21<sup>st</sup> ANNUAL REPORT 2012

## CREUTZFELDT-JAKOB DISEASE SURVEILLANCE IN THE UK

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www.cjd.ed.ac.uk

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## SUMMARY

he national surveillance programme for Creutzfeldt-Jakob disease (CJD) in the UK was initiated in May 1990. In 1999, the National CJD Research & Surveillance Unit (NCJDRSU) 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 in response to concerns regarding the care of CJD patients. The team currently comprises two care coordinators (who are senior nurses) with secretarial and clinical neurological support from within the NCJDRSU where it is based.

The information provided in this 21<sup>st</sup> Annual Report continues to indicate that the number of sporadic cases remains relatively stable (the data for 2012 may still be incomplete). Detailed clinical and epidemiological information has been obtained for the great majority of patients. Although the general autopsy rate in the UK is low, it remains relatively high in suspected cases of CJD (being around 60% of all referred cases to the NCJDRSU). The number of brain specimens examined for sporadic CJD in the neuropathology laboratory in 2012 was 30 (compared with 36 in 2011).

In 1990-2012 average annual mortality rates from sporadic CJD in England, Wales, Scotland and Northern Ireland were, respectively, 1.01, 1.21, 1.05 and 0.77/million/year. The differences between these rates are not statistically significant (p=0.7). 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.

Up to 31<sup>st</sup> December 2012, 176 cases of definite or probable vCJD had been identified in the UK (122 definite and 54 probable who did not undergo post mortem). All 176 cases have died. 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 159 clinically affected definite and probable cases of vCJD with available genetic analysis have been methionine homozygotes. Analysis of vCID diagnoses and deaths from January 1994 to December 2011 indicates that a peak has passed. While this is an encouraging finding, the incidence of vCID 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 asymptomatic infections (either preclinical or subclinical) in the population than might be indicated by the present numbers of confirmed clinical cases.

The NCJDRSU continues to collaborate with health departments and public health teams throughout the UK in relation to a range of activities, for example, in relation to the follow up of those identified as at increased risk of CJD. The activities of the NCJDRSU 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. No further cases of vCJD attributed to blood transfusion were identified in 2010. However, a case was identified in 2010 who had evidence of vCJD infection in the spleen (but no evidence of clinical vCJD), considered probably due to blood products (treatment for haemophilia).

The recently described form of prion disease originally termed Protease Sensitive Prionopathy and renamed Variably Protease Sensitive Prionopathy, is of uncertain nosological significance but is presently considered a form of sporadic prion disease, alongside sporadic CJD. The NCJDRSU has so far identified at total of 9 such cases in the UK and is continuing to monitor this form of disease.

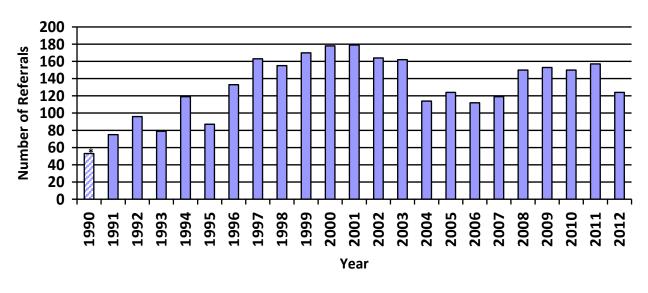
The success of the National CJD Research & Surveillance Unit continues to depend on the extraordinary level of co-operation from the neurology and neuropathology communities and other medical and paramedical staff throughout the UK. Ongoing support is provided by the Infectious Disease Epidemiology Unit,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

### **CLINICAL SURVEILLANCE**

he national surveillance of CJD in the UK was initiated in May 1990. Surveillance is funded by the Department of Health, UK and by the Scottish Government Health Department. The NCJDRSU 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, genetic, iatrogenic and vCJD referred up to 31st December 2012 (with data ascertained up to 31<sup>st</sup> May 2013). 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 <u>www.cjd.ed.ac.uk/criteria.htm</u>. Cases classified as definite or probable are included in all analyses.

#### 2.1 Referrals to NCJDRSU

The NCJDRSU 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 (Figure 1). Numbers fluctuate from year to year, partly explained by changes in the number of non-CJD cases referred to the NCJDRSU. 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.





\*from 1 May 1990

#### 2.2 Sporadic Creutzfeldt-Jakob Disease

Between 1st January 1970 and 31st December 2012, 1792 cases of sporadic CJD were identified in the UK, of which 7 cases were alive on 31st December 2012. Of these UK cases, 1295 (72%) were classified as definite cases with the remainder classed as probable. Four further cases have been identified (3 in Jersey and one in the Isle of Man) but they are not included in the following UK analyses.

Figure 2 shows the number of deaths each year from sporadic CJD for the UK between 1985 and 2012. The number of deaths identified each year has increased over time. A similar phenomenon has been observed in other European countries, and may reflect improved case ascertainment, particularly in those aged over 70 years.

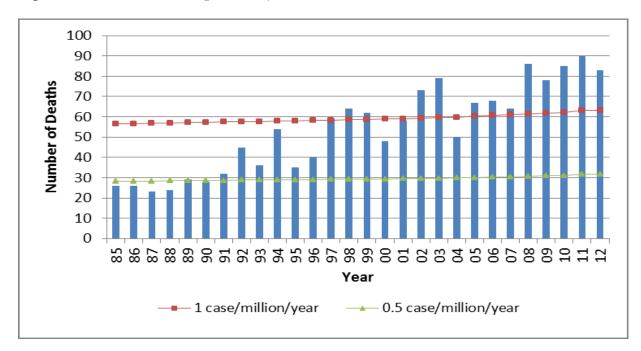
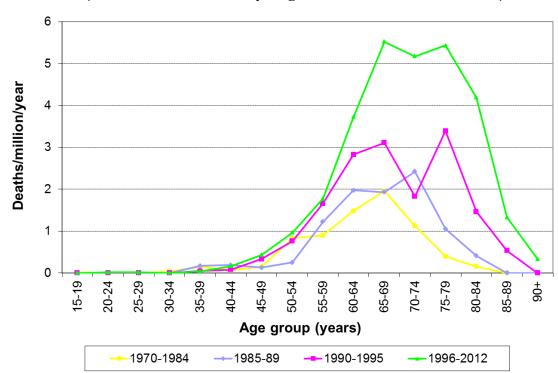


Figure 2 Deaths from sporadic CJD, UK, 1985-2012

Figure 3 shows average annual age-specific mortality rates over the time periods 1970-84, 1985-89, 1990-95 and 1996-2012. These data also emphasise the very small numbers of cases of sporadic CJD occurring in individuals aged <50 years. 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. Comparison between the different time periods, indicate an increase in age-specific recorded mortality over time in all age groups over 50. These observations are consistent with improved case ascertainment in all ages over 50 years, but with the greatest increase occurring in the elderly.



Age-specific mortality rates from sporadic CJD in the UK 1970-2012 (note: from 1970-1984 only England and Wales, thereafter UK)

1970-84 Mortality rates calculated using mid-1981 England & 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 1996-12 Mortality rates calculated using mid-2001 UK population estimates based on the 2001 Census

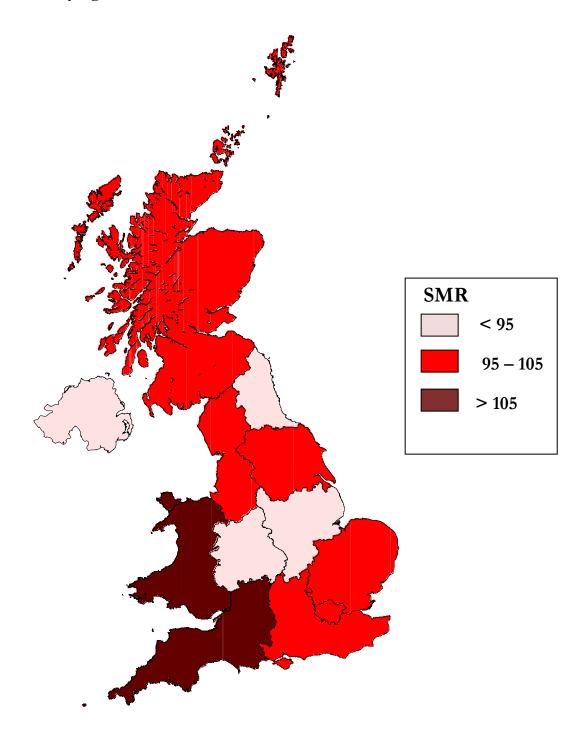
#### Geographical distribution of sporadic CJD

Figure 3

Over the period 1990-2012 the average crude annual mortality rates from sporadic CJD per million population were 1.01 in England, 1.21 in Wales, 1.05 in Scotland and 0.77 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=0.7).

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 2012 were calculated (Figure 4). An SMR of 100 equates to the national average mortality rate; an SMR above or below this value reflects relative high or low mortality, respectively. After adjusting for the age/sex distribution of the population, the variation in mortality rates between the different regions is not statistically significant (p=0.5).

Figure 4 Standardised sporadic CJD mortality ratios (SMRs) 1 January 1990 - 31 December 2012, by region of residence at death



## Table 1aDeaths from definite and probable sporadic CJD shown by region and local<br/>authority of residence at death: 1st January 1990 to 31st December 2012

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	TOTAL FOR	1151	1 01				
ENGLAND		1131	1.01				

\* number of deaths/million/annum based on mid-2001 population estimates in England (source: ONS) over the 23 -year period of the study. Postcode of residence obtained from AFD Postcode Plus.

WALES†	No. of cases	WALES†	No. of cases
Isle of Anglesey	4	Neath Port Talbot	0
Gwynedd	6	The Vale of Glamorgan	3
Conwy	5	Cardiff	5
Denbighshire	1	Bridgend	2
Flintshire	2	Rhondda, Cynon, Taff	6
Wrexham	5	Merthyr Tydfil	2
Powys	10	Caerphilly	7
Ceredigion	3	Blaenau Gwent	0
Pembrokeshire	2	Torfaen	3
Carmarthenshire	2	Monmouthshire	2
Swansea	7	Newport	4
TOTAL FOR WALES (MORTALITY RATE*)81 (1.21)†unitary authorities			

Table 1b	Deaths from definite and probable sporadic CJD: Wales, Scotland and NI
	1 <sup>st</sup> January 1990 to 31 <sup>st</sup> December 2012

SCOTLAND†	No. of cases	SCOTLAND†	No. of cases
Aberdeen City	4	Highland	2
Aberdeenshire	7	Inverclyde	2
Angus	1	Midlothian	1
Argyll & Bute	3	Moray	3
Clackmannanshire	1	North Ayrshire	4
Dumfries & Galloway	3	North Lanarkshire	5
Dundee City	6	Orkney Islands	0
East Ayrshire	1	Perth & Kinross	1
East Dunbartonshire	3	Renfrewshire	6
East Lothian	3	Scottish Borders	3
East Renfrewshire	1	Shetland Islands	3
Edinburgh, City of	18	South Ayrshire	3
Eilean Siar	0	South Lanarkshire	6
Falkirk	4	Stirling	2
Fife	8	West Dunbartonshire	2
Glasgow City	12	West Lothian	4
TOTAL FOR SCOTLAND	122	†council areas	
(MORTALITY RATE*)	LITY RATE*) (1.05)		

NORTHERN IRELAND <sup>†</sup>	No. of cases	NORTHERN IRELAND <sup>†</sup>	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	5
Belfast	8	Magherafelt	0
Carrickfergus	0	Moyle	0
Castlereagh	0	Newry & Mourne	1
Coleraine	1	Newtownabbey	0
Cookstown	0	North Down	0
Craigavon	4	Omagh	1
Derry	1	Strabane	1
TOTAL FOR N IRELAND	30		•
(MORTALITY RATE*)	(0.77)	†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 23-year period of the study. Postcode of residence obtained from AFD Postcode Plus.

#### 2.3 Variant Creutzfeldt-Jakob Disease

Up to 31<sup>st</sup> December 2012, 176 cases of definite or probable vCJD had been identified in the UK (122 definite and 54 probable cases who did not undergo post mortem; no cases still alive). Seventy-five (43%) of the 176 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 68 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. The age- and sex-specific mortality rates for vCJD over the time period 1 May 1995 to 31 December 2012 are shown in Figure 5. The median duration of illness from the onset of first symptoms to death was 14 months (range 6-114) compared with a median duration of illness for cases of sporadic CJD of 4 months (range 1 to 80) during the period 1990-2012.

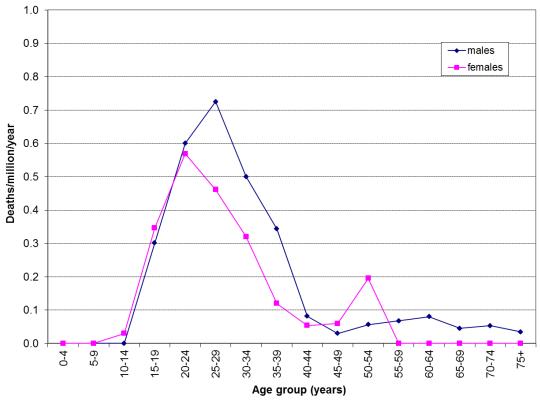


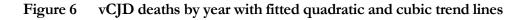
Figure 5 Age- and sex-specific mortality rates from vCJD in the UK 1 May 1995 - 31st December 2012

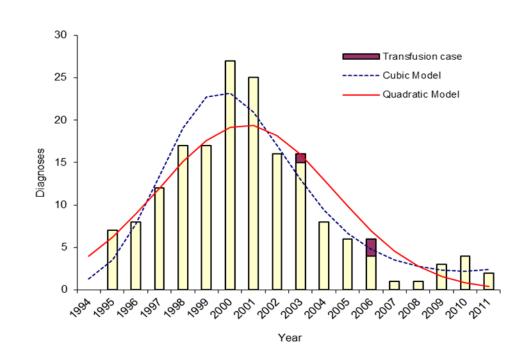
Mortality rates calculated using ONS mid-2001 population estimates

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 the Seventeenth Annual Report 2008 (<u>http://www.cjd.ed.ac.uk/archive.htm</u>). To date, no case of vCJD has been identified in the UK in individuals born after 1989.

#### Deaths from vCJD

Results from modelling the incidence of vCJD deaths indicate the epidemic peaked in about the year 2000 when there were 28 deaths and has since declined to a current incidence of about one to two deaths per year<sup>1</sup>. There have been no new deaths of vCJD in 2012 (see Figure 6). Data were last reviewed in 2012 and further details are given in the full report which is available at http://www.cjd.ed.ac.uk/documents/cjdq72.pdf





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. To date, however, there is no evidence of a second wave. 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.

#### Geographical distribution of vCJD

Tables 2a and 2b present data on the geographical distribution by residence at onset (for all 176 vCJD cases) and residence at death (for 173 vCJD cases who had died by 31<sup>st</sup> December 2012 and were resident in the UK at death), along with the crude mortality rate per million population per annum of each standard region.

<sup>&</sup>lt;sup>1</sup> Analysis undertaken by N J Andrews, Senior Statistician, Statistics Unit, Centre for Infections, Health Protection Agency. Further detail is available at http://www.cjd.ed.ac.uk/cjdq72b.pdf

## Table 2aCases of definite and probable variant CJD shown by residence at onset (n=141)<br/>and residence at death (n=142†) in England (region & local authority)

	No.	No.		1	No.	No.	
	resident	resident	Mortality rate*		resident	resident	Mortality
	at onset	at death			at onset	at death	rate*
North East	11	11	0.25	East	13	13	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	2	2	
Tyne & Wear	5	3		Hertfordshire	3	3	
				Norfolk	3	3	
North West	27	27	0.23	Suffolk	3	3	
Blackburn with Darwen UA	0	0					
Blackpool UA	1	1		London	19	17	0.13
Halton UA	0	0		Inner London	7	7	
Warrington UA	2	2		Outer London	12	10	
Cheshire	5	6					
Cumbria	1	1		South East	23	20	0.14
Greater Manchester	10	9		Bracknell Forest UA	1	1	
Lancashire	4	4		Brighton and Hove UA	0	0	
Merseyside	4	4		Isle of Wight UA	0	1	
				Medway UA	0	1	
Yorkshire and the Humber	17	18	0.20	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	4		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	0.14	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	17	16	0.18
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	
0 -				North Somerset UA	0	0	
West Midlands	6	10	0.11	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	1	1	
	Ň	· ·		Somerset	4	5	
				Wiltshire	4	3	
TOTAL FOR ENIOLANIA	4 4 4	1.40	0.47			5	
TOTAL FOR ENGLAND	141	142	0.16				

\* number of deaths/million/annum based on mid 2001 population estimates (source: ONS): 1 May 1995 to 31 Dec 2012. Postcode of residence obtained from AFD Postcode Plus.

† excludes 3 cases who died abroad.

Table 2b	Cases of definite and probable variant CJD shown by residence at onset (n=35)
	and residence at death (n=31): Wales, Scotland and NI

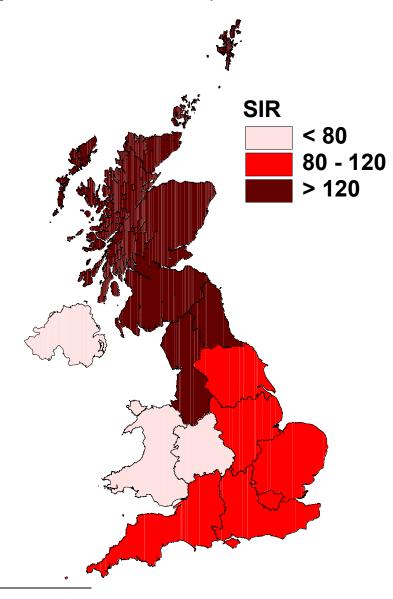
SCOTLAND+resident at onsetAberdeen City1Aberdeenshire0Angus0Argyll & Bute0Clackmannanshire0Dumfries & Galloway0Dundee City0East Ayrshire1East Dunbartonshire1East Lothian0Edinburgh, City of2Eilean Siar0Falkirk1Fife2Glasgow, City of3TOTAL24(MORTALITY RATE*)No. resident	No. resident at death	WALES <sup>+</sup> No. resident a onset		No. resident at death
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Banbridge0Belfast1Carrickfergus0Castlereagh0Coleraine0Cookstown0	0	Limavady	0	0
Belfast1Carrickfergus0Castlereagh0Coleraine0Cookstown0	0	Lisburn	1	1
Carrickfergus0Castlereagh0Coleraine0Cookstown0	1	Magherafelt	0	0
Castlereagh0Coleraine0Cookstown0	0	Moyle	0	0
Coleraine0Cookstown0	0	Newry & Mourne	0	0
Cookstown 0	0	Newtownabbey	1	1
	0	North Down	0	0
Craigavon 0				
0	0	Omagh	0	0
Derry 0	0	Strabane	0	0
TOTAL3(MORTALITY RATE*)	3 (0.10)	†district council areas		

\* number of deaths/million/annum based on mid-2001 population estimates (source: ONS): 1 May 1995-31 Dec 2012. Postcode of residence obtained from AFD Postcode Plus.

Cases have been widely spread throughout the UK, although there remains a relatively high incidence amongst those who lived in the north (Scotland, North East, North West, Yorkshire & Humberside; 16.9 million people, 74 vCJD cases) compared to the south (Wales, East Midlands, West Midlands, South West, South East, London, East of England; 31.7 million people, 98 vCJD cases) of Great Britain in 1991.<sup>2</sup> The rate ratio controlling for age and sex is 1.42 (95% CI 1.05-1.92), ie 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. 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 7.

Investigations into geographically associated cases of vCJD (either through proximity of residence or through an occupational, educational or social/recreational link with the same location) have found no convincing evidence of factors that may have augmented local risks for vCJD<sup>3</sup>.

## Figure 7 Standardised vCJD incidence ratios (SIRs) up to 31<sup>st</sup> December 2012, by region of residence on 1st January 1991

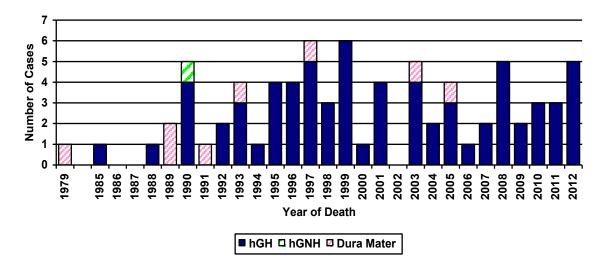


<sup>&</sup>lt;sup>2</sup> Cousens S, Smith PG, Ward H, Everington D, Knight RSG, Zeidler M, Stewart G, Smith-Bathgate EAB, Macleod MA, Mackenzie J, Will RG. Geographical distribution of variant Creutzfeldt-Jakob disease in Great Britain, 1994-2000. Lancet 2001; 357: 1002-1007.

<sup>&</sup>lt;sup>3</sup> 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.

#### 2.4 Iatrogenic Creutzfeldt-Jakob disease

Since 1970, up to 31st December 2012, 79 cases of CJD attributable to iatrogenic exposure have been identified, 8 in individuals receiving dura mater implants, 70 in individuals who had received human-derived growth hormone (hGH) and one in a recipient of human gonadotrophin (hGN) who was treated in Australia. Seventy-eight of these individuals have died (Figure 8) and one was still alive as at 31<sup>st</sup> December 2012. The mean age at death of the hGH/hGN group was 34 years (with a range of 20-51 years) and for the dura mater cases 46<sup>1</sup>/<sub>2</sub> years (range 27-78 years).



#### Figure 8 Deaths from iatrogenic CJD, 1979-2012

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.<sup>4</sup> A study of the accumulated UK experience with dura mater-related CJD, including incubation periods, was undertaken and the results published in 2006.<sup>5</sup>

#### 2.5 Transfusion Medicine Epidemiology Review

The Transfusion Medicine Epidemiology Review (TMER) is a collaborative project between the UK NCJDRSU 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. Cases (definite and probable) are notified to the UKBS by NCJDRSU; a search establishes whether any have acted as donors or received blood transfusions. Donation/transfusion records are checked and all components traced through hospital records. Details of all identified recipients/donors are forwarded to NCJDRSU for subsequent checking to ensure none appear on the NCJDRSU database as a case of CJD. Further details are given in the 19<sup>th</sup> Annual Report (see <a href="http://www.cjd.ed.ac.uk">http://www.cjd.ed.ac.uk</a>)

Four instances of probable transfusion transmitted infection have been identified. The first recipient (Case 1) developed symptoms of vCJD  $6^{1}/_{2}$  years after receiving a transfusion of red cells donated  $3^{1}/_{2}$ 

<sup>&</sup>lt;sup>4</sup> 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.

<sup>&</sup>lt;sup>5</sup> 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.

years before the donor (Donor 1) developed symptoms of vCJD<sup>6</sup>. 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<sup>7</sup>; at post mortem protease-resistant prion protein (PrP<sup>res</sup>) 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<sup>8</sup>. 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<sup>9</sup>.

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 eight paediatric neurologists and one geneticist which allocates the cases to a diagnostic category<sup>10-11</sup>.

As of 31<sup>st</sup> December 2012, after nearly 16 years of surveillance, 3342 patients with suspected PIND had been reported and the Expert Group had discussed 2273 of these. 1416 cases had a confirmed underlying cause other than vCJD, being categorised into over 150 known neurodegenerative diseases<sup>3</sup>. 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 on this project: Dr C. Verity, Prof A. Nicoll, Ms L. Stellitano, Ms AM Winstone)

<sup>&</sup>lt;sup>6</sup> 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.

<sup>&</sup>lt;sup>7</sup> 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.

<sup>&</sup>lt;sup>8</sup> 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.

<sup>&</sup>lt;sup>9</sup> Health Protection Agency. Fourth case of transfusion-associated variant-CJD. Health Protection Report 2007;1(3):

<sup>&</sup>lt;sup>10</sup> 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.

<sup>&</sup>lt;sup>11</sup> 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.

## **CASE-CONTROL STUDY**

B etween 1998 and 2008 a case-control study of CJD was funded in the UK, courtesy of the Department of Health and Scottish Government, 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, as part of routine surveillance activities, 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. 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.

A general population control group, recruited in 2002-2003, has been used in research comparing risk factors of the control group with cases of vCJD and sCJD, based on information provided by the families of cases and controls at interview (for details of the methodology and findings please see below<sup>12·13</sup>). Results from the case-control study of reported risk factors for variant CJD are consistent with dietary exposure to contaminated beef products being the main route of infection of vCJD, but recall bias cannot be excluded as an explanation. For sporadic CJD, an analysis of reported medical risk factors, found 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<sup>13</sup>.

A case-control study of risk factors for vCJD in dental practice was completed in 2012. The study found no evidence of an association, however, there were significant limitations to the study, arising primarily from poor availability of data, and associations may have been missed<sup>14</sup>.

Although funding for the case-control study has now ceased, 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 continues to be undertaken on data gathered already, such as the ongoing examination of medical risk factor data obtained directly from primary care records. *Ad hoc* studies that may require extra funding will continue to be undertaken as necessary.

<sup>&</sup>lt;sup>12</sup> Ward HJT et al. Risk factors for variant Creutzfeldt-Jakob disease: a case-control study. Ann Neurol 2006; 59: 111-120.

<sup>&</sup>lt;sup>13</sup> Ward HJT et al. Risk factors for sporadic Creutzfeldt-Jakob disease. Ann Neurol 2008; 63: 347-354.

<sup>&</sup>lt;sup>14</sup> Molesworth et al. Risk factors for variant Creutzfeldt-Jakob disease in dental practice: a case-control study. British Dental Journal 2012; 213: E19.

### LABORATORY ACTIVITIES

aboratory 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 NCJDRSU 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 NCJDRSU continues to maintain its diagnostic and research activities, with most of the cases investigated referred from other centres across the UK (see Table 3). 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 number of referred cases of vCJD declined in 2012, with no cases being examined. There was a laso a slight reduction in the number of sporadic CJD cases than in the previous year, and there was a larger reduction in both the number of cases referred in which sporadic CJD was suspected, but not confirmed on the results of the investigations performed in our laboratory, and of cases in which an alternative diagnosis of neurodegenerative disorders (such as Alzheimer's disease) was made. No cases of vCJD were referred from outside the UK, reflecting the decline in suspect cases of vCJD overseas. Two cases of variably protease-sensitive prionopathy were identified prospectively in 2012, in contrast to the previous 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 3). The laboratory is also involved as a reference centre for an HPA study on the prevalence of vCJD infection in appendix tissue samples from the UK, and 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 NCJDRSU. We are also grateful to the relatives of patients with CJD for allowing us to study this group of devastating disorders.

	CURRENT YEAR	PREVIOUS YEAR
REFERRED CASES (UK)		
Sporadic CJD	30	36
Genetic CID	2	2
Variant CID	0	2
Iatrogenic CJD (GHT)	0	2
Iatrogenic CJD (Lyodura)	0	0
Gerstmann-Straussler-Scheinker Syndrome	1	0
Fatal Familial Insomnia	0	0
Variably protease sensitive prionopathy	2	0
No evidence of CJD (no alternative pathological diagnosis)	10	23
Alzheimer's disease	2	1
Dementia with Lewy Bodies	3	3
Motor neurone disease	0	0
Other forms of brain disease‡	2	6
REFERRED CASES (EU)		
Sporadic CJD	4	2
Genetic CID	0	0
Variant CJD	0	0
Gerstmann-Straussler-Scheinker Syndrome	1	0
Other forms of brain disease	1	0
REFERRED CASES (ROW)		
Other forms of brain disease	1	0
UK vCJD SCREENING STUDIES		
Haemophilia cases - UKHCDO	1	1
Primary Immunodeficiency cases – PIDSUK	4	2
Enhanced Surveillance of "at risk" individuals (HPA)	0	4
OTHER REFERRALS AND STUDIES		
European Collaborative Study on FFI/sFFI	0	5
European Collaborative Study on variant CJD	0	0
Animal studies	3	0
Historical cases	1	0
TOTAL NUMBER OF CASES	71	89

#### Breakdown of Laboratory Activities: Period 1<sup>st</sup> January 2012– 31<sup>st</sup> December 2012 Table 3

Abbreviations:

Growth Hormone Therapy European Union Rest of World GHT

EU

ROW

#### 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 NCJDRSU. Small quantities of cerebral cortex or cerebellum are homogenised, treated with protease and the size and relative abundance of the protease resistant prion protein (PrP<sup>res</sup>) fragments determined by Western blot analysis. The recognised PrP<sup>res</sup> types, their nomenclature and their association with different human prion diseases are shown in Figure 9 and described in the accompanying legend. 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<sup>res</sup> and increase the sensitivity of the test.

# PrPres types 1A 2A 1+2(A) 2B 1B 1A/B 2A/B 8kDa Image: Straight of the straight of the

#### Figure 9

Figure 9 shows the diagrammatic representation of the main protease resistant prion protein (PrP<sup>res</sup>) types found in the human prion disease brain as determined by proteinase K digestion and Western blot analysis. The classification of the banding pattern has two components, one numerical depending on the migration of the bands and the other alphabetical depending on their relative abundance. The pattern is termed type 1 if the non-glycosylated (bottom) band is ~21kDa, type 2 if the non-glycosylated band is ~19kDa or type 1+2 if both bands are found. In cases and samples in which both types are present but one type predominates the less abundant type is places in parentheses [ie type 1(+2) or type 2(+1)]. The pattern is given the suffix A if the middle or bottom (mono-, or non-glycosylated bands predominate, B if the top (di-glycosylated) band predominates or A/B if the glycosylated bands (middle and top) predominate at the expense of the non-glycosylated (bottom) band. A pattern dominated by a low molecular mass unglycosylated band is here termed 8kDa. The faint ladder of bands that sometimes accompanies the 8kDa band is shown in grey. Types 1A, 2A, 1+2(A) are characteristic of sporadic and, iatrogenic CJD. Type 2B is associated with variant CJD. Types 1B, 1A/B and 2A/B are often found in genetic CJD, GSS and FFI. The 8kDa pattern is characteristic of some cases of GSS and of VPSPr.

#### UK Referrals

A total of 36 UK cases with frozen tissue were received and analysed in 2012, which is a reduction compared with the previous year. The results of the analysis were as follows:

Diagnosis	Туре	PrP <sup>res</sup> +ve CNS
CJD (n=23)	Sporadic	22 <sup>1</sup>
	Genetic	1
VPSPr (n=1)	1	
GSS (n=1)	1	
Alternative final diagnos	is or not determined $(n=11)$	$0/11^{2,3}$

Table 4Breakdown of cases analysed in 2012

Alternative linar diagnos

<sup>1</sup>Includes one brain biopsy <sup>2</sup>Includes three brain biopsies

<sup>3</sup>Includes two patients from the PIDS Study

Further sub-classification by PrPres type and PRNP genotype yields the following results:

Table 5 PrPres type / PRNP genotype breakdown of CJD cases analysed in 2012

Diagnosis	PRNP genotype	Type 1A	Type 2A	Type 1+2(A)	8kDa	Type 1B
	MM	12 <sup>1</sup>	1	1		
Sporadic CJD	MV	4				
1 0	VV		4			
Genetic CJD	E200K-129MM					1
VPSPr	VV				1	
GSS	P84S-129MV				1	

<sup>1</sup>includes one brain biopsy

#### Historical UK referrals

Western blot analysis was performed on frozen brain tissue from five historical UK cases, four under the NCJDRSU / MRC Prion Unit sharing arrangement (sCJD PrP<sup>res</sup> types 2A, 1A(+2) and 1A and genetic CJD E200K PrP<sup>res</sup> type 2A/B) and one from Derriford Hospital, Plymouth (vCJD, type 2B PrP<sup>res</sup>).

#### Non-UK referrals

Western blot analysis was performed on frozen tissue from 8 non-UK cases. Five were sCJD cases from Sweden (one sCJD MM1A, one sCJD MV1A, two sCJD MM2A and one case of GSS S132G-VV with an 8kDa PrP<sup>res</sup>), two were from Spain (both vCJD, type 2B PrP<sup>res</sup>) and one from Italy (vCJD, type 2B PrP<sup>res</sup>).

#### 4.3 Brain banking activities

The bank of fixed and frozen tissues in the Research and Surveillance Unit was used extensively in 2012 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 3 years and additional support is now being sought. 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

#### Genetic CJD

One hundred and twenty-eight cases of genetic CJD (excluding cases of GSS) have been identified since 1970 by the NCJDRSU (these data are incomplete as formal investigation of genetic CJD in the UK is undertaken by the National Prion Clinic in London). Of the 128 cases, 112 were resident in England, 9 were resident in Wales, 3 were resident in Northern Ireland and 4 were resident in Scotland. Seventeen cases were still alive as at 31<sup>st</sup> December 2012. Sixty-two of the cases had insertions in the coding region of the PrP gene, 36 carried the mutation at codon E200K, 12 at codon D178N, 3 at codon V210I, one at codon D167G, 2 at codon V163STOP, one at codon G54S and one at codon E211Q. 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 29-95 years).

#### PRNPCodon 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 6). There appears to be evidence (p=0.003) of a change in the *PRNP* codon 129 distribution in sporadic CJD between the periods 1990-1995 and 1996-2012. 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 6	PRNP codon 129 genotypes of cases of sporadic	CJD in the	U <b>K, 1990-2</b> 0	12

Deaths from sporadic CJD	MM(%)	MV(%)	VV(%)
Deaths from 1 January 1990 – 31 December 1995	101 (75)	16 (12)	17 (13)
Deaths from 1 January 1996 – 31 December 2012	428 (60)	145 (20)	144 (20)
Total	532 (62)	163 (19)	162 (19)
Genotype distribution for the normal population <sup>15</sup>	(44)	(45)	(11)

#### PRNP codon 129 distribution in vCJD

All clinical cases for whom genetic data are available (n=160, 90%) were methionine homozygotes at *PRNP* codon 129 of the PrP gene.

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

<sup>&</sup>lt;sup>15</sup> Bishop et al. *PRNP* variation in UK sporadic and variant Creutzfeldt-Jakob disease highlights genetic risk factors and a novel non-synonymous polymorphism. BMC Medical Genetics 2009;10:146-155.

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

#### Introduction

The laboratory received 278 cerebrospinal fluid (CSF) samples from January 2012 – December 2012, from patients residing in the United Kingdom (UK) and from patients in non-UK countries. Four CSF samples were blood-stained and as such unsuitable for analysis. The origin and numbers of these samples are given in Table 7.

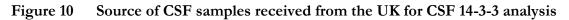
## Table 7Origin of CSF samples sent to the NCJDRSU for CSF 14-3-3 analysis from<br/>January 2012 – December 2012

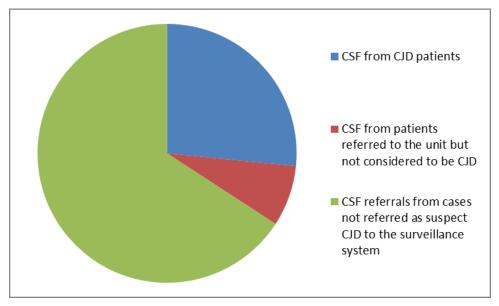
Origin of CSF samples	Total number CSF samples (%)
CSF from UK patients	2401
CSF from non-UK countries	38 <sup>2</sup>
Total number	278

<sup>1</sup> Three CSF samples were blood-stained and as such unsuitable for analysis.

<sup>2</sup> One CSF sample was blood-stained and as such unsuitable for analysis.

Of the 237 analysable CSF samples received from patients within the United Kingdom, 81 samples were from patients who were finally referred to the NCJDRSU as a suspected case of CJD. Of these, 63 patients were finally diagnosed as having definite, probable or possible CJD (Table 8). Of the remaining 18 patients, 16 patients are under review but do not meet the criteria for CJD. In none of these patients is there a definite alternative diagnosis. The 2 remaining patients died before being seen, were 14-3-3 positive and are considered as late referrals and are currently under review. The remaining 156 CSF samples were sent to the NCJDRSU 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 NCJDRSU 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 NCJDRSU.





The final diagnosis of the 63 patients referred to the NCJDRSU who were diagnosed with some form of CJD is given in Table 8.

Diagnosis	Number of cases	Number of positive CSF 14-3-3
Neuropathologically confirmed sporadic CJD	25	24
Probable sporadic CJD	31	30
Possible sporadic CJD	3	0
Neuropathologically confirmed genetic CJD	1 (insert mutation)	1
Neuropathologically confirmed iatrogenic CJD*	2	0
Probable Iatrogenic CJD*	1	0

Table 8 The CSF 14-3-3 results in patients diagnosed with CJD or prion disease

\* Secondary to administration of human cadaveric growth hormone.

Of the patients with probable sCJD, 23 died without undergoing a post-mortem, 4 have died and neuropathological confirmation of sCJD is awaited. Of the remaining 4 patients, 2 have died and it is unclear whether a post-mortem has been performed and 2 patients are still alive. Of the 23 patients who died without post-mortem examination, 7 had EEG traces that were considered typical for sCJD and/or MRI appearances considered typical for sCJD whilst 16 had EEG traces or MRI appearances that were not considered typical. Therefore 16 of the 23 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 or MRI support.

Of the 156 CSF samples sent from patients who were not formally referred to the NCJDRSU, 22 were positive for CSF 14-3-3 and alternative diagnoses were found for these cases (Table 9).

 Table 9
 Alternative diagnoses for patients with positive CSF 14-3-3

Diagnosis	Number of patients
Alzheimer's disease	4
Lewy body dementia	3
Improved	3
Vascular dementia	2
Autoimmune encephalitis	2
Meningitis	1
Hypoxic brain injury	1
Hepatic cirrhosis	1
Paraneoplastic syndrome	
CNS infection/inflammation	1
Unknown	3*

\* the final diagnoses in these 3 patients is not yet known, but none of these patients were referred to NCJDRSU as suspect CJD cases

### NATIONAL CJD CARE TEAM

stablished by the Department of Health, the National CJD Care Team is based within the National CJD Research & Surveillance Unit and was formed in order to optimise the care of patients suffering from all forms of CJD. The 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 with secretarial and clinical neurological support from within the Unit.

When a referral is made to the NCJDRSU the research registrar will take that referral and, if appropriate, ask the Care Co-ordinator to attend that first visit to meet with the family. Once a diagnosis of probable or possible CJD is made, if the co-ordinator has not already met the family, the coordinator makes direct contact with the family and offers the opportunity to meet and to assist with care planning. Referrals are also made to the Care Team from Leah Davidson (who coordinates the care of iatrogenic CJD cases) and the National Prion Clinic in London. Once contact is made, the coordinator can meet on a regular basis with the patient, family and professionals involved in care. This will depend on need and will provide support and 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 as long as needed. This does not always involve a visit in person. Contact by telephone, text or email is just as important and may 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. This is a sum of money from The Department of Health 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 and equipment provision. Health and Social Services will provide the basic elements of the individual patient's care package. The Care package involves an individual assessment of need and will vary accordingly. It is essential that care packages are flexible and can change quickly to meet the rapidly changing needs of the patient. The aim is to provide a package of care that will meet the needs both for the patient and their family in a timely manner.

In addition to collaborations with national organisations in the United Kingdom, the Care Team liaises closely with international organisations, including the Australian and American CJD Support Groups and is an Official Friend of the CJD International Support Alliance.

A breakdown of patient visits, case conferences and teaching sessions during 2012 is shown in Table 10. Care Fund payments from 1<sup>st</sup> January to 31<sup>st</sup> December 2012 are shown in Table 11.

## Table 10Patient Visits, Case Conferences and Teaching Sessions and Family contacts1st January to 31st December 2012

Month	Patient Visits/Case Conferences/Teaching Sessions
Patient Visits	92
Case Conferences	35
Teaching	23
Debrief	3
Letters	74
Emails	178
Texts	106
Telephone calls	1042

## Table 11Care Fund Payments1st January to 31st December 2012

Description	£
Adaptations	45,265.00
Alternative Therapy	340.00
Counselling	0.00
Equipment	10,598.00
Nursing	174,216.00
Other	0.00
Physiotherapy	2,900.00
Social Care	2,690.00
Transport	48,516.00
TOTAL	284,525.00

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