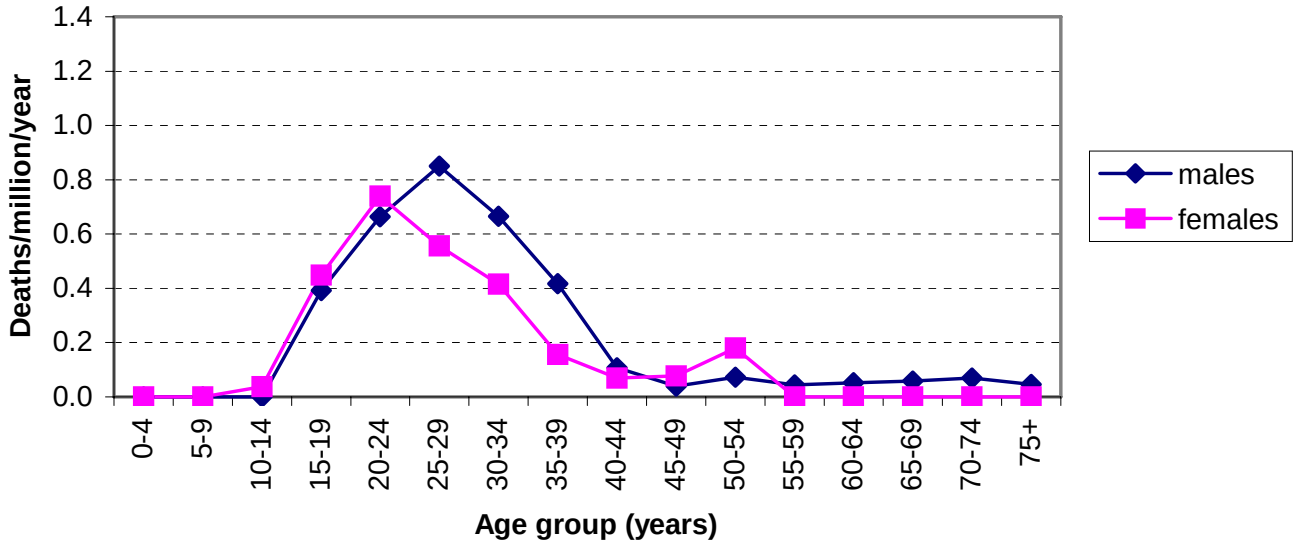
Figure 5 Standardised mortality ratios (SMRs) by standard region, UK 1 January 1990 - 31 December 2008



2.3 Variant Creutzfeldt-Jakob Disease

Up to 31st December 2008, 167 cases of definite or probable vCJD had been identified in the UK (115 definite, 49 probable who did not undergo post mortem and 3 probable cases still alive). Seventy-three (44%) of the 167 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 2008 are shown in Figure 6. The median duration of illness from the onset of first symptoms to death was 14 months (range 6-40) compared with a median duration of illness for cases of sporadic CJD of 4 months (range 1 to 74) during the period 1990-2008.

Figure 6 Age- and sex-specific mortality rates from vCJD in the UK 1 May 1995 - 31st December 2008



Mortality rates calculated using 2001 Census

In 2008 the NCJDSU was referred for the first time an individual who met the clinical criteria in life for possible vCJD and who was heterozygous (methionine/valine) at codon 129 of the *PRNP* gene. This individual died in 2009 after a disease of 22 months duration. Consent for a post-mortem was not given. The clinical picture was typical of vCJD seen to date, which is reassuring for surveillance purposes since the clinicopathological phenotype of vCJD in this genotype is unknown. To put this possible vCJD case in perspective, it is useful to examine the final diagnostic outcome of the 116 suspect vCJD cases that were classified as possible vCJD at some point during their diagnostic pathway (that is, they met the criteria for possible vCJD at some point between referral to NCJDSU and death or other final diagnostic outcome). Of the 116 possible vCJD cases, 94 (81%) had a final classification of definite or probable vCJD, 10 (9%) had a final diagnosis of definite sCJD, 5 (4%) had alternative diagnoses to CJD (Alzheimer's disease, Wilson's disease, viral encephalitis, syphilis, SSPE), one was diagnosed with genetic CJD, one improved clinically and for one individual the diagnosis remains unclear, but clinically was suggestive of vCJD. Four cases (3%) have resulted in a final classification of possible vCJD, 3 were methionine homozygotes at codon 129 and the recent case heterozygous (methionine/valine) at *PRNP* codon 129. On the basis of our knowledge of the natural history of other human prion diseases, clinical cases of vCJD in *PRNP* codon 129 genotypes other than methionine homozygotes could be anticipated.

Incidence of vCJD diagnoses and deaths from January 1994 - December 2008

Each year data on diagnosed cases of vCJD in the UK are reviewed in order to investigate trends in the underlying rate at which disease diagnoses and deaths are occurring. The following analysis reviews the data to the end of December 2008.

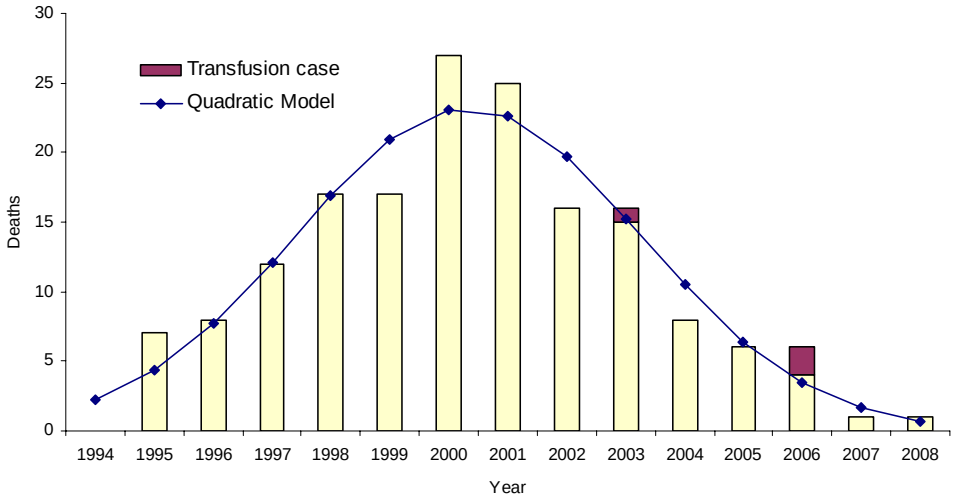
Methods

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. Assuming that most exposure to BSE ceased in the early 1990's, the age at death has not increased as might have been expected. In order to examine this further the cases were stratified by year of death and birth cohort (pre-1970, 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=0.50). The fitted trend is shown in Figure 7 and estimates that the current annual incidence of diagnoses is 0.7. The peak is estimated to have occurred in mid 2000.

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



Prediction for diagnoses in 2009

Extrapolation of the model with the quadratic term predicts a total of less than one diagnosis in 2009 with a 95% prediction interval of 0 to 2. The cubic model also gives an estimate of less than one diagnosis with 95% CI 0 to 2.

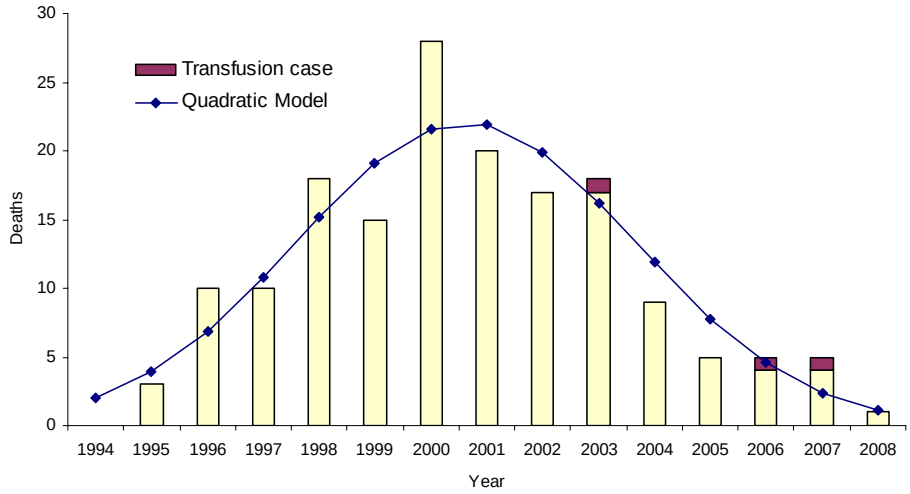
Assessment of Predictions made at the end of December 2007

The quadratic and cubic models both predicted one diagnosis (95% prediction interval 0 to 3). The observed number of one diagnosis agrees well with both models.

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=0.14). The fitted trend is shown in Figure 8 and estimates that the current annual incidence of deaths is 1.1. The peak is estimated to have occurred in mid 2000.

Figure 8 Quadratic-exponential model for vCJD deaths incidence trend



Predictions for deaths in 2009

Extrapolation of the model with the quadratic term predicts a total of less than one death in 2009 with a 95% prediction interval of 0 to 2. The cubic model predicts 1.4 deaths with 95% prediction interval 0 to 4.

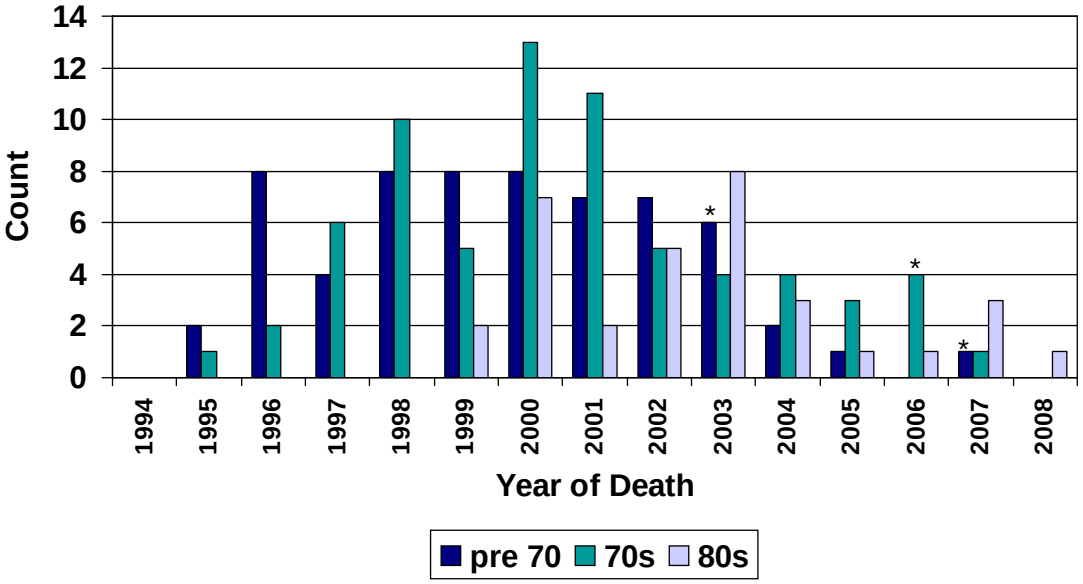
Assessment of Predictions made at the end of December 2007

The quadratic model predicted one death with a 95% prediction interval of 0 to 4. The cubic model predicted 2.5 deaths with a 95% prediction interval of 0 to 6. The actual observed number of deaths was one, which is consistent with both models, but closer to the simpler quadratic model.

Deaths by birth 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 those born in the 1970s and the 1980s. This analysis reveals strong evidence of differences between the cohorts 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 suggests either lower exposure or lower susceptibility in the very young, which is consistent with the lack of cases to date in individuals born in the 1990s. An alternative explanation for the stable age distribution could be shorter incubation periods in those exposed as teenagers/young adults than those exposed as young children. Note that both of these explanations would only be expected to yield a temporarily 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 one diagnosis/death per year. Extrapolating the best fitting model (the quadratic model) gives an estimate of less than one death in 2009 (95% prediction interval 0 to 2).

An analysis of deaths by birth cohort (pre 1970, 1970s, 1980s) indicates that the shape of the epidemic differs between cohorts, mainly due to the fact that deaths among 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 subgroups. There is also the possibility of ongoing person to person spread. Four cases of transfusion association vCJD infection have been identified to date, among individuals who received blood in 1999 or earlier from donors who were later diagnosed with clinical vCJD. 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 167 cases of vCJD in the UK. Cases have been widely spread throughout the UK. Table 3 presents data on the geographical distribution by county of residence at onset (for all 167 vCJD cases) and residence at death (for 161 vCJD cases who had died by 31st December 2008 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=167)

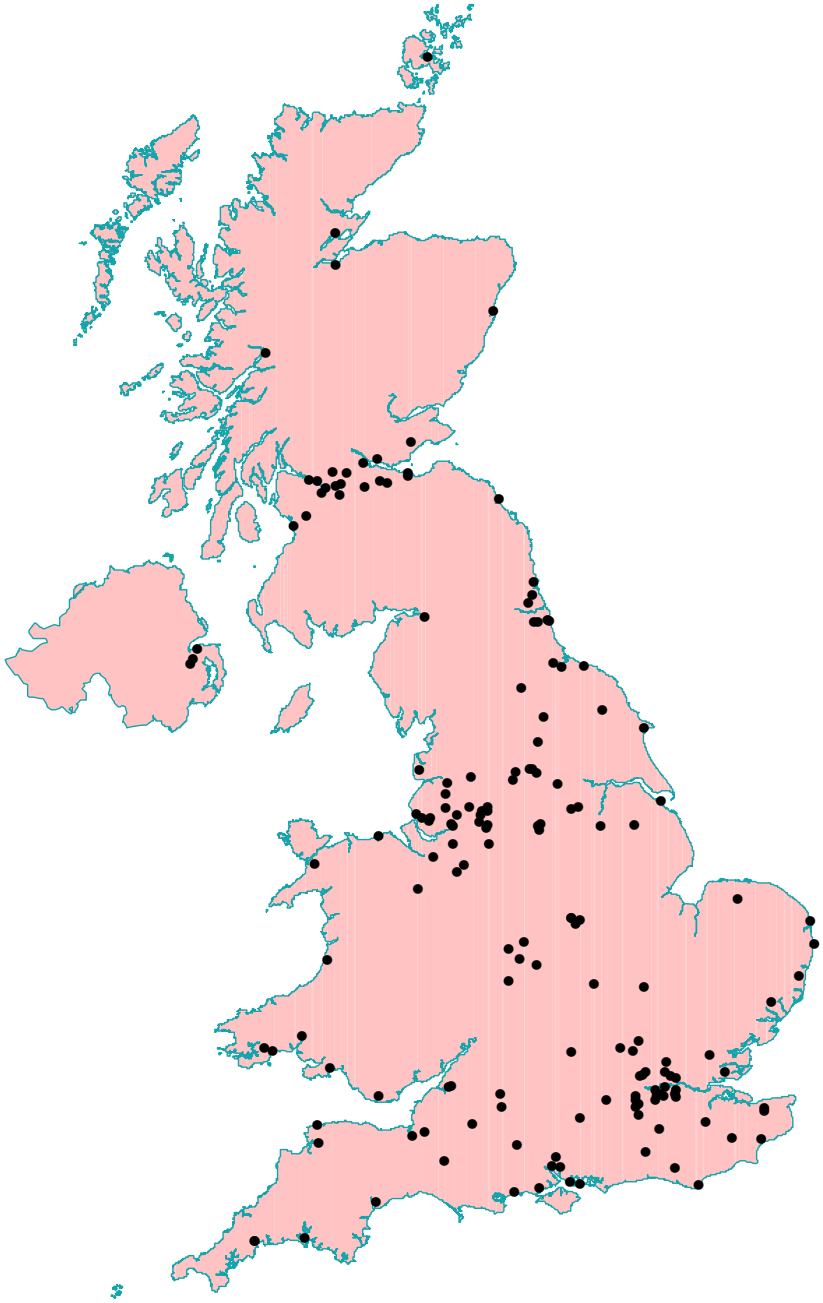


Table 3 Cases of definite and probable vCJD shown by region and county of onset (n=167†) and region and county of death (n=161‡)

	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 (0.28)**
East Midlands		
Derbyshire	0	1
Leicestershire	4	5
Lincolnshire	2	2
Northamptonshire	1	1
Nottinghamshire	0	0
Total	**7**	**9 (0.16)**
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 (0.16)**
North West		
Cheshire	7	8
Greater Manchester	10	9
Lancashire	4	4
Merseyside	4	4
Total	**25**	**25 (0.29)**
WALES		
Clwyd	1	0
Dyfed	3	3
Gwent	0	0
Gwynedd	1	1
Mid Glamorgan	0	0
Powys	1	1
South Glamorgan	1	1
West Glamorgan	1	0
WALES TOTAL	**8**	**6 (0.15)**
NORTHERN IRELAND TOTAL	**3**	**2 (0.09)**

	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 (0.25)**
East Anglia		
Cambridgeshire	1	1
Norfolk	2	3
Suffolk	3	2
Total	**6**	**6 (0.21)**
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 (0.20)**
West Midlands		
Hereford & Worcs.	0	1
Shropshire	1	1
Staffordshire	0	0
Warwickshire	1	2
West Mids (Met)	4	6
Total	**6**	**10 (0.14)**
ENGLAND TOTAL	**132**	**131 (0.20)**
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 (0.31)**

* 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 2008.

† includes cases still alive at 31st December 2008.

‡ 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 167 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	6 (2.43)
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	167 (3.40)

Figure 11 Standardised incidence ratios (SIRs) up to 31st December 2008 of vCJD by standard region on 1st January 1991

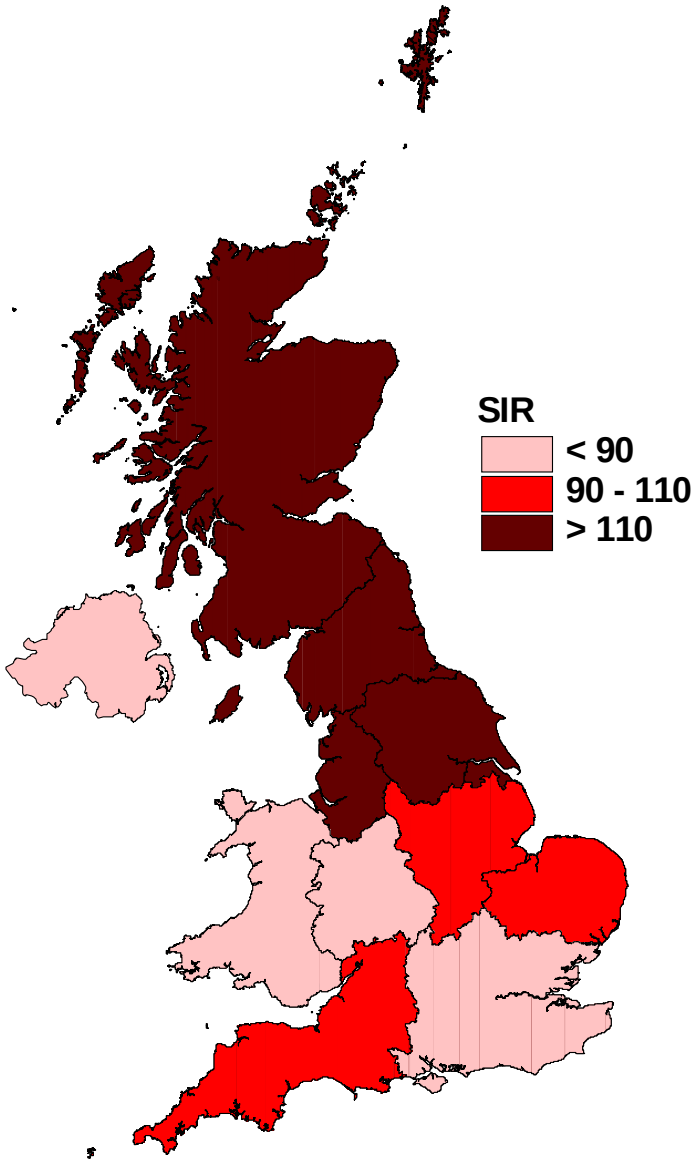


Table 5 shows the distribution of cases between the "North" and the "South" according to place of residence in 1991. We originally performed an analysis of the first 51 cases, distinguishing two areas. The "North" comprised four standard regions: Scotland, North, Yorkshire and Humberside, North West. 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 1.52 (95% c.i., 1.12, 2.07), 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.

vCJD 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)	91 (2.92)
Total (rate ratio*)	47.8 million	51 (1.94)	164 (1.52)

*North versus South, adjusted for age and sex

Northern cases were slightly older at onset than southern cases (median of 27 years versus 25 years; p=0.6), similar proportions were male (55% of northern and 56% of southern cases).

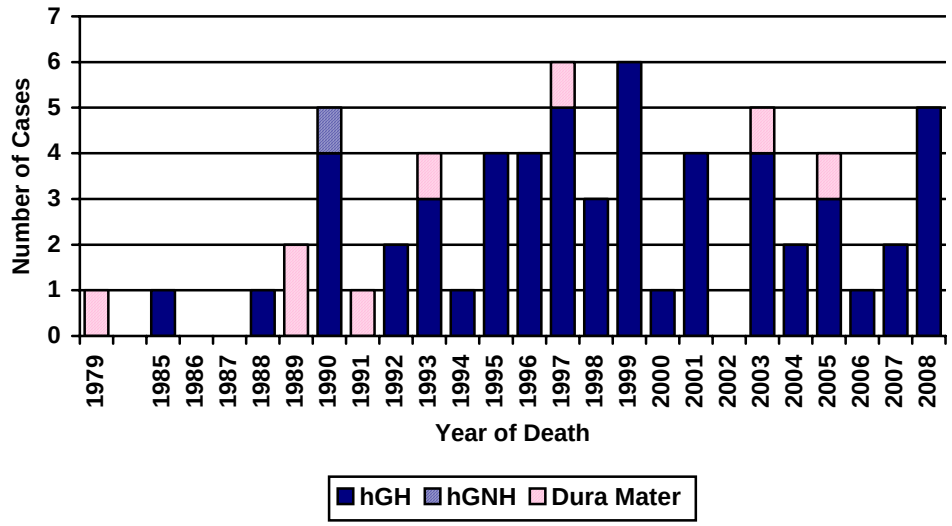
Geographically Associated Cases of vCJD

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. A paper describing this study is in preparation in collaboration with the Health Protection Agency.

2.4 Iatrogenic Creutzfeldt-Jakob disease

Since 1970, up to 31st December 2008, 67 cases of CJD attributable to iatrogenic exposure have been identified, 8 in individuals receiving dura mater implants, 58 in individuals who had received human-derived growth hormone (hGH) and one in a recipient of human gonadotrophin (hGN). Sixty-five of these individuals have died (Figure 12) and 2 were still alive as at 31st December 2008.

Figure 12 Deaths from iatrogenic CJD, 1979-2008



The mean age at death of the hGH/hGN group was 32 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, were 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 probable) 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 to ensure none appear on the NCJDSU database as a case of CJD.

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

[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.

relevant blood donors identified. The identity of donors is notified to NCJDSU for subsequent checking to ensure none appear on the NCJDSU database as a case of CJD.

Results

Thirty-one vCJD cases were reported, via information obtained at interview with a relative of the patient, to have been blood donors. Four additional cases who were not reported to have been blood donors were found to be registered with UK Blood Transfusion Services (UKBTS). One of these cases was found to have been a blood donor while the other three cases were registered as donors 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 identifiable 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]; at post mortem protease-resistant prion protein (PrP^{res}) was detected in the spleen but not in the brain. This was 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 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 the donor (Donor 3) developed symptoms of vCJD[7].

In the reverse study, 14 vCJD cases were reported, via information obtained at interview with a relative of the patient or from medical notes, 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 – Donor 1 and Donor 3 – had already been identified as cases of 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 2008, after nearly 12 years surveillance, 2571 patients with suspected PIND had been reported and the Expert Group had discussed 1767 of these. 1068 cases had a confirmed underlying cause other than vCJD, being categorised into over 120 known neurodegenerative diseases. There have been 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 UK 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

Between May 1990 and December 2006 a case-control study of CJD was carried out in the UK to investigate potential risk factors for variant and sporadic CJD. Recruitment of controls ceased at the end of 2006 though NCJDSU continues to collect data on potential risk factors for suspected cases of 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. Between 1990 and 2006 there were 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 were 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 medical 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 identification of friends by relatives of cases at a difficult point in their lives, and was, therefore, discontinued towards the end of 2006.

As detailed in Table 6 of Annual Report 2006,[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 proved the most successful in terms of numbers recruited and response rate. It has been used in analyses 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[11].

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.

In addition, because of the decline in the number of new vCJD cases, funding for the core case control study ceased in May 2008, having been funded since 1998 by three consecutive research grants (courtesy of the Department of Health and Scottish Government).

However, the Unit continues to collect risk factor information for all suspect cases of human prion diseases 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 (see Section "On going analyses" below). *Ad hoc* studies, for example, examining the risk of dental treatment, that may require extra funding, will also be undertaken as necessary (see Section "Dental Study" below). If in the future it is thought necessary, funding will be sought to recruit further controls.

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

[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.

explanation for the findings regarding diet. There was no convincing evidence of increased risk through medical, surgical or occupational exposure, or exposure to animals.

See section below, "On-going analyses" for details regarding an analysis of medical risk factor data obtained directly from primary care records.

Sporadic CJD

A publication in 2008 described 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 (Odds Ratio 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 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.

See section below, "On-going analyses" for details regarding an analysis of medical risk factor data obtained directly from primary care records.

On going analyses

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 those obtained from relatives and are not subject to recall bias.

For cases, records are obtained prospectively as the cases are identified. For the general population controls, we have written consent from three-quarters (approximately 620) to access their primary care medical records. To assemble this information was a huge task and involved visiting practices throughout the UK. This data collection was completed during 2008. The data have been entered onto a database and validated. Once they have been checked, the analysis will commence comparing them with medical data from vCJD cases. In theory a similar analysis is planned for sCJD in the future, though this is dependent on the number of medical records we hold for sCJD cases, which during the peak years of the vCJD epidemic were not sought due to lack of resources.

Dental study

For public health purposes, it is important to assess whether dental treatment is a potential route of iatrogenic transmission of vCJD in the UK. A risk assessment by the Department of Health (2006)

[12] Ward HJT et al. Risk factors for sporadic Creutzfeldt-Jakob disease. Ann Neurol 2008; 63: 347- 354.

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 thought.

However, to date there has been no evidence in humans of transmission of CJD by dental treatment. A previous study found no significant associations between dental treatment and vCJD[13]. However, the study was limited to data reported by relatives, which may be unreliable. Therefore, there was a need to examine dental records of cases (and controls) directly to obtain more accurate information. A study (funded by Department of Health) demonstrated the feasibility of collating information from dental records and a study aiming to investigate dental treatment as a possible risk factor for vCJD by examining the actual records of cases of vCJD and general population controls has been funded by the Department of Health for 18 months, since early 2008, and is ongoing.

Dental records are being traced with the assistance of the Dental Practice Boards for vCJD cases (n=161) and general population controls with consent (approximately 500) resident in England, Wales and Scotland. Two dental professionals collate details of dental treatments onto a standardised data collection form. Where dental histories are only partially available or unavailable further information is sought through centralised 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 summer 2009 and to begin analysis once the data have been entered and validated.

[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. Despite this trend, more cases of sCJD from the UK were submitted for examination in 2008 than in the preceding year. No cases of vCJD from the UK were examined in 2008 and no tissue samples from vCJD cases outside UK were received although two vCJD cases from Spain were referred for consultation and confirmation of the diagnosis by telepathology. This year, a case of protease-sensitive prionopathy was identified on neuropathological and biochemical grounds, the first case of this disorder identified in the UK since its description by Gambetti et al in the USA in 2008.

In addition to the UK CJD surveillance work, the neuropathology laboratory is involved in vCJD screening studies in three groups of patients identified as being at increased risk of vCJD through exposure to blood products or plasma products (Table 6). This year, the laboratory identified a UK adult haemophiliac patient with PrP^{res} in a restricted distribution in the spleen. This patient had been entered into a joint study with the UK Haemophilia Centre Doctors' Organisation and NCJDSU. The patient had no neurological signs or symptoms, and no neuropathological evidence of vCJD. This case raises the possibility of transmission of vCJD infectivity via plasma products, and is the subject of ongoing investigations. As in 2007, 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 2008, the commonest alternative diagnosis to CJD was Alzheimer pathology in

combination with other pathological abnormalities. Unusually, a case of a diffuse infiltrating glioma in the brain was identified in a referred case.

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 2008– 31st December 2008

	CURRENT YEAR	PREVIOUS YEAR
REFERRED CASES (UK)		
Sporadic CJD	28	23
Familial CJD	2	0
Variant CJD (vCJD)	0	0
Iatrogenic CJD (Growth Hormone)	0	3
Iatrogenic CJD (Lyodura)	0	0
Gerstmann-Straussler-Scheinker Syndrome	0	0
Fatal Familial Insomnia	0	0
No evidence of CJD (no alternative pathological diagnosis)	26	12
Alzheimer's disease	1	0
Dementia with Lewy Bodies	1	0
Motor neurone disease	0	1
Other forms of brain disease†	4	6
REFERRED CASES (EU)		
Sporadic CJD	2	5
Familial CJD	1	0
Variant CJD	0	1
GSS	0	0
Other forms of brain disease	6	4
REFERRED CASES (ROW)		
Sporadic CJD	2	1
Variant CJD	0	0
Familial CJD	0	0
Other forms of brain disease	0	1
UK vCJD SCREENING STUDIES		
Haemophilia cases	3	6
Primary immunodeficiency cases	7	10
Blood product recipient cases	0	2
TOTAL NUMBER OF CASES	**83**	**75**

† Other :

Alzheimer pathology + arteriosclerosis	1
Cerebral oedema + Alzheimer type pathology	1
Infiltrating astrocytic glioma	1
?Metabolic disorder. Alzheimer pathology	1

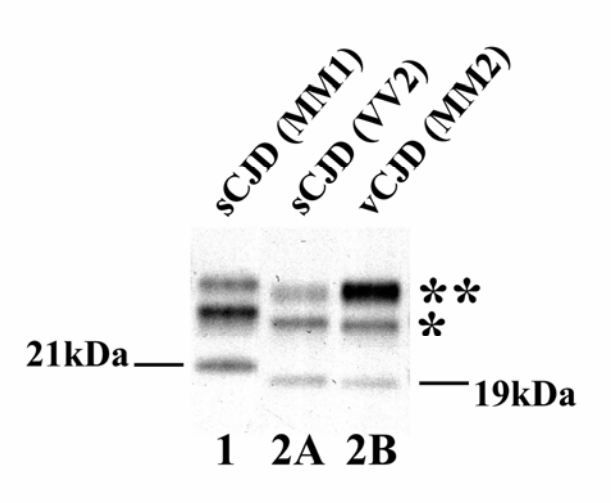
Abbreviations:

GHT	Growth Hormone Therapy
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 and treated with proteases. The presence of protease-resistant prion protein (PrP^{res}), its size and relative abundance of the three PrP^{res} glycoforms is 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 13. In certain familial forms the type 1 mobility is accompanied by a predominance of the diglycosylated band and this PrP^{res} type is termed 1B. Low molecular weight (<10kDa) PrP^{res} fragments have also been recognised to characterise certain cases of Gerstmann-Straussler-Scheinker (GSS) disease, and the more recently described protease sensitive prionopathy (PSPr).

Figure 13: 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 variant CJD (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 35 UK cases with frozen tissue were received and analysed in 2008, 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 2008

Diagnosis	Type	PrP^{res} +ve CNS
CJD (n=25)	Sporadic	23/23
	Familial	2/2
Alternative final diagnosis or not determined		0/10[1]

[1] includes two at risk individuals, one of whom (from the PIDS study) was negative for PrP^{res} in peripheral and CNS tissues, but the other of whom (from a study of at risk UK haemophiliacs) was positive for PrP^{res} in one sample of spleen analysed by high sensitivity Western blotting.

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 2008

Diagnosis	*PRNP* genotype	Type 1	Type 2A	<10 kDa
Sporadic CJD	M/M	9[1]	2	-
	M/V	5	-	-
	V/V	-	6[2]	1[3]
Familial CJD	E200K-MM	1[4]	-	-
	4 repeat insertion-MM	1	-	-

[1]includes one patient with the panencephalopathic variant of sporadic CJD.
[2]includes one patient who received a corneal graft.
[3]patient with a biochemical and pathological phenotype consistent with the newly described protease sensitive prionopathy.
[4]characteristic type 1B glycoform ratio.

Two of these results merit further comment. First, Table 7 above includes a case classified as having undetectable PrP^{res} in the CNS, however this patient was enrolled in a UK study of haemophiliacs considered to be at risk of developing CJD due to potential exposure to contaminated blood products (see Neuropathology section, above). Although PrP^{res} was undetectable in the CNS by Western blot using sodium phosphotunstic acid precipitation, a sample of the spleen from this case was positive by this same method. Due to its public health implications this finding was reported by the Health Protection Agency (http://www.hpa.org.uk/webw/HPAweb&HPAwebStandard/HPAweb_C/1234859690542?p=1231252394302) in advance of peer-reviewed publication (Ironside *et al*, in preparation). Second, Table 8 includes a case of apparently sporadic CJD in which PrP^{res} was detectable, predominantly in the form of low molecular weight bands. The pathology, genetics and prion protein biochemistry are all consistent with this being a case of protease sensitive prionopathy (PSPr), recently described by Gambetti and colleagues (Ann. Neurol 2008;63:697-708). Because protease sensitive prionopathy is a newly described human prion disease and has not been reported previously in the UK, the clinical and pathological details of this case are the subject of a separate report (Head *et al*, Neuropathol Applied Neurobiol. "Accepted Article"; doi: 10.1111/j.1365-2990.2009.01040.x)

Non-UK referrals

Western blot analysis was performed on frozen tissue from five non-UK cases. There were two referrals from Sweden, one of which was negative for PrP^{res} and the other of which had characteristic 1B PrP^{res} type associated with familial CJD E200K-MM. Type 1 PrP^{res} was also found in a panencephalopathic

variant of sporadic CJD (MM) from Greece. The characteristic low molecular weight fragment and ladder PrP^{res} profile was confirmed in a case of protease sensitive prionopathy requested from the United States of America.

4.3 Brain banking activities

The bank of fixed and frozen tissues in the Surveillance Unit was used extensively in 2008 for diagnostic and collaborative research purposes with colleagues in the UK and overseas. Funding from MRC was renewed in 2008 to support the activities of the Bank until October 2009, and an application for additional continued funding has been submitted to MRC. The local management of the Bank has been modified 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 2006 and the Human Tissue Act 2004.

4.4 Molecular Genetics

Familial CJD

Ninety-eight 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 98 cases, 87 were resident in England, 8 were resident in Wales, 2 were resident in Northern Ireland and one was resident in Scotland. Seventeen cases were still alive as at 31st December 2008. Fifty of the cases had insertions in the coding region of the PrP gene, 27 carried the mutation at codon E200K, 5 at codon D178N (M allele, ie FFI), 2 at codon D178N (V allele) 2 at codon V210I, 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).

***PRNP* Codon 129 distribution in sporadic CJD**

The distribution of *PRNP* codon 129 genotypes in sporadic CJD has been analysed since the inception of the Unit in 1990. The overall distribution of *PRNP* codon 129 genotypes in sporadic CJD is 63% MM, 19% MV, 18% VV (see Table 9). There appears to be evidence (p=0.008) of a change in the *PRNP* codon 129 distribution in sporadic CJD between the periods 1990-1995 and 1996-2008. The explanation for this remains unclear and is being investigated further. It should be noted that not all cases are genotyped (data available on 62%) and, therefore, changes in *PRNP* codon 129 distribution may reflect changes in the way in which cases are selected for analysis.

Table 9 *PRNP* codon 129 genotypes of cases of sporadic CJD in the UK, 1990-2008

Deaths from sporadic CJD	**MM(%)**	**MV(%)**	**VV(%)**
Deaths from 1 May 1990 – 31 December 1995	97 (75)	16 (12)	17 (13)
Deaths from 1 January 1996 – 31 December 2008	310 (60)	107 (21)	100 (19)
Total	407 (63)	123 (19)	117 (18)
Genotype distribution for the normal population Pooling data from five studies	(39)	(50)	(11)

PRNP codon 129 distribution in vCJD

All clinical cases for whom genetic data are available (n=147, 88%) were methionine homozygotes at *PRNP* 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

Introduction

The laboratory received 372 cerebrospinal fluid (CSF) samples from January 2008–December 2008, from patients residing in the United Kingdom (UK) and from patients in non-UK countries. Twelve 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 2008 – December 2008.

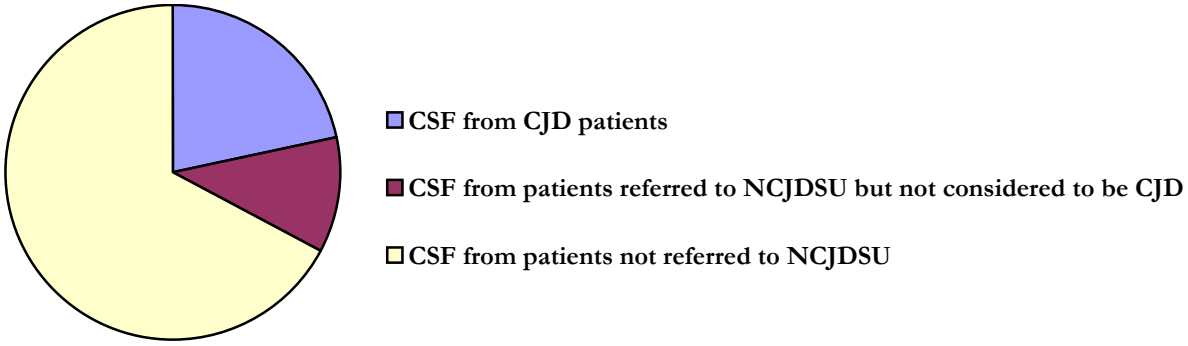
Origin of CSF samples	Total number CSF samples (%)
CSF from UK patients	330 (89%)*
CSF from non-UK countries	42 (11%)**
Total number	372 (100%)

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

Of the 320 analysable CSF samples received from patients within the United Kingdom, 69 samples were from patients who finally diagnosed with definite or probable CJD, 2 were from patients who were diagnosed as possible cases of sCJD, one was from a patient with possible vCJD and the remaining 33 samples were from patients diagnosed as not having CJD.

The remaining 215 CSF samples were sent to the National CJD Surveillance Unit for the analysis of CSF 14-3-3 and S-100b but Creutzfeldt-Jakob disease was not considered to be a likely clinical diagnosis in any of these 215 patients. In any situation where a CSF request is made from a case where CJD is reasonably suspected but which has not been referred as a suspect case in the surveillance system, the referrer is encouraged to do so. The Unit's CSF laboratory is experiencing an increasing number of requests for CSF protein tests in cases where CJD is either very unlikely or essentially excluded on the basis of the clinical details or other investigation results. This is occurring in other surveillance system laboratories in other countries. This matter is being considered in a prospective audit of CSF requests to the laboratory and the results should be available for the next Annual Report. In addition, it is intended to present the Unit's accumulated data on the practical diagnostic utility of these CSF proteins to UK clinical neurologists, which may allow for more focussed requests.

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



Of those patients diagnosed with CJD, 27 had neuropathologically confirmed sCJD, 38 were classified as probable sCJD, one was classified as probable vCJD and 2 were classified as probable iatrogenic CJD secondary to growth hormone therapy. The CSF 14-3-3 results in these patients are given in Table 11.

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

Diagnosis	Number of cases	Number of positive CSF 14-3-3
Definite sporadic CJD	27	23
Probable sporadic CJD	38	38
Possible sporadic CJD	2	0
Probable variant CJD	1*	2
Possible variant CJD	1	1
Probable iatrogenic CJD	2	1

* Two CSF samples were obtained from a single patient with variant CJD undergoing therapeutic intervention.

Of the patients with probable sCJD, 29 died with no post-mortem, 2 have died and neuropathological confirmation of sCJD is awaited. The remaining 7 patients are still alive. Of the 29 patients who died without post-mortem examination, 6 had EEG traces that were considered typical for sCJD whilst 13 had either EEG traces that were not considered typical or an EEG was not performed. It was unclear whether the remaining 10 patients had an EEG performed. Therefore 23 of the 29 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 215 CSF samples sent from patients who were not formally referred to the NCJDSU 29 had a positive CSF 14-3-3. In 25 of these patients an alternative diagnosis was identified. The diagnoses in the remaining 4 cases is unknown but CJD was very unlikely on clinical grounds or in light of the results of other investigations.

Section

5

NATIONAL CJD CARE TEAM

Established by the Department of Health, 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 who are senior nurses 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. They provide valuable expertise in nursing patients with CJD and can anticipate and prevent problems arising. By offering skilled advice and education, the care team enable local teams to provide a higher standard of care and remains involved on a consultancy basis as long as needed. Now that there are 2 care co-ordinators, more families are having the benefit of contact with a care co-ordinator. 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 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 needs 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 and is an official Friend of the CJD International Support Alliance.

From the establishment of the first National Care Coordinator post in 2000 until 31st December 2008, the care team have been in contact with, and/or provided access to care funds, to 89 variant cases, 169 sporadic cases, 49 familial cases and 15 iatrogenic cases.

The National Care Coordinators undertook 239 patient visits and case conferences during 2008 (Table 12).

Table 12 Patient Visits and Case Conferences
1st January to 31st December 2008

Month	Cases Alive	Cases in contact with	Case Conferences/Visits/ Teaching Sessions
January	47	25	17
February	46	23	22
March	49	25	13
April	46	25	17
May	44	16	11
June	47	27	25
July	43	24	15
August	46	23	22
September	51	31	33
October	52	25	30
November	57	23	15
December	55	21	14

Expenditure from the National CJD Care Fund during 2008 was £546,522.78, bringing the overall expenditure of the Care Fund since 2000 to £2,564,511.63. A breakdown of expenditure during 2008 is shown in Table 13.

Table 13 Care Fund Payments
1st January to 31st December 2008

Adaptations	58,954.95
Alternative Therapy	2,536.00
Car Hire	98,099.27
Counselling	1,300.00
Equipment	15,995.59
Nursing	355,026.41
Physiotherapy	9,467.00
Social Care	2,463.56
Transport	2,680.00
TOTAL	**546,522.78**

Section

6

PUBLICATIONS IN 2008

1. Appleford NE, Wilson K, Houston F, Bruce LJ, Morrison A, Bishop M, Chalmers K, Miele G, Massey E, Prowse C, Manson J, Will RG, Clinton M, MacGregor I, Anstee DJ. alpha-Hemoglobin stabilizing protein is not a suitable marker for a screening test for variant Creutzfeldt-Jakob disease. Transfusion 2008; 48(8): 1616-26.

2. Bell JE, Alafuzoff I, Al-Sarraj S, Arzberger T, Bogdanovic N, Budka H, Dexter DT, Falkai P, Ferrer I, Gelpi E, Gentleman SM, Giaccone G, Huitinga I, Ironside JW, Klioueva N, Kovacs GG, Meyronet D, Palkovits M, Parchi P, Patsouris E, Reynolds R, Riederer P, Roggendorf W, Seilhean D, Schmitt A, Schmitz P, Streichenberger N, Schwalber A, Kretzschmar H. Management of a twenty-first century brain bank: experience in the BrainNet Europe consortium. Acta Neuropathol 2008; 115: 497-507.

3. Bishop MT, Kovacs GG, Sanchez-Juan P, Knight RSG. Cathepsin D SNP associated with increased risk of variant Creutzfeldt-Jakob disease. BMC Medical Genetics 2008; 9:31.

4. Bishop MT, Ritchie DL, Will RG, Ironside JW, Head MW, Thomson V, Bruce M, Manson JC. No major change in vCJD agent strain after secondary transmission via blood transfusion. PLoS One 2008; 3(8):1-6.

5. Heath CA, Will RG. Clinical aspects of variant Creutzfeldt-Jakob disease. In: Duyckaerts C, editor. Handbook of Clinical Neurology, Vol 89 (3rd series) Dementias. Amsterdam: Elsevier B.V., 2008: 765-778.

6. Hizume M, Kobayashi A, Teruya K, Ohashi H, Ironside JW. Mohri S, Kitamoto T. Human PrP 219K is converted to PrPSc,but shows heterozygous inhibition in vCJD infection. J Biol Chem 2008 [epub ahead of print]. *(printed 2009; 284(6): 3603-9)*

7. Knight R. Clinical features and diagnosis of human prion diseases. Future Neurology 2008; 3(4): 473-481.

8. Krasnianski A, Kallenberg K, Collie DA, Meissner B, Schulz-Schaeffer WJ, Heinemenn U, Varges D, Summers DM, Kretzschmar HA, Talbot T, Will RG, Zerr I. MRI in the classical MM1 and the atypical MV2 subtypes of sporadic CJD: an inter-observer agreement study. Eur J Neurol 2008; 15:762-771.

9. Ironside JW, Ghetti B, Head MW, Piccardo P, Will RG. Prion Diseases. In: Love S, Louis DN, Ellison DW, editors. Greenfield's Neuropathology. London: Hodder Arnold, 2008: 1197-1273.

10. Ironside JW, Head MW. Biology and neuropathology of prion disease. Handb Clin Neurol 2008; 89: 779-97.

11. Jansen C, Head MW, Rozemuller AJ, Ironside JW. Panencephalopathic Creutzfeldt-Jakob disease in the Netherlands and UK: clinical and pathological characteristics of nine patients. Neuropath Appl Neurobiol 2008; [epub ahead of print]. *(printed 2009; 35(3): 272-82)*

12. Jones M, Peden AH, Yull H, Wight D, Bishop MT, Prowse CV, Turner ML, Ironside JW, Macgregor IR, Head MW. Human platelets as a substrate source for the in vitro amplification of the abnormal prion protein (PrP) associated with variant Creutzfeldt-Jakob disease. Transfusion 2008; [epub ahead of print]. *(printed 2009; 49(2): 376-84)*

13. Jones M, Peden AH, Wight D, Prowse C, Macgregor I, Manson J, Turner M, Ironside JW, Head MW. Effects of human PrPSc type and PRNP genotype in an in-vitro conversion assay. Neuroreport 2008; 19: 1783-6.

14. Jones M, Wight D, McLoughlin V, Norrby K, Ironside JW, Connolly JG, Farquhar CF, Macgregor IR, Head MW. An antibody to the aggregated synthetic prion protein peptide (PrP106-126) selectively recognizes disease-associated prion protein (PrP9Sc)) from human brain specimens. Brain Pathol 2008; [epub ahead of print]. *(printed 2009; 19(2): 293-302)*

15. Miele G, Seeger H, Marino D, Eberhard R, Heikenwalder M, Stoeck K, Basagni M, Knight R, Green A, Chianini F, Wüthrich RP, Hock C, Zerr I, Aguzzi A. Urinary alpha1-antichymotrypsin: a biomarker of prion infection. PLoS ONE. 2008;3(12):e3870.

16. Murray K, Ritchie DL, Bruce M, Young CA, Doran M, Ironside JW, Will RG. Sporadic Creutzfeldt-Jakob disease in two adolescents. JNNP 2008; 79:14-18.

17. Parchi P, Notari S, Weber P, Schimmel H, Budka H, Ferrer I, Haik S, Hauw JJ, Head MW, Ironside JW, Limido L, Rodriguez A, Strobel T, Tagliavini F, Kretzschmar HA. Inter-Laboratory Assessment of PrP(Sc) Typing in Creutzfeldt-Jakob Disease: a western blot study within the NeuroPrion Consortium. Brain Pathol 2008; [epub ahead of print]

18. Sikorska B, Liberski PP, Sobow T, Budka H, Ironside JW. Ultrastructural study of florid plaques in variant Creutzfeldt-Jakob disease: a comparison with amyloid plaques in kuru, sporadic Creutzfeldt-Jakob disease and Gerstmann-Straussler-Scheinker disease. Neuropathol Appl Neurobiol 2008; [epub ahead of print]. *(printed 2009; 35(1): 46-59)*

19. Stewart LA, Rydzewska LHM, Keogh GF, Knight RSG. Systematic review of therapeutic interventions in human prion disease. Neurology 2008; 70:1272-1281.

20. Uro-Coste E, Cassard H, Simon S, Lugan S, Bilheude JM, Perret-Liaudet A, Ironside JW, Haik S, Bassset-Leobon C, Lacroux C, Peoch K, Streichenberger N, Langeveld J, Head MW, Grassi J, Hauw JJ, Schelcher F, Delisle MB, Andrreoletti O. Beyond PrP res type 1/type 2 dichotomy in Creutzfeldt-Jakob disease. PLos Pathog 2008; 4: e1000029.

21. Ward HJT, Everington D, Cousens SN, Smith-Bathgate B, Gillies M, Murray K, Knight RSG, Smith PG, Will RG. Risk factors for sporadic Creutzfeldt-Jakob disease. Ann Neurol 2008; 63:347-354.

22. Ward HJT, Knight RSG. Surgery and risk of sporadic Creutzfeldt-Jakob disease. Neuroepidemiology 2008; 31:241-242.

23. Will R, Head M. A new prionopathy. Ann Neurol 2008; 63(6):677-678.

24. Will RG. Cold comfort pharm. Practical Neurology 2008; 8:60-61.

25. Will RG. Bovine Spongiform Encephalopathy. In: Mahy BWJ, van Regenmortel MHV, editors. Encylopedia of Virology. Oxford: Elsevier, 2008: 368-374.

Section

7

Staff based at the National CJD Surveillance Unit, Western General Hospital, Edinburgh in 2008

Dr H Ward	Director, NCJDSU
Professor RG Will	Consultant Neurologist
Dr RSG Knight	Consultant Neurologist
Professor JW Ironside	Consultant Neuropathologist
Professor JE Bell, Dr C Smith	Honorary Consultants in Neuropathology
Dr G Chohan, Dr C Pennington	Clinical Research Fellows
Mrs B Smith-Bathgate	National Care Co-ordinator
Ms M Leitch	National Care Co-ordinator
Dr MW Head	Reader, with responsibility for prion protein biochemistry
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 P Watt	Dental Hygienist
Ms F Ord	Dental Hygienist
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
Mrs S Macdonald	Secretariat - Care Team
Ms K Anderson	Secretariat - Case-control study

Staff funded by Other Sources

Ms T Lindsay (EU)	European Study Co-Ordinator
Mrs C Donaldson (EU)	Secretariat
Dr A Peden (CSO)	Postdoctoral Research Fellow
Dr M Jones (SNBTS/CSO)	Postdoctoral Research Fellow
Ms K Sherwood (UoE)	PhD student
Ms Z Krejciova	PhD student
Mr YP Choi	PhD student

Infectious Disease Epidemiology Unit, London School of Hygiene and Tropical Medicine

Professor PG Smith	Professor of Tropical Epidemiology, Infectious Disease Epidemiology Unit
Professor SN Cousens	Professor of Epidemiology and Medical Statistics, Infectious Disease Epidemiology Unit