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CREUTZFELDT-JAKOB DISEASE SURVEILLANCE IN THE UK

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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 Eighteenth Annual Report continues to indicate that the number of sporadic cases remains relatively stable (the data for 2009 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 saw 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. The mortality rate for 2009 is 1.27 (although data for 2009 may still be incomplete). Although the post mortem rate for patients with suspected CJD has declined, in line with general autopsy rates in the UK, it remains relatively high (around 60%). The number of brain specimens examined for sporadic CJD in the neuropathology laboratory remained similar to 2008 with 29 samples in 2009 compared with 28 in 2008.

In 1990-2009 average annual mortality rates from sporadic CJD in England, Wales, Scotland and Northern Ireland were, respectively, 0.95, 1.13, 1.01 and 0.59/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=119) and Northern Ireland (SMR=72) respectively. The variation in the observed mortality rates between the different regions within the UK is not statistically significant ($p=0.7$).

Up to the end of the first quarter of 2010, 172 cases of definite or probable vCJD had been identified in the UK (117 definite, 51 probable who did not undergo post mortem and 4 probable cases still alive). 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 152 clinically affected definite and probable cases of vCJD with available genetic analysis have been methionine homozygotes. Analysis of vCJD diagnoses and deaths from January 1994 to December 2009 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 (two of the positive specimens from VV individuals) 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.

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.

A study has been undertaken to investigate dental treatment as a possible risk factor for vCJD. The study (funded by the Department of Health, UK) attempted to trace and examine the dental records of 162 vCJD cases and 610 general population controls resident in England, Wales and Scotland. A report of the findings is currently being reviewed by the Department of Health and a paper is in preparation for publication.

The recently described form of prion disease termed Protease Sensitive Prionopathy is of uncertain nosological significance but is presently considered a form of sporadic prion disease, alongside sporadic CJD. The NCJDSU has identified a UK instance of this disease in 2008, a further case this year and is currently reviewing its archives to see if any more instances can be identified.

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 2009 (with data ascertained up to 31st May 2010). 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 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, 2008 and 2009 saw a rise in referrals of those aged ≥30 to the NCJDSU bringing totals to 147 for both years, closer to previous levels (Figure 1a).

The recent fall and rise is partly explained by changes in the number of non-CJD cases referred to the NCJDSU, particularly in those aged ≥30 which are now back to pre-2004 levels, as shown in Figure 1b. (The decline in vCJD cases is less likely to explain the reduction in referrals in those aged 30 years and older because this older age group contains more sporadic cases). The percentage of non-cases amongst referrals has altered, being around 50% in 2000, decreasing to around 18% by 2007 but with higher percentages around 30% in 2008 and 2009. The decrease in percentage is an indication of better knowledge in referring clinicians and improved diagnostic processes. The recent increase is of uncertain significance. The number of referrals who turn out to have definite/probable CJD appear also to be increasing towards pre-2004 levels. This would be consistent with year on year variation in referral and classification of suspect cases, particularly since the introduction of 14-3-3 as a routine test in 1999, having 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 2009: Age < 30 and age ≥ 30**

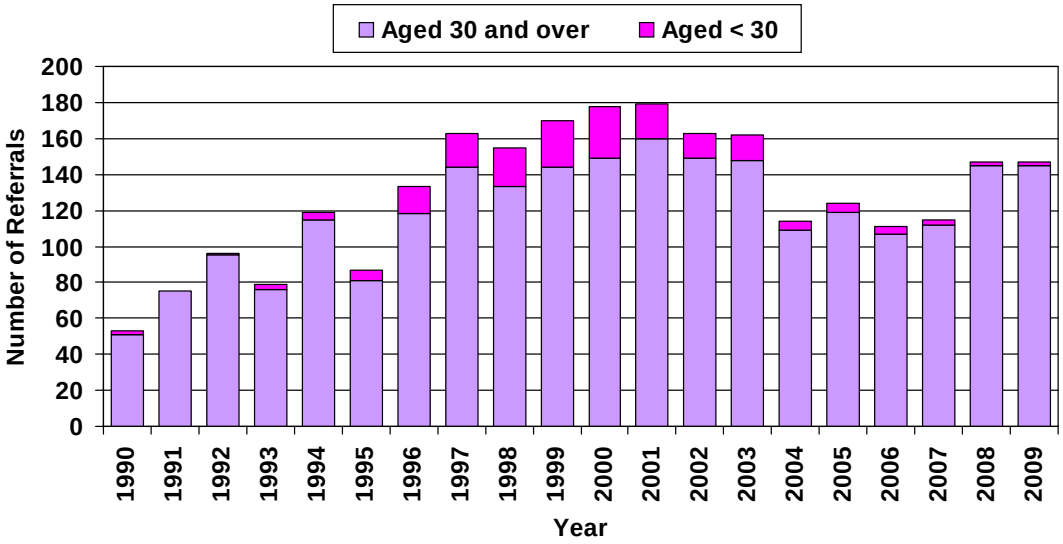
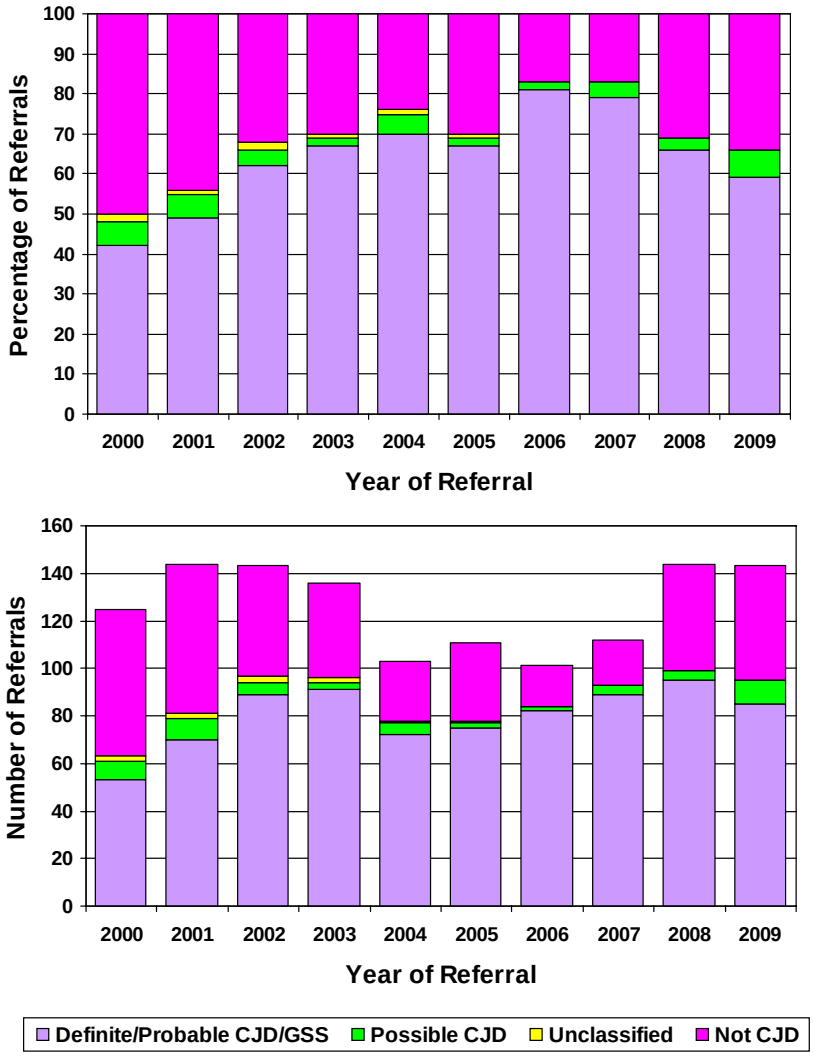


Figure 1b **Diagnostic classification of referrals: 2000-2009***
(shown as percentages and absolute numbers)



*excludes suspect vCJD referrals and vCJD cases

2.2 Sporadic Creutzfeldt-Jakob Disease

Between 1st January 1970 and 31st December 2009, 1536 cases of sporadic CJD were identified in the UK, of which 15 cases were alive on 31st December 2009. Three further cases were identified (2 in Jersey and one in the Isle of Man) but they are not included in the following UK analyses. Of these UK cases, 1128 (73%) 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 2009, Figure 2b shows similar data for England and Wales between 1970 and 2009 and Figure 2c shows the number of deaths from sporadic CJD in Scotland and Northern Ireland between 1985 and 2009.

Over the period 1990-2009 the average crude annual mortality rates from sporadic CJD per million population were 0.95 in England, 1.13 in Wales, 1.01 in Scotland and 0.59 in Northern Ireland (Tables 1a and 1b). 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 of cases of sporadic CJD (deaths and cases still alive as of 31st December 2009) 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 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, 1985-2009

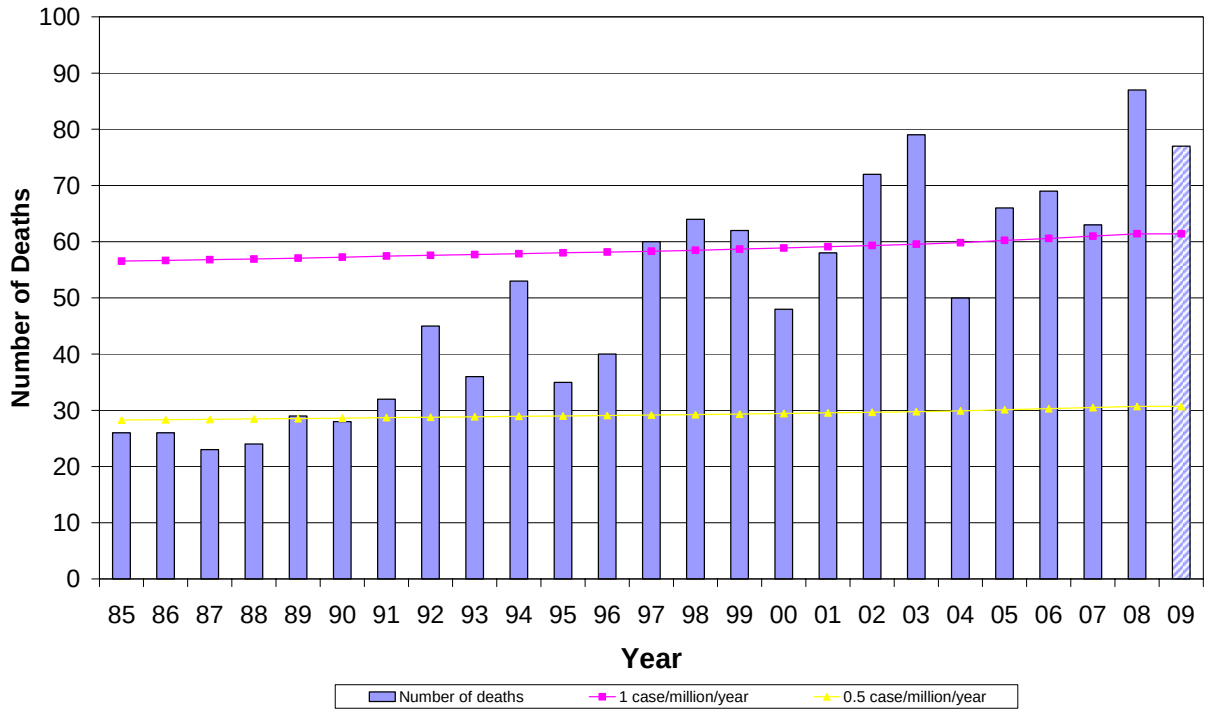


Figure 2b **Deaths from sporadic CJD, England and Wales, 1970-2009**

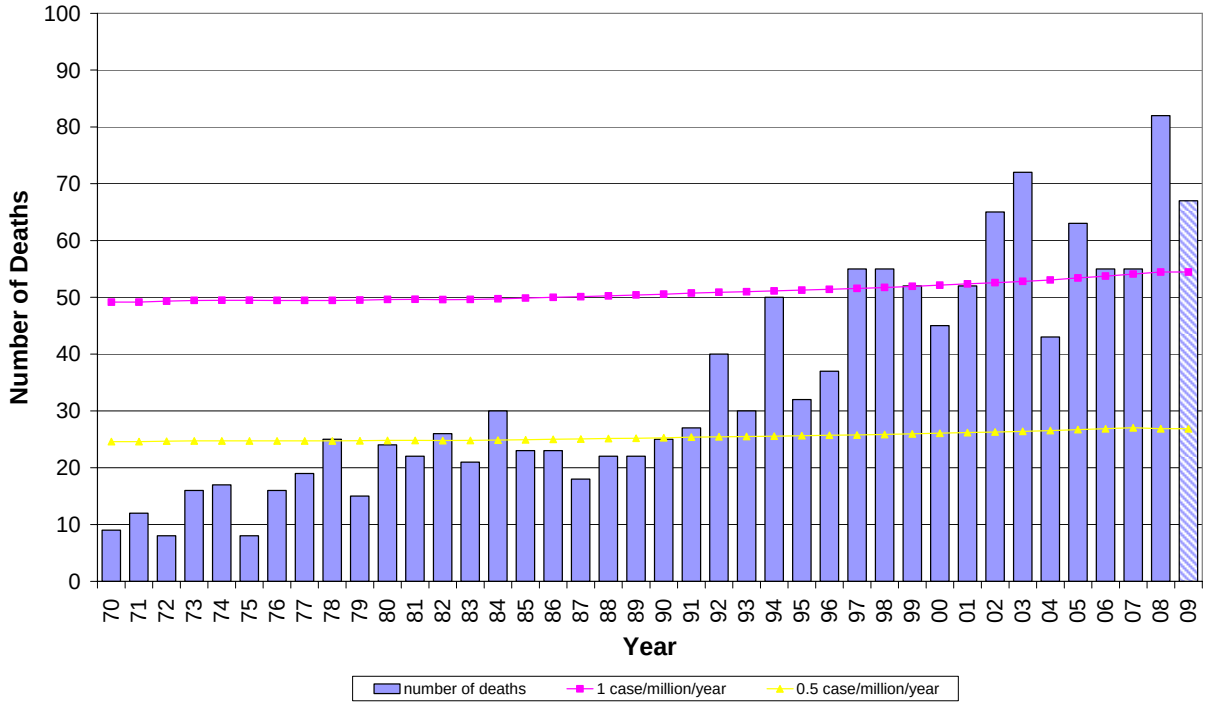


Figure 2c **Deaths from sporadic CJD, Scotland and Northern Ireland 1985-2009 (please note different scale from Figs 1a and 1b)**

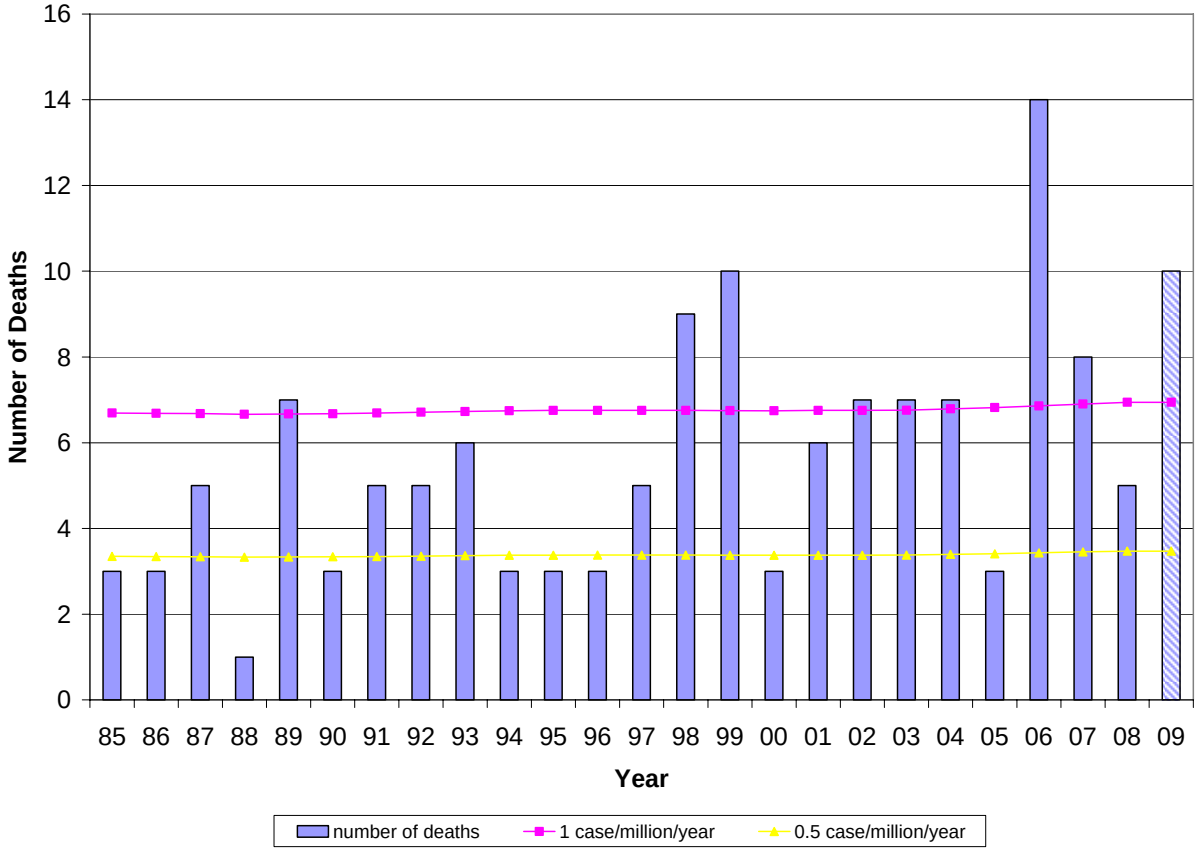


Table 1a Deaths from definite and probable sporadic CJD shown by region and local authority of residence at death: 1st January 1990 to 31st December 2009

ENGLAND	No. of cases	Mortality Rate*	ENGLAND	No. of cases	Mortality Rate*
North East	**43**	**0.85**	**East**	**115**	**1.06**
Darlington UA	2		Luton UA	2	
Hartlepool UA	3		Peterborough UA	1	
Middlesbrough UA	1		Southend-on-Sea UA	4	
Redcar & Cleveland UA	3		Thurrock UA	3	
Stockton-on-Tees UA	2		Bedfordshire	7	
Durham	6		Cambridgeshire	7	
Northumberland	7		Essex	36	
Tyne & Wear	19		Hertfordshire	18	
			Norfolk	18	
North West	**131**	**0.97**	Suffolk	19	
Blackburn with Darwen UA	5				
Blackpool UA	3		**London**	**114**	**0.78**
Halton UA	2		Inner London	37	
Warrington UA	5		Outer London	77	
Cheshire	10				
Cumbria	13		**South East**	**152**	**0.95**
Greater Manchester	38		Bracknell Forest UA	2	
Lancashire	25		Brighton and Hove UA	1	
Merseyside	30		Isle of Wight UA	3	
			Medway UA	2	
Yorkshire and the Humber	**96**	**0.96**	Milton Keynes UA	1	
East Riding of Yorkshire UA	4		Portsmouth UA	2	
Kingston Upon Hull, City of UA	4		Reading UA	2	
North East Lincolnshire UA	1		Slough UA	0	
North Lincolnshire UA	2		Southampton UA	2	
York UA	4		West Berkshire UA	4	
North Yorkshire	18		Windsor and Maidenhead UA	3	
South Yorkshire	29		Wokingham UA	3	
West Yorkshire	34		Buckinghamshire	5	
			East Sussex	11	
East Midlands	**68**	**0.81**	Hampshire	27	
Derby UA	4		Kent	25	
Leicester UA	4		Oxfordshire	15	
Nottingham UA	3		Surrey	19	
Rutland UA	0		West Sussex	25	
Derbyshire	15				
Leicestershire	14		**South West**	**126**	**1.27**
Lincolnshire	11		Bath & North East Somerset UA	3	
Northamptonshire	2		Bournemouth UA	7	
Nottinghamshire	15		Bristol, City of UA	10	
			North Somerset UA	7	
West Midlands	**91**	**0.86**	Plymouth UA	8	
Herefordshire, County of UA	3		Poole UA	3	
Stoke-on-Trent UA	1		South Gloucestershire UA	6	
Telford and Wrekin UA	1		Swindon UA	2	
Shropshire	4		Torbay UA	3	
Staffordshire	29		Cornwall and Isles of Scilly	14	
Warwickshire	7		Devon	14	
West Midlands (Met County)	36		Dorset	10	
Worcestershire	10		Gloucestershire	14	
			Somerset	16	
			Wiltshire	9	
TOTAL FOR ENGLAND	**936**	**0.95**			

* number of deaths/million/annum based on mid-2001 population estimates in England (source: ONS) over the 20-year period of the study. Postcode of residence obtained from AFD Postcode Plus.

Table 1b Deaths from definite and probable sporadic CJD: Wales, Scotland and NI 1st January 1990 to 31st December 2009

WALES†	No. of cases	WALES†	No. of cases
Isle of Anglesey	4	Neath Port Talbot	0
Gwynedd	5	The Vale of Glamorgan	3
Conwy	5	Cardiff	3
Denbighshire	1	Bridgend	2
Flintshire	1	Rhondda, Cynon, Taff	5
Wrexham	4	Merthyr Tydfil	1
Powys	6	Caerphilly	6
Ceredigion	3	Blaenau Gwent	0
Pembrokeshire	1	Torfaen	3
Carmarthenshire	2	Monmouthshire	2
Swansea	5	Newport	4
TOTAL FOR WALES (MORTALITY RATE*)	**66 (1.13)**	†unitary authorities	

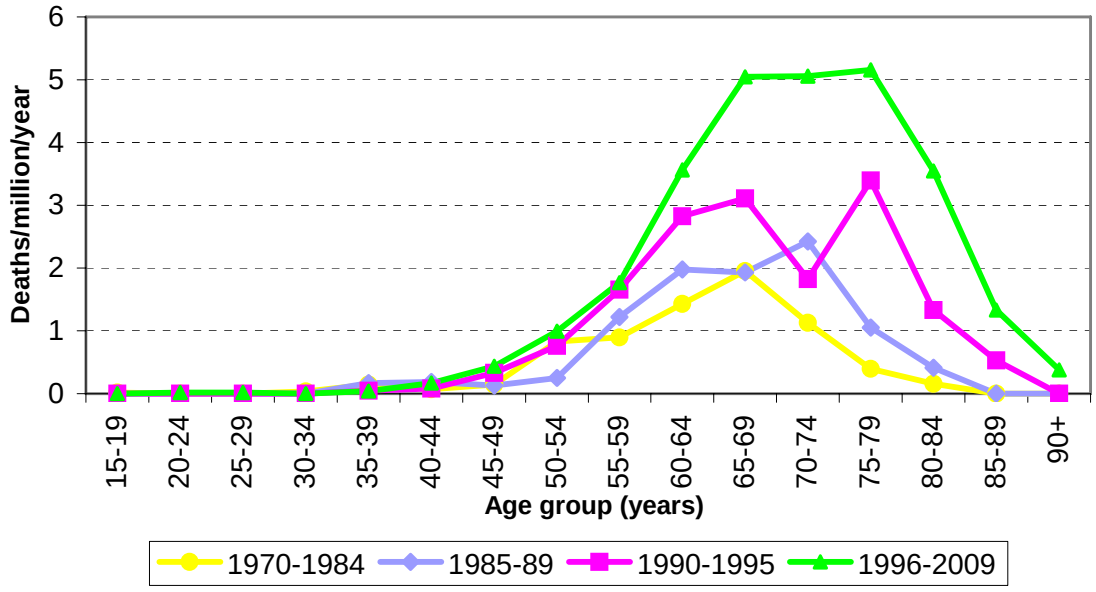
SCOTLAND†	No. of cases	SCOTLAND†	No. of cases
Aberdeen City	4	Highland	2
Aberdeenshire	7	Inverclyde	1
Angus	1	Midlothian	1
Argyll & Bute	2	Moray	1
Clackmannanshire	1	North Ayrshire	4
Dumfries & Galloway	2	North Lanarkshire	2
Dundee City	5	Orkney Islands	0
East Ayrshire	1	Perth & Kinross	0
East Dunbartonshire	3	Renfrewshire	4
East Lothian	3	Scottish Borders	3
East Renfrewshire	1	Shetland Islands	3
Edinburgh, City of	16	South Ayrshire	1
Eilean Siar	0	South Lanarkshire	6
Falkirk	3	Stirling	2
Fife	8	West Dunbartonshire	1
Glasgow City	10	West Lothian	4
TOTAL FOR SCOTLAND (MORTALITY RATE*)	**102 (1.01)**	†council areas	

NORTHERN IRELAND†	No. of cases	NORTHERN IRELAND†	No. of cases
Antrim	1	Down	2
Ards	1	Dungannon	0
Armagh	1	Fermanagh	0
Ballymena	0	Larne	1
Ballymoney	1	Limavady	0
Banbridge	1	Lisburn	3
Belfast	5	Magherafelt	0
Carrickfergus	0	Moyle	0
Castlereagh	0	Newry & Mourne	0
Coleraine	0	Newtownabbey	0
Cookstown	0	North Down	0
Craigavon	2	Omagh	1
Derry	1	Strabane	0
TOTAL FOR N IRELAND (MORTALITY RATE*)	**20 (0.59)**	†district council areas	

* based on mid-2001 population estimates for unitary authorities in Wales, council areas within Scotland and district council areas in Northern Ireland (ONS) over the 20-year period of the study. Postcode of residence obtained from AFD Postcode Plus.

Figure 3 shows average annual age-specific mortality rates over the time periods 1970-84, 1985-89, 1990-95 and 1996-09. The median ages of cases at death during these four time periods were 63, 65, 66 and 68 years, respectively. In all four time periods, the mortality rates below 40 years of age were extremely low (< 0.2/million/year). Thereafter, in all four 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.

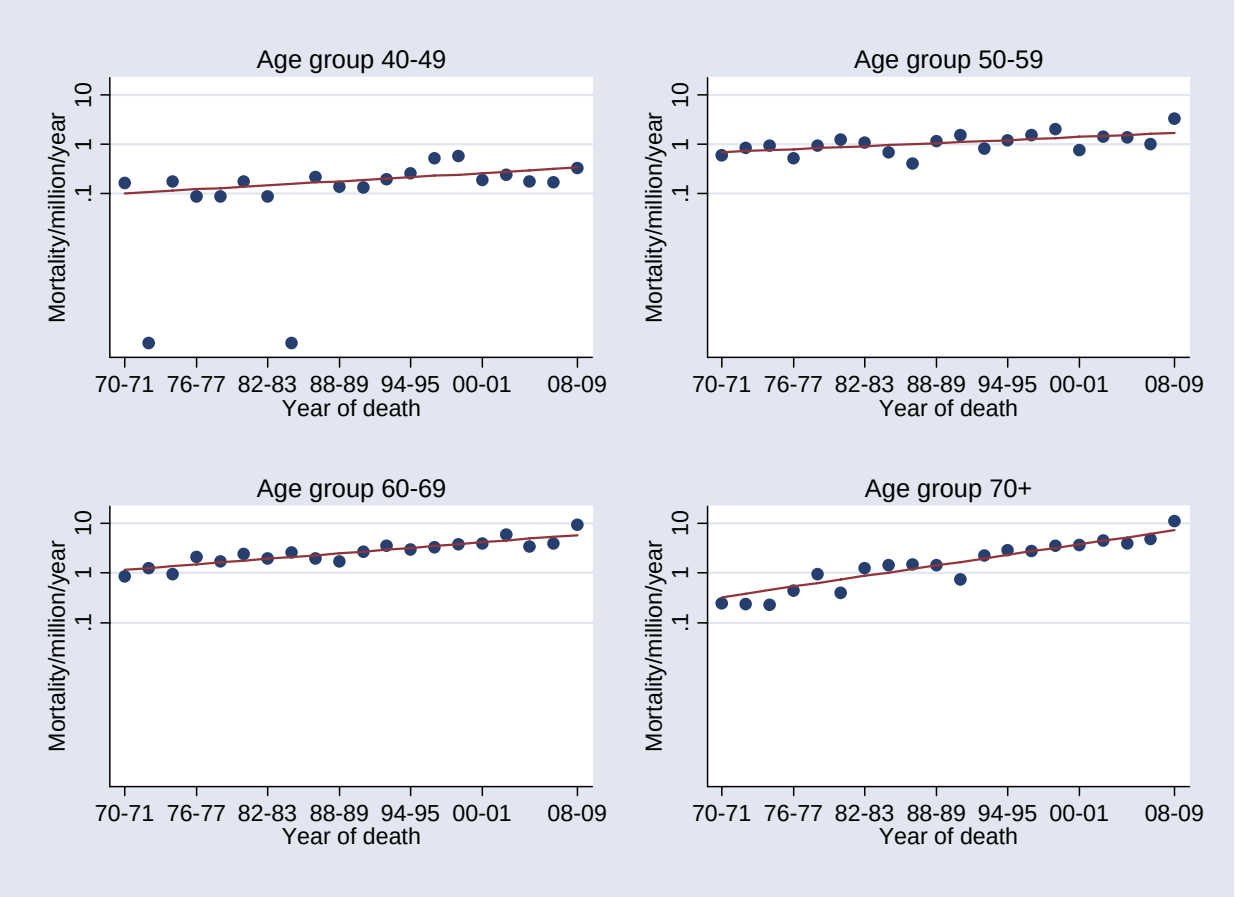
Figure 3 Age-specific mortality rates from sporadic CJD in the UK 1970-2009 (note: from 1970-1984 only England and Wales, thereafter UK)



1970-84 Mortality rates calculated using mid-1981 England and Wales population estimates based on the 1981 Census
1985-89 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
1996-09 Mortality rates calculated using mid- 2001 UK population estimates based on the 2001 Census

An analysis of age-specific trends from 1970 to 2009 (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 $p=0.014$, $p<0.001$, $p<0.001$, $p<0.001$ 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: 1970-2009



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

Table 2 presents the actual annual numbers of deaths (and number alive on 31 December 2009) from sporadic CJD (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	4	5	0	0	0	9
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	8	10	5	0	0	24
1989	0	0	0	1	6	10	10	2	0	29
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	22	19	6	1	64
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	0	0	1	0	9	30	37	10	0	87
2009[2]	0	0	0	3	15	28	26	5	0	77
Alive[3]	0	0	0	2	4	6	3	0	0	15
Total	1	2	15	58	285	620	457	96	2	1536

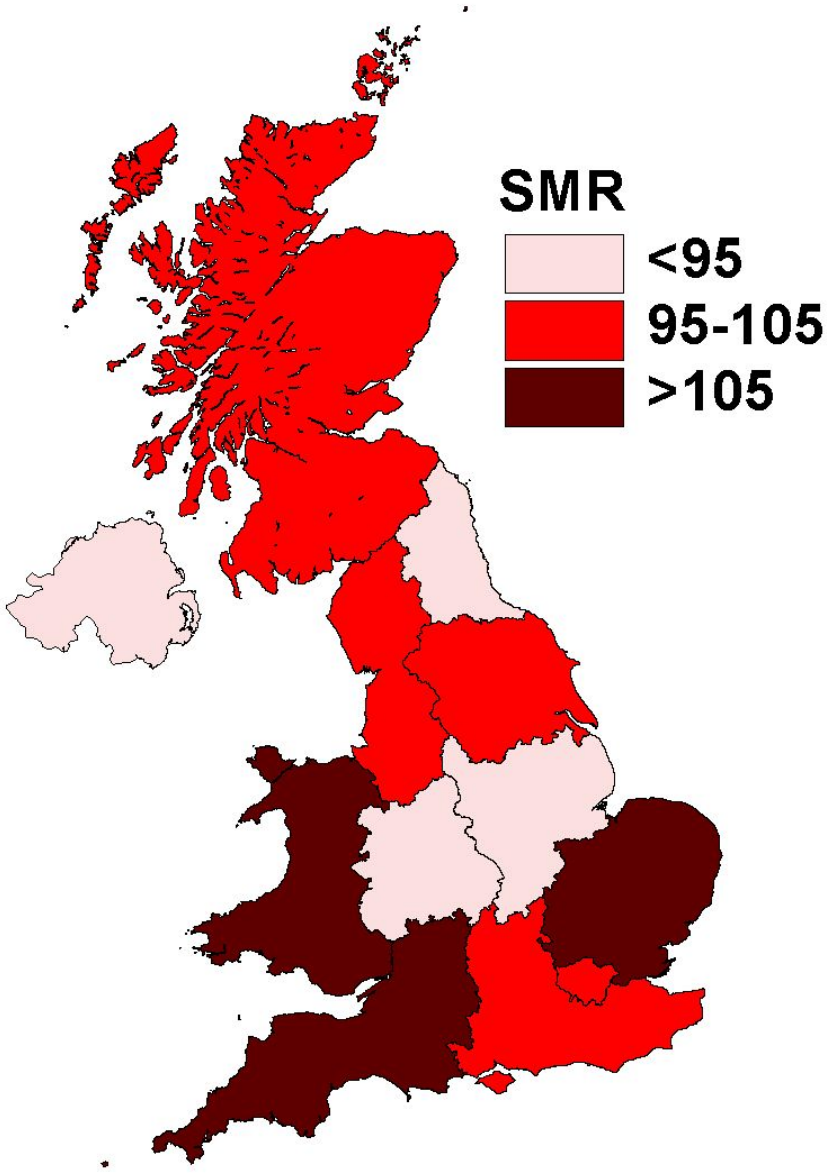
[1] Up to 1984, cases from England and Wales only. From 1985 onwards, cases from Scotland and Northern Ireland are included.

[2] Deaths to 31 December 2009. Data for 2009 not yet complete.

[3] Additional cases alive on 31st December 2009.

Age- and sex- standardised mortality ratios (SMRs) for the 12 government office regions of the UK for the period 1st January 1990 to 31st December 2009 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=0.7). Regions of relatively high mortality are South West (SMR=119), Wales (SMR=110) and East (SMR=108). Low mortality rates were observed in Northern Ireland (SMR=72), East Midlands (SMR=83) and North East (SMR=85). The highest SMR (119 in South West) arose from 126 cases observed compared with 106 expected, an excess of just over one case every year compared to the national average. For Wales and East, the total numbers of excess cases was approximately 4 and 2 respectively.

Figure 5 Standardised mortality ratios (SMRs) by standard region, UK 1 January 1990 - 31 December 2009

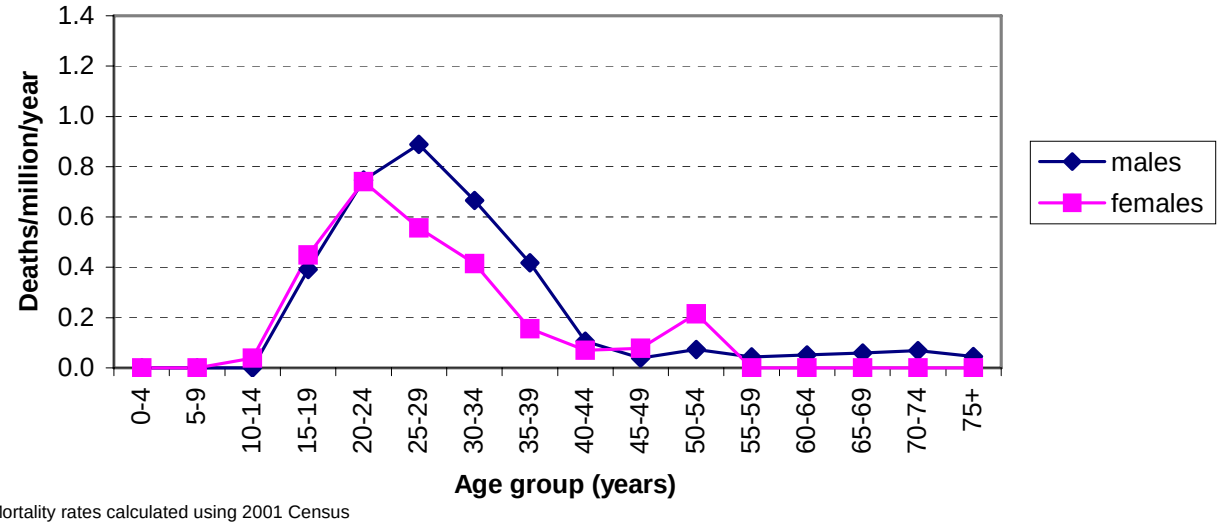


2.3 Variant Creutzfeldt-Jakob Disease

Up to the end of the first quarter of 2010, 172 cases of definite or probable vCJD had been identified in the UK (117 definite, 51 probable who did not undergo post mortem and 4 probable cases still alive). Seventy-three (44%) of the 172 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 2009 are shown in Figure 6. The median duration of illness from the onset of first symptoms to death was 14 months (range 6-84) compared with a median duration of illness for cases of sporadic CJD of 4 months (range 1 to 74) during the period 1990-2009.

All definite and probable cases of vCJD with genetic analysis have been *PRNP*-129 MM individuals (a single case of possible vCJD with an MV genotype was described in last year's report).

Figure 6 Age- and sex-specific mortality rates from vCJD in the UK 1 May 1995 - 31st December 2009



Mortality rates calculated using 2001 Census

Incidence of vCJD diagnoses and deaths

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[1] reviews the data to 31st December 2009 with data ascertained to the end of March 2010. This includes a case who was notified and died in 2009 but was not diagnosed until 2010.

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. The age at death has not increased as may have been expected, assuming that most exposure to BSE ceased in the early 1990s. In order to examine this further, the cases were stratified by year of death

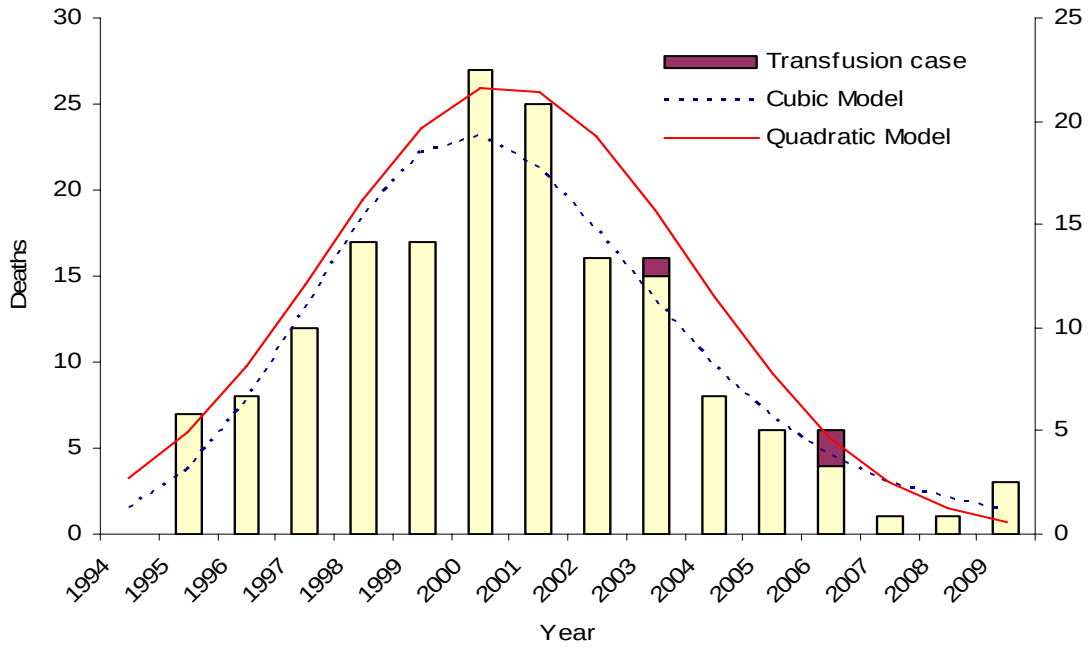
[1] Analysis (pp 14-17) undertaken by N J Andrews, Senior Statistician, Statistics Unit, Centre for Infections, Health Protection Agency

and birth cohort (pre 1970, 1970s and 1980s). Trends in deaths over time were compared between these cohorts.

Results for Diagnoses

A quadratic trend model provides a good fit to the data (Figure 7), however there was some evidence (p=0.04) that a cubic model, which would give a longer tail to the epidemic, fitted better. This is due to the somewhat greater than expected number of diagnoses in 2009. The peak is estimated to have occurred in mid 2000.

Figure 7: vCJD diagnoses by year with fitted quadratic and cubic trend lines



Prediction for diagnoses in 2010

Extrapolation of the model with the quadratic term predicts a total of less than one diagnosis in 2010 with a 95% prediction interval of 0 to 1. The cubic model gives an estimate of one diagnosis with 95% CI 0 to 3.

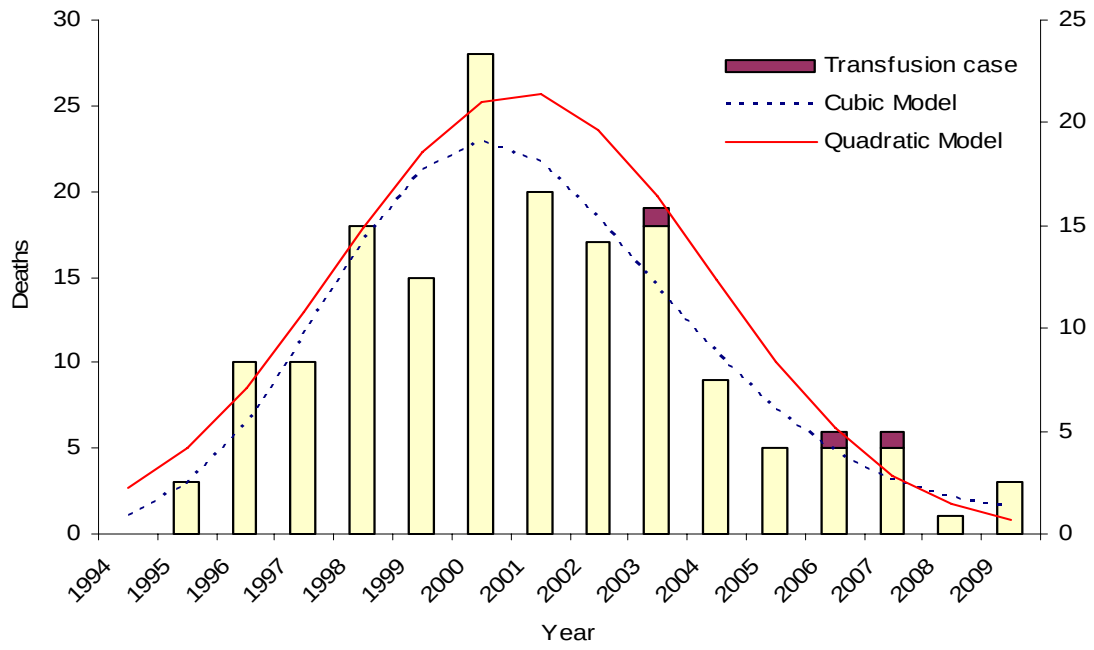
Assessment of Predictions made at the end of December 2008

The quadratic and cubic models gave a prediction of less than one diagnosis (95% prediction interval 0-2). The observed number of 3 was a little higher than predicted.

Results for Deaths

A quadratic trend model provides a good fit to the data (Figure 8), however there was some evidence (p=0.01) that a cubic model fitted better. This is due to the somewhat greater than expected number of deaths in 2009. The peak is estimated to have occurred in mid 2000.

Figure 8 vCJD deaths by year with fitted quadratic and cubic trend lines



Predictions for deaths in 2010

Extrapolation of the model with the quadratic term predicts a total of less than one death in 2010 with a 95% prediction interval of 0 to 1. The cubic model gives an estimate of one death with 95% CI 0 to 3.

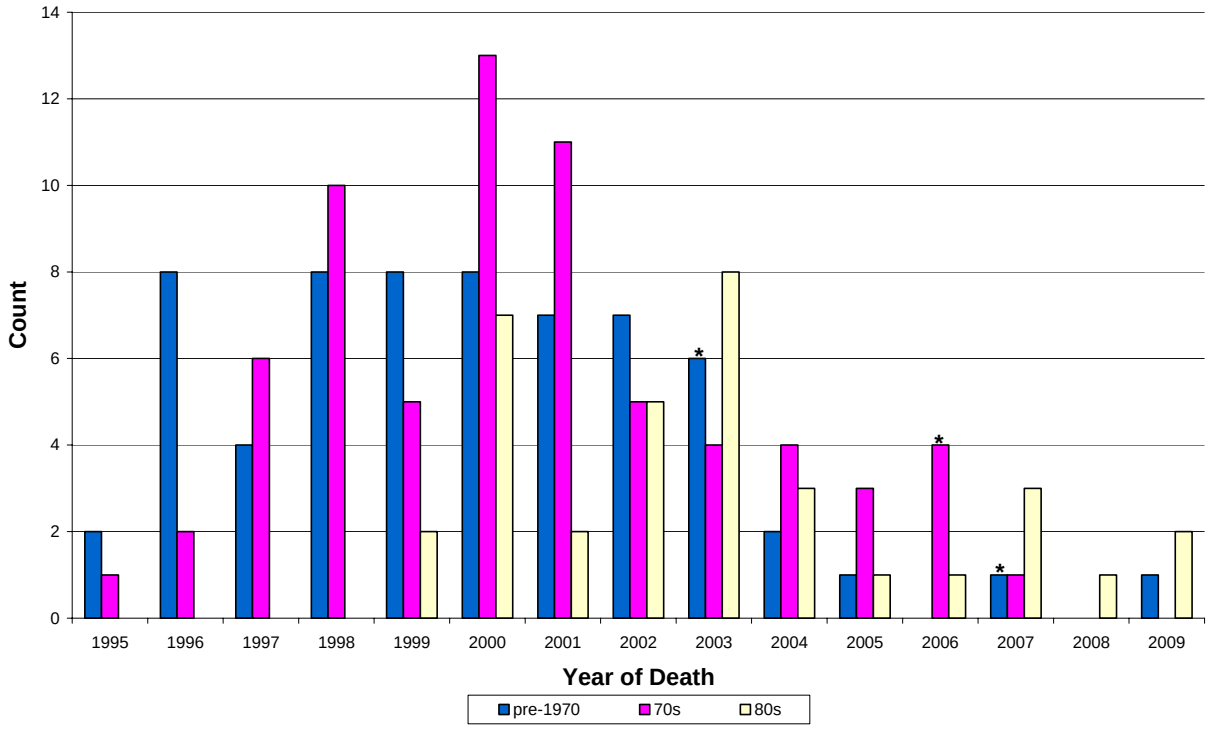
Assessment of Predictions made at the end of December 2008

The quadratic model gave a prediction of one death with a 95% prediction interval of 0 to 2. The cubic model gave a prediction of 1.4 deaths with a 95% prediction interval of 0 to 4. The actual observed number was 2, which is consistent with both models.

Deaths by birth cohort

The epidemic curves vary significantly ($p<0.001$) by birth cohort. 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 compatible with no cases having been seen to date in individuals born in the 1990s.

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 cubic model) gives an estimate of one death in 2010 (95% prediction interval 0 to 3).

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 subgroups. There is also the possibility of ongoing person to person spread as seen with 4 cases of transfusion association vCJD infection to date, 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 172 cases of vCJD in the UK. Cases have been widely spread throughout the UK. Tables 3a and 3b present data on the geographical distribution by residence at onset (for all 172 vCJD cases) and residence at death (for 164 vCJD cases who had died by 31st December 2009 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=172)

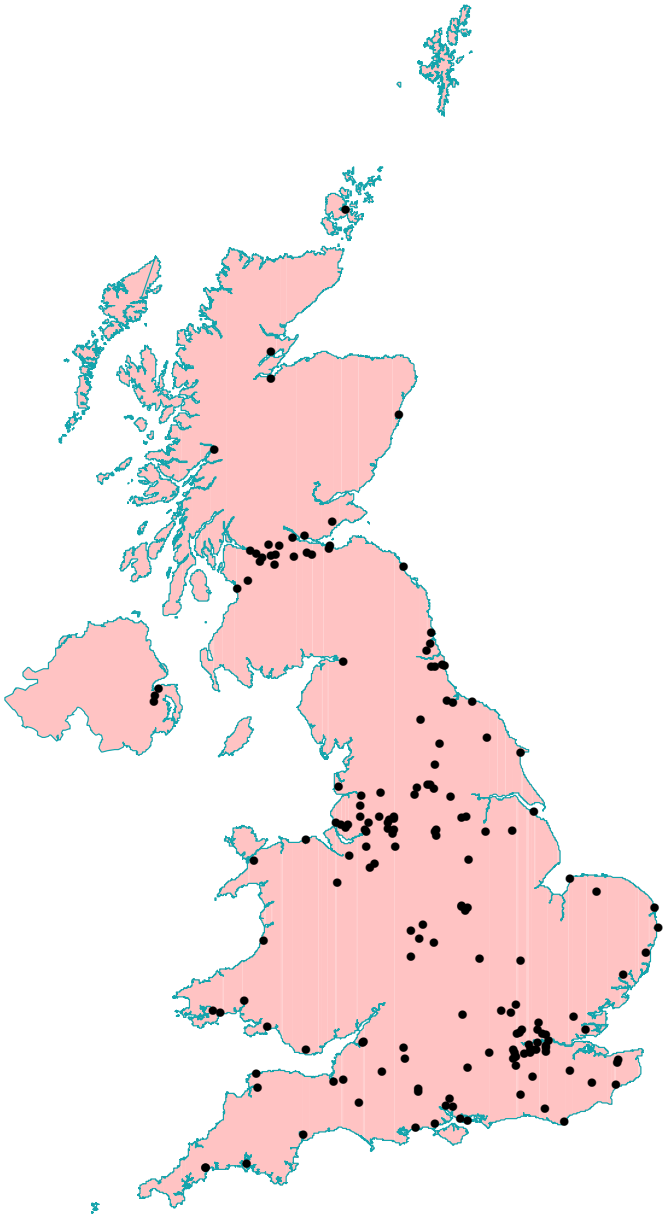


Table 3a Cases of definite and probable variant CJD shown by residence at onset (n=137†) and residence at death (n=134‡) in England (region and local authority)

	No. resident at onset	No. resident at death	Mortality rate*		No. resident at onset	No. resident at death	Mortality rate*
North East	**11**	**11**	**0.30**	**East**	**12**	**11**	**0.14**
Darlington UA	0	0		Luton UA	0	0	
Hartlepool UA	0	0		Peterborough UA	0	0	
Middlesbrough UA	1	1		Southend-on-Sea UA	1	1	
Redcar & Cleveland UA	1	1		Thurrock UA	0	0	
Stockton-on-Tees UA	1	1		Bedfordshire	0	0	
Durham	0	1		Cambridgeshire	1	1	
Northumberland	3	4		Essex	1	1	
Tyne & Wear	5	3		Hertfordshire	3	3	
				Norfolk	3	2	
North West	**26**	**26**	**0.26**	Suffolk	3	3	
Blackburn with Darwen UA	0	0					
Blackpool UA	1	1		**London**	**18**	**15**	**0.14**
Halton UA	0	0		Inner London	6	6	
Warrington UA	2	2		Outer London	12	9	
Cheshire	5	6					
Cumbria	1	1		**South East**	**23**	**20**	**0.17**
Greater Manchester	10	9		Bracknell Forest UA	1	1	
Lancashire	3	3		Brighton and Hove UA	0	0	
Merseyside	4	4		Isle of Wight UA	0	1	
				Medway UA	0	1	
Yorkshire and the Humber	**17**	**17**	**0.23**	Milton Keynes UA	0	0	
East Riding of Yorkshire UA	1	1		Portsmouth UA	1	2	
Kingston Upon Hull, UA	0	0		Reading UA	0	0	
North East Lincolnshire UA	1	1		Slough UA	0	0	
North Lincolnshire UA	0	0		Southampton UA	1	0	
York UA	0	0		West Berkshire UA	0	0	
North Yorkshire	4	3		Windsor & Maidenhead UA	0	0	
South Yorkshire	5	5		Wokingham UA	0	0	
West Yorkshire	6	7		Buckinghamshire	0	1	
				East Sussex	2	2	
East Midlands	**8**	**10**	**0.16**	Hampshire	5	2	
Derby UA	0	0		Kent	5	4	
Leicester UA	0	0		Oxfordshire	1	1	
Nottingham UA	0	0		Surrey	6	4	
Rutland UA	0	0		West Sussex	1	1	
Derbyshire	0	1					
Leicestershire	4	5		**South West**	**16**	**14**	**0.19**
Lincolnshire	2	2		Bath & NE Somerset UA	0	0	
Northamptonshire	1	1		Bournemouth UA	1	1	
Nottinghamshire	1	1		Bristol, City of UA	1	1	
				North Somerset UA	0	0	
West Midlands	**6**	**10**	**0.13**	Plymouth UA	0	0	
Herefordshire, County of UA	0	0		Poole UA	0	0	
Stoke-on-Trent UA	0	0		South Gloucestershire UA	1	0	
Telford and Wrekin UA	0	0		Swindon UA	0	0	
Shropshire	1	1		Torbay UA	0	1	
Staffordshire	0	0		Cornwall and Isles of Scilly	2	1	
Warwickshire	2	3		Devon	3	3	
West Midlands (Met County)	3	5		Dorset	0	0	
Worcestershire	0	1		Gloucestershire	0	0	
				Somerset	4	5	
				Wiltshire	4	2	
TOTAL FOR ENGLAND	**137**	**134**	**0.18**				

* number of deaths/million/annum based on mid 2001 population estimates (source: ONS): 1 May 1995 to 31 Dec 2009. Postcode of residence obtained from AFD Postcode Plus.

† includes cases alive at 31st Dec 2009 ‡ excludes 3 cases who died abroad.

Table 3b Cases of definite and probable variant CJD shown by residence at onset (n=35) and residence at death (n=30): Wales, Scotland and NI

WALES†	No. resident at onset	No. resident at death	WALES†	No. resident at onset	No. resident at death
Isle of Anglesey	0	0	Neath Port Talbot	0	0
Gwynedd	1	1	The Vale of Glamorgan	1	1
Conwy	0	0	Cardiff	0	0
Denbighshire	1	0	Bridgend	0	0
Flintshire	0	0	Rhondda, Cynon, Taff	0	0
Wrexham	0	0	Merthyr Tydfil	0	0
Powys	1	1	Caerphilly	0	0
Ceredigion	0	0	Blaenau Gwent	0	0
Pembrokeshire	2	2	Torfaen	0	0
Carmarthenshire	1	1	Monmouthshire	0	0
Swansea	1	0	Newport	0	0
TOTAL (MORTALITY RATE*)	**8**	**6 (0.14)**	†unitary authorities		

SCOTLAND†	No. resident at onset	No. resident at death	SCOTLAND†	No. resident at onset	No. resident at death
Aberdeen City	1	1	Highland	3	2
Aberdeenshire	0	0	Inverclyde	0	0
Angus	0	0	Midlothian	0	0
Argyll & Bute	0	0	Moray	0	0
Clackmannanshire	0	0	North Ayrshire	0	0
Dumfries & Galloway	0	0	North Lanarkshire	3	3
Dundee City	0	0	Orkney Islands	1	0
East Ayrshire	1	1	Perth & Kinross	0	0
East Dunbartonshire	1	1	Renfrewshire	1	1
East Lothian	0	0	Scottish Borders	0	0
East Renfrewshire	1	1	Shetland Islands	0	0
Edinburgh, City of	2	2	South Ayrshire	1	1
Eilean Siar	0	0	South Lanarkshire	1	1
Falkirk	1	1	Stirling	0	0
Fife	2	2	West Dunbartonshire	0	0
Glasgow, City of	3	3	West Lothian	2	2
TOTAL (MORTALITY RATE*)	**24**	**22 (0.30)**	†council areas		

N IRELAND†	No. resident at onset	No. resident at death	N IRELAND†	No. resident at onset	No. resident at death
Antrim	0	0	Down	0	0
Ards	0	0	Dungannon	0	0
Armagh	0	0	Fermanagh	0	0
Ballymena	0	0	Larne	0	0
Ballymoney	0	0	Limavady	0	0
Banbridge	0	0	Lisburn	1	1
Belfast	1	0	Magherafelt	0	0
Carrickfergus	0	0	Moyle	0	0
Castlereagh	0	0	Newry & Mourne	0	0
Coleraine	0	0	Newtownabbey	1	1
Cookstown	0	0	North Down	0	0
Craigavon	0	0	Omagh	0	0
Derry	0	0	Strabane	0	0
TOTAL (MORTALITY RATE*)	**3**	**2 (0.08)**	†district council areas		

* number of deaths/million/annum based on mid-2001 population estimates (source: ONS): 1 May 1995-31 Dec 2009. Postcode of residence obtained from AFD Postcode Plus.

Age- and sex- standardised incidence ratios (SIRs) based on cases' place of residence in 1991 (shortly after the time when exposure to the BSE agent is assumed to have peaked) are shown in Figure 11 for the 11 standard regions of the UK.

Figure 11 Standardised incidence ratios (SIRs) up to 31st December 2009 of vCJD by standard region on 1st January 1991

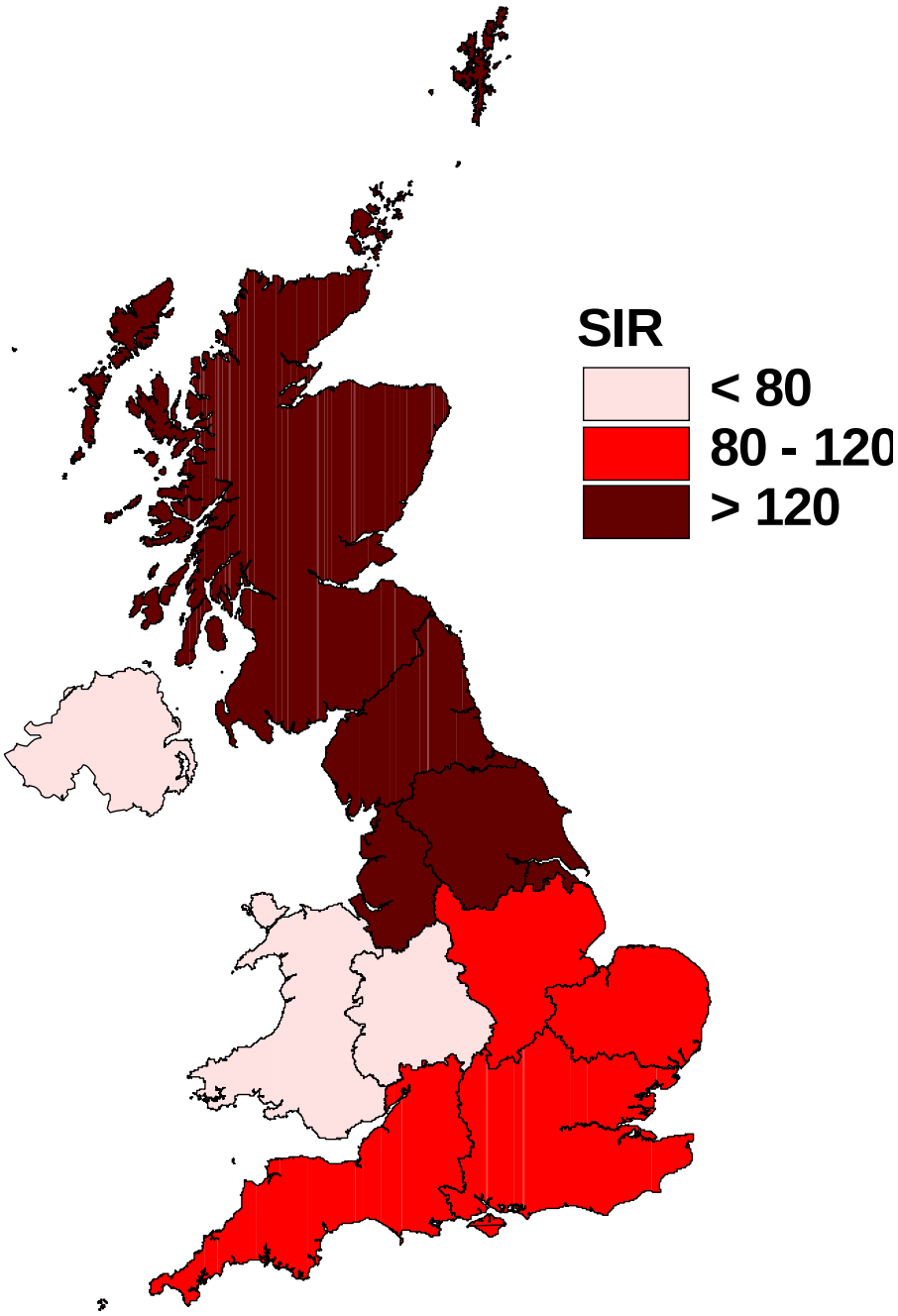


Table 4 shows the distribution of cases between the "North" and the "South" according to place of residence in 1991. We originally performed an analysis of the first 51 cases, distinguishing two areas. The "North" comprised four standard regions: Scotland, North, Yorkshire and Humberside, North West. 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 1.44 (95% c.i., 1.06, 1.95), 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[2]. This relatively high incidence of cases of 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 4 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)	96 (3.08)
Total (rate ratio*)	47.8 million	51 (1.94)	169 (1.44)

*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=0.7), 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. Because of the low number of new cases, none have been undertaken since 2006. 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

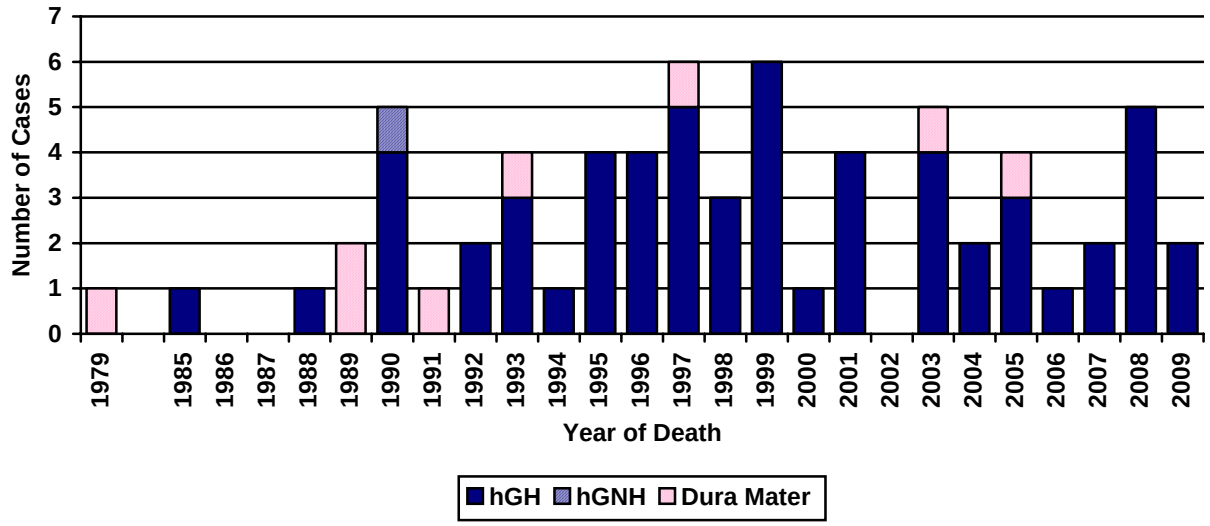
[2] Cousens S, Smith PG, Ward H, Everington D, Knight RSG, Zeidler M, Stewart G, Smith-Bathgate EAB, Macleod MA, Mackenize J, Will RG. Geographical distribution of variant Creutzfeldt-Jakob disease in Great Britain, 1994-2000. Lancet 2001; 357: 1002-1007.

the relevant time period. A paper describing this study has recently been published in collaboration with the Health Protection Agency[3]

2.4 Iatrogenic Creutzfeldt-Jakob disease

Since 1970, up to 31st December 2009, 69 cases of CJD attributable to iatrogenic exposure have been identified, 8 in individuals receiving dura mater implants, 60 in individuals who had received human-derived growth hormone (hGH) and one in a recipient of human gonadotrophin (hGN). Sixty-seven of these individuals have died (Figure 12) and 2 were still alive as at 31st December 2009.

Figure 12 Deaths from iatrogenic CJD, 1979-2009



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.[4]

A study of the accumulated UK experience with dura mater-related CJD, including incubation periods, was undertaken and the results published in 2006.[5]

[3] Molesworth AM, Cousens SN, Gill ON, Ward HJT on behalf of the local investigation teams. Variant Creutzfeldt-Jakob disease in the United Kingdom: a countrywide or local risk? J Epid Comm Health 2010; 64: 616-621.

[4] 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.

[5] 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.

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 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[6]. 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[7]; 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[8]. 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[9].

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6 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.

7 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.

8 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.

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

In the reverse study, 15 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 15 cases, one was not transfused, 4 had transfusions which pre-dated available records (pre-1980), and 10 had records of transfusion which could be traced. These 10 individuals had received 209 donor exposures (with one patient given 103 components), which have been traced to 192 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).

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 and one geneticist which allocates the cases to a diagnostic category [10-11].

As of 31st December 2009, after nearly 13 years surveillance, 2833 patients with suspected PIND had been reported and the Expert Group had discussed 1898 of these. 1164 cases had a confirmed underlying cause other than vCJD, being categorised into over 120 known neurodegenerative diseases[3]. 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)

[10] 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.

[11] 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.

3. Verity C, Winstone AM, Stellitano L, Will R, Nicoll, A. The epidemiology of progressive intellectual and neurological deterioration in childhood. Arch Dis Child 2010; 95:361-364

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. 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 including hospital controls (1990-1997), general medical practice community controls (1998-2002), general population community controls (2002-2003) and friend nominated controls (2003-2006), further details of which are detailed in Annual Report 2006[12]. The general population community 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[13]

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[13]. 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

[12] National CJD Surveillance Unit 15th Annual Report, 2006. National CJD Surveillance Unit, Edinburgh, 2007.
[13] 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.

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[14]. 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.

In the light of the decline in the number of new vCJD cases observed since 2000, recruitment of controls ceased at the end of 2006; funding for the core case-control study ceased in May 2008, having been funded since 1998 by 3 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 primary care records (see section "On-going analyses" below). *Ad hoc* studies that may require extra funding have been and will continue to be undertaken as necessary (for example see section "Dental Study" below). If in the future it is thought necessary, funding will be sought to recruit further controls.

On going analyses

Analysis of primary care records

The aim of this study is to investigate the possibility of secondary transmission of CJD through medical procedures, using data acquired directly from the primary care records of both cases and general population controls. 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 after the death of a case is 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. Analysis has commenced comparing them with medical data from vCJD cases; a similar analysis will be considered for sCJD in the future.

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

Dental study

The present study was funded by Department of Health to investigate dental treatment as a possible risk factor for vCJD using data acquired directly from the examination by dental professionals of dental records of cases and general population controls. The tracing of dental records was completed in 2009. We attempted to trace and examine the dental records of 162 vCJD cases and 610 general population controls resident in England, Wales and Scotland with the assistance of general dental practitioners and the NHS Dental Practice Boards. Data have been examined to determine if two or more cases had dental treatment at the same practice within a similar time-frame, with statistical analysis to determine if there is evidence of an association between dental treatment and vCJD. A report of the findings is currently being reviewed by the Department of Health and a paper is in preparation for publication.

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, with most of the cases investigated referred from other centres across the UK (see Table 5). 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 numbers of cases and autopsy rate for vCJD have declined in the UK, the latter in keeping with national trends, with one case being examined in 2009. A referred case of vCJD from Europe was also examined and the diagnosis confirmed. Despite this trend, the autopsy rate for sCJD has been maintained, with one more case being submitted for examination in 2009 than in the preceding year. This year, another case of protease-sensitive prionopathy was identified on neuropathological and biochemical grounds, representing the second such case identified in the UK. A significant number of cases submitted for examination were given an alternative neuropathological diagnosis, details of which are in Table 5. This referral pattern has not changed significantly over the past year.

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 5). The laboratory is also involved in a series of international collaborative studies in relation to neuropathological diagnosis of CJD and other human prion diseases.

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 5 Breakdown of Laboratory Activities: Period 1st January 2008– 31st December 2009

	CURRENT YEAR	PREVIOUS YEAR
REFERRED CASES (UK)		
Sporadic CJD	29	28
Familial CJD	0	2
Variant CJD	1	0
Iatrogenic CJD (GHT)	0	0
Iatrogenic CJD (Lyodura)	0	0
Gerstmann-Straussler-Scheinker Syndrome	0	0
Fatal Familial Insomnia	0	0
No evidence of CJD (no alternative pathological diagnosis)	11	26
Alzheimer's disease	4	1
Dementia with Lewy Bodies	3	1
Motor neurone disease	2	0
Other forms of brain disease†	10	4
REFERRED CASES (EU)		
Sporadic CJD	6	2
Familial CJD	1	1
Variant CJD	1	0
GSS	0	0
Other forms of brain disease	4	6
REFERRED CASES (ROW)		
Sporadic CJD	1	2
Variant CJD	0	0
Familial CJD	1	0
Other forms of brain disease	0	0
UK PRION SCREENING STUDIES		
Haemophilia cases - UKHCDO	1	3
Primary immunodeficiency cases – PIDSUK	9	7
Blood product recipient cases	0	0
OTHER REFERRALS AND STUDIES		
Animal studies	9	2
European Collaborative Study	3	0
TOTAL NUMBER OF CASES	**96**	**85**

† Other :

Alzheimer pathology + arteriosclerosis	1	Frontotemporal Lobar Degeneration	1
Cerebral oedema + Gliosis	1	Cerebrovascular Disease	1
Cerebral Hypoxia	1	Intravascular B Cell Lymphoma	1
Cerebellar Atrophy (SCA)	1	Malignant Melanoma	1
Meningioencephalitis	1	Multiple Sclerosis and Frontotemporal Lobar Degeneration	1

Abbreviations:

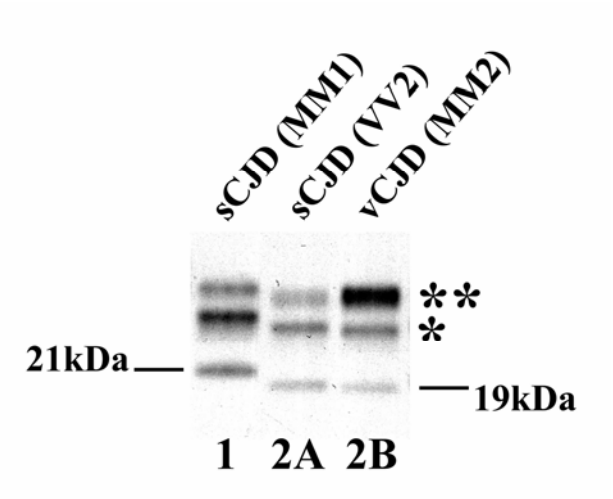
GHT Growth Hormone Therapy
EU European Union
ROW Rest of World

4.2 Prion Protein Laboratory

Prion protein detection and typing

Prion protein typing is carried out as a routine diagnostic test on all suspected cases of CJD from which frozen brain tissue is received by the NCJDSU. Small quantities of cerebral cortex or cerebellum are homogenised, treated with protease and the size and relative abundance of the three PrP^{res} glycoforms determined by Western blot analysis. The prion protein isotype 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} type 2 in which 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 variant CJD. A typical result is shown in Figure 13. 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).

UK Referrals

A total of 39 UK cases with frozen tissue were received and analysed in 2009, representing an increase 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 6 Breakdown of cases analysed in 2009

Diagnosis	Type	PrP^{res} +ve CNS
CJD (n=27)	Sporadic	27/27[1]
Alternative final diagnosis or not determined		0/12[2]

[1] includes one case in which a suboptimal (desiccated) tissue sample was received.
[2] includes one brain biopsy specimen

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

Table 7 PrP^{res} type / *PRNP* genotype breakdown of CJD cases analysed in 2009

Diagnosis	*PRNP* genotype	Type 1	Type 2A	Type 1+2	<10 kDa
Sporadic CJD (n=27)	M/M	14[1,2]	5	-	-
	M/V	1	3	1[3]	1[4]
	V/V	-	2	-	-

1 includes one case in which a suboptimal (desiccated) tissue sample was received
2 includes one case with the panencephalopathic variant of sporadic CJD
3 A case with PrP^{res} type 2A in the cerebral cortex and type 1 in the cerebellum
4 A case with a neuropathological and biochemical phenotype consistent with a diagnosis of PSPr (manuscript in preparation)

Non-UK referrals

Western blot analysis was performed on frozen tissue from four non-UK cases. There were three referrals from Sweden and all three were found to be cases of sporadic CJD (one of the VV1 and two of the MM2 subtypes). The fourth non-UK referral was a case of variant CJD (PrP^{res} type 2B) from the Netherlands.

European collaborative study

As part of an ongoing collaborative study with the Dutch Surveillance Centre for Prion Diseases, three further non-UK cases were examined by Western blotting. The first was found to be a case of PSPr showing the characteristic <10kDa PrP^{res} fragments (Jansen et al, DOI:10.1136/jnnp.2009.175646). The second two cases were siblings from a Dutch family with a novel 7-OPRI mutation who were found to have type 1 PrP^{res} and an inconsistent presence of <10kDa PrP^{res} fragments (Jansen et al, Acta Neuropathol. DOI:10.1007/s00401-010-0656-3).

4.3 Brain banking activities

The bank of fixed and frozen tissues in the Surveillance Unit was used extensively in 2009 for diagnostic and collaborative research purposes with colleagues in the UK and overseas. Funding from MRC was renewed in 2009 to support the activities of the Bank for a further 2 years. The Bank is a member of the MRC Network of UK Brain Banks, under the Directorship of Professor JW Ironside. This network will strengthen banking activities and ensure uniform high standards of operation. The Bank has a website, on which further details are available including instructions on how to request tissue samples for research (http://www.edinburghbrainbanks.ed.ac.uk/CJD/indexcjd.htm). The activities of the Bank comply with current guidelines from the Royal College of Pathologists, the Human Tissue (Scotland) Act 2006 and the Human Tissue Act 2004.

4.4 Molecular Genetics

Familial CJD

One hundred and four 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 104 cases, 93 were resident in England, 8 were resident in Wales, 2 were resident in Northern Ireland and one was resident in Scotland. Nineteen cases were still

alive as at 31st December 2009. Fifty-three of the cases had insertions in the coding region of the PrP gene, 29 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 2 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 8). There appears to be evidence (p=0.005) of a change in the *PRNP* codon 129 distribution in sporadic CJD between the periods 1990-1995 and 1996-2009. 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 8 *PRNP* codon 129 genotypes of cases of sporadic CJD in the UK, 1990-2009

Deaths from sporadic CJD	**MM(%)**	**MV(%)**	**VV(%)**
Deaths from 1 January 1990 – 31 December 1995	100 (75)	16 (12)	17 (13)
Deaths from 1 January 1996 – 31 December 2009	340 (60)	116 (21)	110 (19)
Total	440 (63)	132 (19)	127 (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=154, 90%) 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 355 cerebrospinal fluid (CSF) samples from January 2009–December 2009, from patients residing in the United Kingdom (UK) and from patients in non-UK countries. Seventeen samples were blood-stained and as such unsuitable for analysis. The origin and numbers of these samples are given in Table 9.

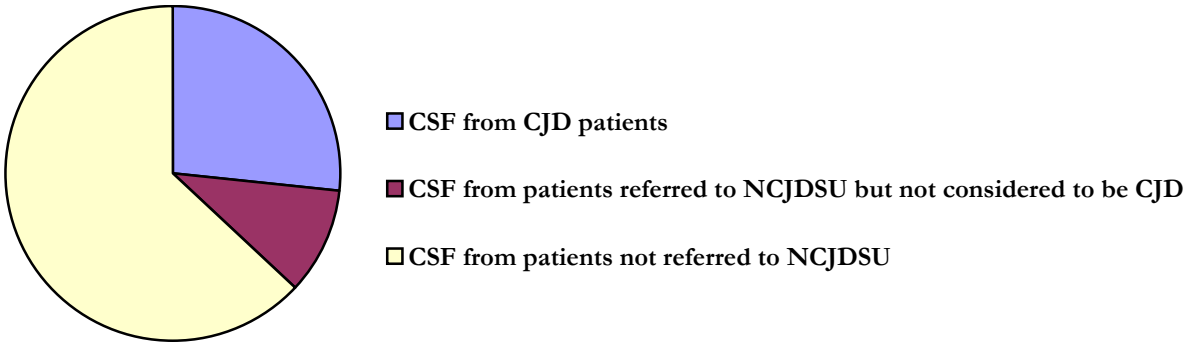
Table 9 Origin of CSF samples sent to the National CJD Surveillance unit (NCJDSU) for CSF 14-3-3 analysis from January 2009-December 2009

Origin of CSF samples	Total number CSF samples (%)
CSF from UK patients	301*
CSF from non-UK countries	54**
Total number	355

* Thirteen and **4 CSF samples were blood-stained and as such unsuitable for analysis

Of the 288 analysable CSF samples received from patients within the United Kingdom, 106 samples were from patients who were finally referred to the National CJD Surveillance Unit (NCJDSU) as a suspected case of CJD. Of these, 77 patients were finally diagnosed as having definite, probable or possible CJD (Table 10), whilst the remaining 29 were diagnosed as not having CJD. The remaining 182 CSF samples were sent to the National CJD Surveillance Unit for the analysis of CSF 14-3-3 and S-100b but in none of these cases did the requesting clinician refer the patient to the NCJDSU as a suspected case of CJD. Many requests for CSF 14-3-3 and S-100b analysis are on patients where the clinical suspicion of CJD is low and the request is made to exclude the diagnosis. However, if a CSF 14-3-3 request is made for a patient where CJD is reasonably suspected the referring clinician is encouraged to formally refer the patient to the NCJDSU.

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



The final diagnosis of the 77 patients referred to the NCJDSU who were diagnosed with some form of CJD is given in Table 10.

Table 10 CSF 14-3-3 results in patients diagnosed with CJD

Diagnosis	Number of cases	Number of positive CSF 14-3-3
Definite sporadic CJD	23	22
Probable sporadic CJD	40	39
Possible sporadic CJD	7	2
Definite variant CJD	1	1
Probable variant CJD	3*	1
Definite Familial CJD	1 (E200K mutation)	1
Probable Familial CJD	1 (E200K mutation)	1
Probable Iatrogenic CJD	1**	1

* One CSF sample was obtained from a single patient with variant CJD undergoing therapeutic intervention.
** Secondary to administration of human cadaveric growth hormone.

Of the patients with probable sCJD, 20 died without undergoing a post-mortem, 8 have died and neuropathological confirmation of sCJD is awaited. Of the remaining 12 patients, 6 have died and it is unclear whether a post-mortem has been performed and 6 patients are still alive. Of the 20 patients who died without post-mortem examination, 5 had EEG traces that were considered typical for sCJD whilst 14 had EEG traces that were not considered typical. For one patient, only a photocopy of the EEG was available and this was not of sufficient quality to be used for classification. Therefore 15 of the 20 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 182 CSF samples sent from patients who were not formally referred to the NCJDSU, 25 had a positive CSF 14-3-3. In 23 of these patients an alternative diagnosis was identified and these are shown in Table 11. The diagnosis in the remaining 2 cases is unknown but CJD was considered unlikely by the requesting clinicians on clinical grounds or in light of the results of other investigations.

Table 11 The diagnosis in those patients with CSF analysis (but not referred as suspect cases in the surveillance system,) 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
Encephalitis/encephalopathy	6
Paraneoplastic syndrome	4
Lewy body dementia	2
Seizures	2
Stroke/vascular disease	2
Fronto-temporal dementia	2
CNS malignancy	2
Clinically not CJD	1
Multiple Sclerosis	1
No evidence CJD on brain biopsy	1

A prospective audit of CSF 14-3-3 analysis showed that the mean time from lumbar puncture to the NCJDSU receiving CSF samples for 14-3-3 analysis is 4.0 ± 1.5 working days. Many clinicians wish to have the results of the routine CSF analysis before deciding whether to proceed with CSF

14-3-3 analysis and this accounts for the longer time taken for some samples to be received by the NCJDSU. The mean time from receipt of CSF samples at NCJDSU to the final report being issued is 3.0 ± 2.5 working days. All requests for CSF 14-3-3 analysis are discussed with the clinical staff at the NCJDSU within 3 days and the clinical team contact the requesting clinician if the clinical details given are suggestive of CJD.

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 order to optimise 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 professionals. The coordinators provide valuable expertise in nursing patients with CJD and can anticipate and prevent some problems that may arise. By offering skilled advice and education the care team enables local teams to provide high standards of care and continues to be involved on as long as needed. Now that there are two care coordinators, 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 preferred by families and other professionals involved. Post bereavement support is offered to the family after the patient dies and assistance is given in 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 provides funding 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 forms of CJD. Health and social services provide the basic elements of the individual patient's care package. The Care package for patients varies according to the individual's needs and it is essential that care packages are flexible. The aim is to provide a package that will provide the appropriate level of care both for the patient and their family.

In addition to collaborations with national organisations in the United Kingdom, the Care Team liaise closely with international organisations, including 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 2009, the care team have been in contact with, and/or provided access to care funds, to 92 variant CJD cases, 220 sporadic CJD cases, 55 familial cases and 16 iatrogenic cases.

The National Care Coordinators undertook 266 patient visits and case conferences during 2009 (Table 12).

Table 12 Patient Visits, Case Conferences and Teaching Sessions 1st January to 31st December 2009

Month	Cases Alive	Cases in contact with	Case Conferences/ Visits/Teaching Sessions
January	71	23	24
February	66	20	26
March	63	25	24
April	57	23	23
May	54	23	15
June	51	23	35
July	50	29	23
August	49	23	16
September	51	29	18
October	54	27	20
November	48	23	27
December	49	29	15

Expenditure from the National CJD Care Fund during 2009 was £212,841.97 (Table 13) bringing the overall expenditure of the Care Fund since 2000 to £2,777,253.60.

Table 13 Care Fund Payments 1st January to 31st December 2009

Adaptations	£8367.66
Alternative Therapy	£3650.42
Car Hire	£66,488.80
Counselling	£200.00
Equipment	£23,630.05
Nursing	£104,304.04
Physiotherapy	£3856.00
Social Care	£1525.00
Transport	£720.00
TOTAL	**£212,741.97**

Section

6

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Section

7

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