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CREUTZFELDT-JAKOB DISEASE SURVEILLANCE IN THE UK

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Table of Contents

SECTION 1

Summary	3
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SECTION 2

Clinical Surveillance	5
2.1 Referrals	5
2.2 Sporadic CJD	6
2.3 Variant CJD	11
2.4 Iatrogenic CJD	15
2.5 Transfusion Medicine Epidemiology Review (TMER)	15
2.6 Study of Progressive Intellectual and Neurological Deterioration (PIND)	16
2.7 Surveillance of potential occupational exposure to CJD	17
2.8 Prion surveillance in primary immunodeficiency patients	17
2.9 Enhanced surveillance of those at increased risk of CJD	18

SECTION 3

Laboratory Activities	19
3.1 Neuropathology – Statement of Progress and Surveillance Activities	19
3.2 Prion Protein Laboratory	21
3.3 Brain Banking Activities	22
3.4 Molecular Genetics	23
3.5 CSF 14-3-3 and other brain specific proteins	24

SECTION 4

Publications	25
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SECTION 5

Staff	27
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SUMMARY

The national surveillance programme for Creutzfeldt-Jakob disease (CJD) in the UK was initiated in May 1990. In 1999, the National CJD 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 annual mortality rate for sporadic CJD (sCJD) was 1.69 cases/million in 2016. Although the data for 2016 may still be incomplete, detailed clinical and epidemiological information has been obtained for the great majority of patients. The general autopsy rate remains relatively high compared to the UK as a whole, in 2016 being nearly 50% of all cases referred to the NCJDRSU. The number of brain tissue specimens examined for sCJD in the neuropathology laboratory in 2016 was 36 cases (compared with 29 cases in 2015).

Over the period 1990-2016 average annual mortality rates from sCJD in England, Wales, Scotland and Northern Ireland were, respectively, 1.13, 1.40, 1.15 and 0.83/million/year. The differences between these rates are not statistically significant ($p=0.4$). The mortality rates from sCJD 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 31st December 2016, 178 cases of definite or probable variant CJD (vCJD) had been identified in the UK (123 definite and 55 probable cases who did not undergo post mortem). All 178 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 – of 161 clinically affected definite and probable cases of vCJD with available genetic analysis, 160 have been methionine homozygotes and one methionine-valine heterozygous at codon 129 of the *PRNP* gene. Analysis of vCJD diagnoses and deaths from January 1994 to December 2011 continues to indicate that the peak has passed. While this is an encouraging finding, the incidence of vCJD may increase again, particularly if further cases in different genetic subgroups with longer incubation periods exist. The identification of an individual of the *PRNP*-129 MV genotype as a confirmed case of vCJD (in addition to the possible case of vCJD reported in the NCJDRSU 17th Annual Report, 2008) and the finding of 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 results of large-scale surveys of the prevalence of abnormal prion protein in appendix and tonsil tissues suggest 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.

To help prevent any possible spread of CJD between people, we continue to ask clinicians to refer all new suspect CJD cases to their local infection control and health protection teams. This is important as a local response may be required with respect to limiting potential secondary transmission and other issues that may arise over time concerning the protection of the wider community. The NCJDRSU continues to assist local health protection teams in local audit and investigations of cases in response to local concerns. The NCJDRSU also continues to collaborate with health departments and public health authorities throughout the UK in relation to a range of activities 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, Prion Surveillance in Primary Immunodeficiency Patients 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 patient was also 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 relatively recently described form of prion disease originally termed Protease Sensitive Prionopathy and renamed Variably Protease Sensitive Prionopathy (VPSPr), is of uncertain nosological significance but is presently considered a form of sporadic prion disease, alongside sCJD. The NCJDRSU has so far identified a total of 13 such cases in the UK and is continuing to monitor this form of disease.

The data concerning CSF RT-QuIC are given in Section 3.5; the sensitivity of CSF RT-QuIC for a diagnosis of sCJD is comparable with that of CSF 14-3-3. The specificity is superior to that of CSF 14-3-3 with no positives in cases with a confirmed alternate diagnosis.

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.

Providing information to the public is an important aspect of the NCJDRSU's activities. We held an Open Family Day in 2014 and plan to repeat this in the near future. We liaise closely with the CJD Support Network, providing articles for their Newsletter, updating their information booklets and giving presentations to their Annual Family Day Meetings. Professor Knight is the current Chair of the Network's Management Committee. Professors Knight and Will are also members of the CJD International Alliance of CJD support organisations.

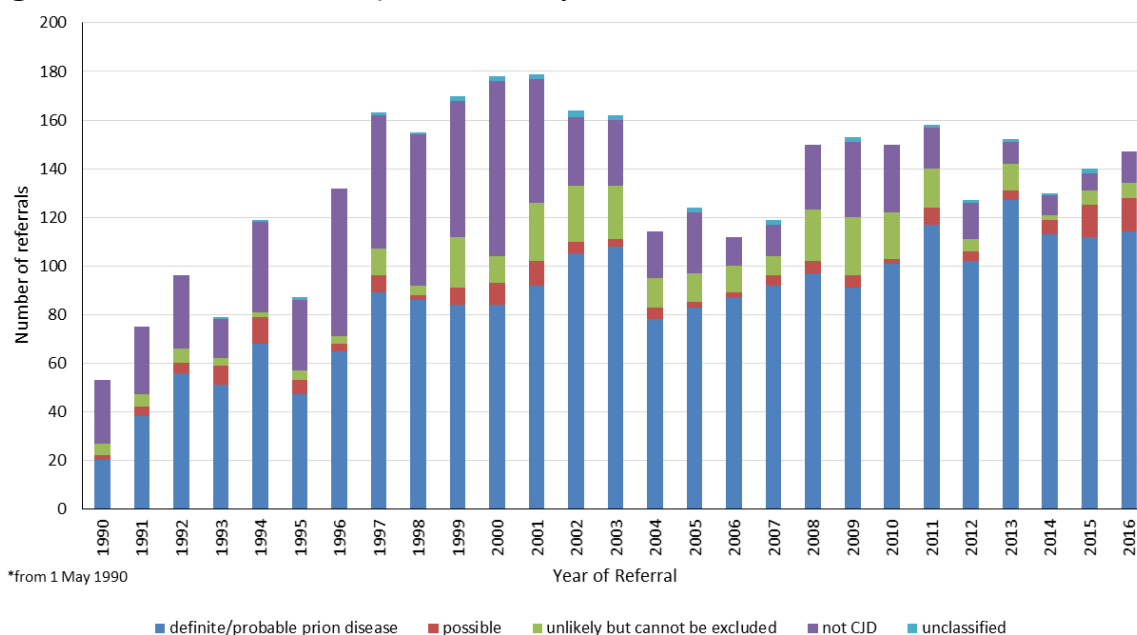
CLINICAL SURVEILLANCE

The 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 sCJD 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 sCJD and vCJD as well as genetic and iatrogenic forms of disease referred up to 31st December 2016 (with data ascertained up to 22nd June 2016). 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. 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. Numbers of referrals fluctuate over time, and may be attributed to variation in case ascertainment and reporting practice, including changes in the number of non-CJD cases referred to the NCJDRSU (see Figure 1)

Figure 1 Referrals to NCJDRSU: 1 May 1990 – 31st December 2016



2.2 Sporadic Creutzfeldt-Jakob Disease

Between 1st January 1970 and 31st December 2016, 2225 cases of sCJD were identified in the UK, of which 16 cases were alive on 31st December 2016. Two cases moved abroad after diagnosis and are therefore lost to follow-up. Of these UK cases, 1529 (69%) were classified as definite cases with the remainder classed as probable. Seven further cases have been identified: 3 in Jersey, 2 in the Isle of Man and 2 cases who were repatriated to the UK when they became ill but had been living abroad. These 7 cases, along with the 2 cases lost to follow up, are not included in the following UK analyses.

Figure 2 shows the annual mortality rates from sCJD for the UK between 1985 and 2016. 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 Mortality Rates from sCJD, UK, 1985-2016

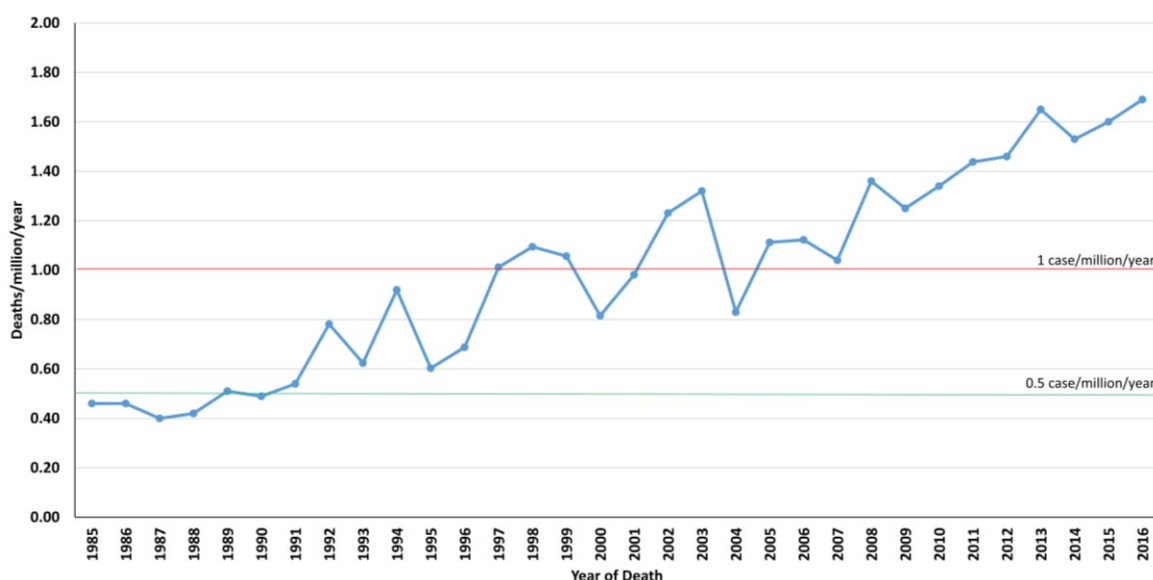
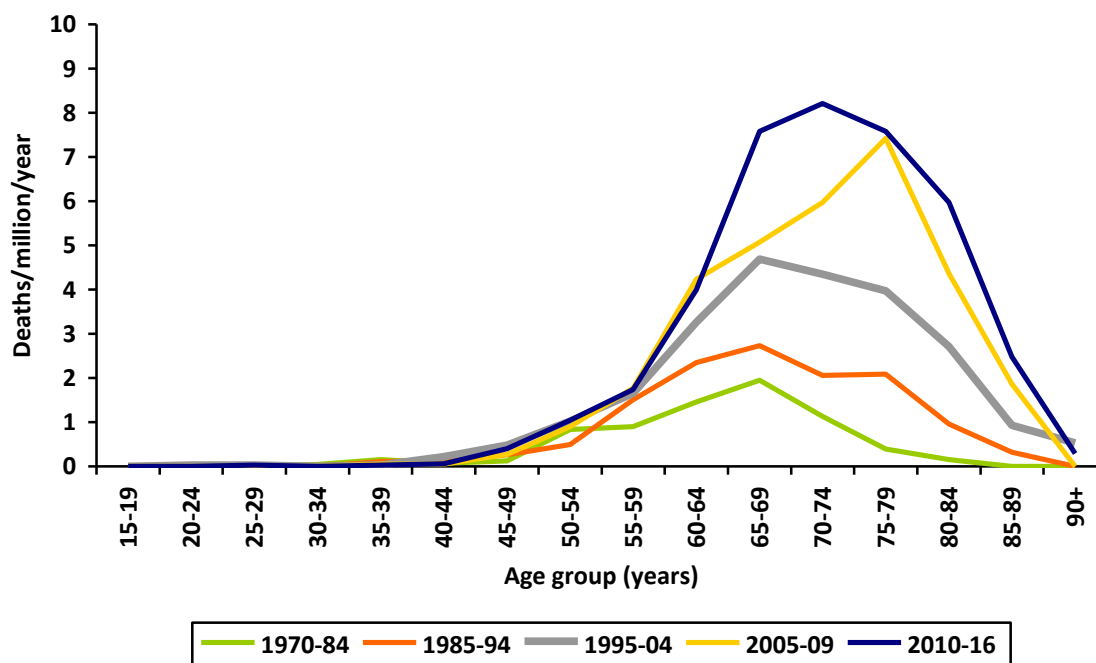


Figure 3 shows average annual age-specific mortality rates over the time periods 1970-1984, 1985-1994, 1995-2004, 2005-2009 and 2010-2016. These data also emphasise the very small numbers of cases of sCJD occurring in individuals aged <50 years. The median ages of cases at death during these four time periods were 63, 65, 67, 69 and 69 years, respectively. In all five time periods, the mortality rates below 40 years of age were low (≤ 0.04 /million/year). Thereafter, in all five 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.

Figure 3 Age-specific mortality rates from sporadic CJD in the UK 1970-2016
(note: from 1970-1984 only England and Wales, thereafter UK)



1970-1984 Mortality rates calculated using mid-1981 England & Wales population estimates based on the 1981 Census
 1985-1994 Mortality rates calculated using mid-1991 UK population estimates based on the 1991 Census
 1995-2004 Mortality rates calculated using mid-2001 UK population estimates based on the 2001 Census
 2005-2009 Mortality rates calculated using mid-2001 UK population estimates based on the 2001 Census
 2010-2016 Mortality rates calculated using mid- 2011 UK population estimates based on the 2011 Census

Geographical distribution of sCJD

Over the period 1990-2016 the average crude annual mortality rates from sCJD per million population were 1.13 in England, 1.40 in Wales, 1.15 in Scotland and 0.83 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 ($p=0.4$).

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 2016 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 ($p=0.2$).

Figure 4 Standardised sporadic CJD mortality ratios (SMRs)
1 January 1990 - 31 December 2016, by region of residence at death

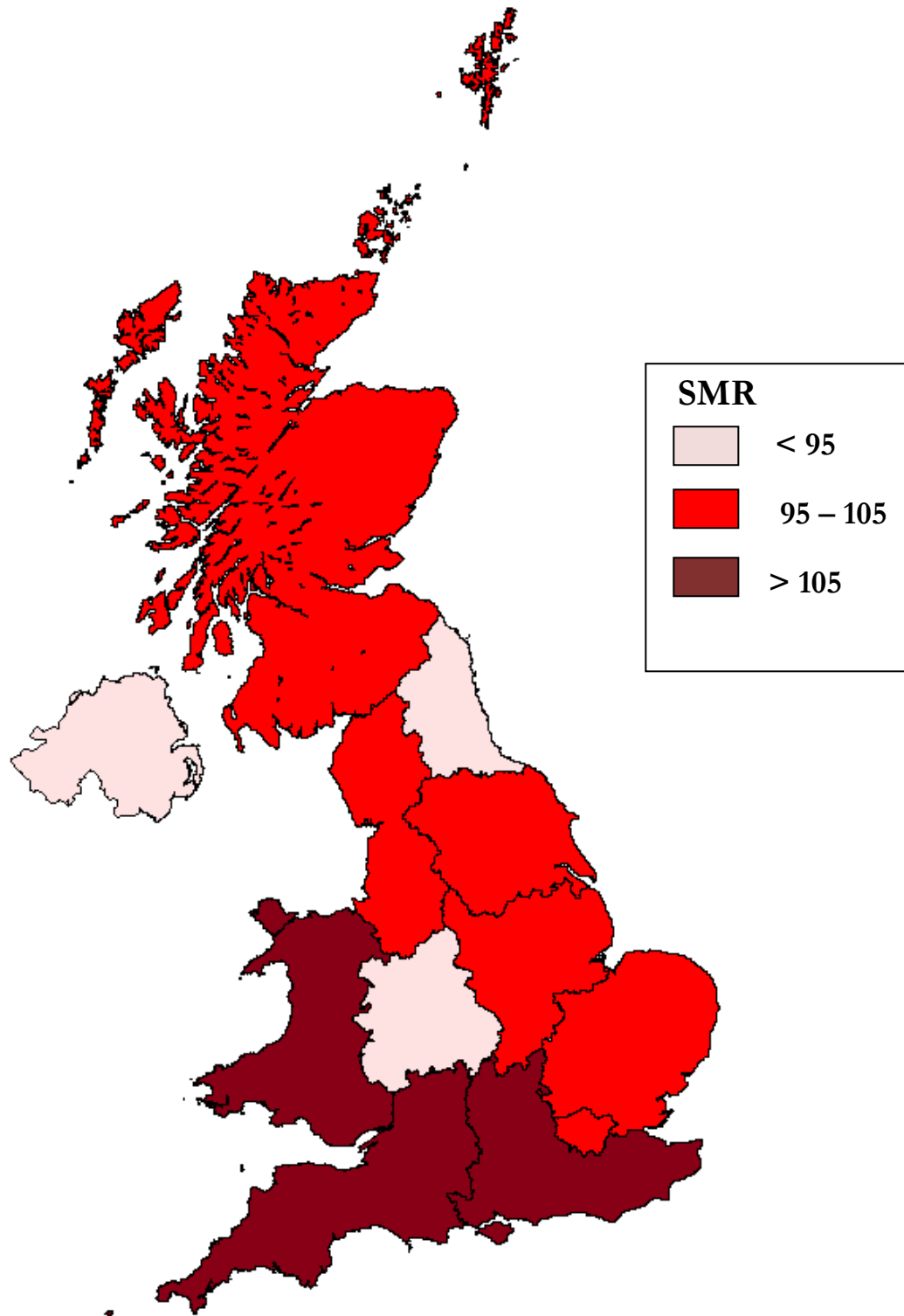


Table 1a Deaths from definite and probable sporadic CJD shown by region and local authority of residence at death: 1st January 1990 to 31st December 2016

ENGLAND	No. of cases	Mortality Rate ¹	ENGLAND	No. of cases	Mortality Rate ¹
North East	62	0.90	East	177	1.21
Darlington UA	2		Luton UA	3	
Hartlepool UA	2		Peterborough UA	2	
Middlesbrough UA	1		Southend-on-Sea UA	5	
Redcar & Cleveland UA	3		Thurrock UA	4	
Stockton-on-Tees UA	3		Bedfordshire	15	
Durham	8		Cambridgeshire	10	
Northumberland	11		Essex	58	
Tyne & Wear	32		Hertfordshire	26	
North West	211	1.15	Norfolk	30	
Blackburn with Darwen UA	7		Suffolk	24	
Blackpool UA	3		London	170	0.86
Halton UA	4		Inner London	49	
Warrington UA	10		Outer London	121	
Cheshire	17		South East	268	1.24
Cumbria	19		Bracknell Forest UA	3	
Greater Manchester	69		Brighton and Hove UA	2	
Lancashire	36		Isle of Wight UA	3	
Merseyside	46		Medway UA	4	
Yorkshire and the Humber	146	1.09	Milton Keynes UA	4	
East Riding of Yorkshire UA	9		Portsmouth UA	4	
Kingston Upon Hull, City of UA	4		Reading UA	5	
North East Lincolnshire UA	5		Slough UA	1	
North Lincolnshire UA	4		Southampton UA	3	
York UA	6		West Berkshire UA	6	
North Yorkshire	25		Windsor and Maidenhead UA	4	
South Yorkshire	41		Wokingham UA	6	
West Yorkshire	52		Buckinghamshire	12	
East Midlands	126	1.11	East Sussex	22	
Derby UA	9		Hampshire	44	
Leicester UA	10		Kent	54	
Nottingham UA	8		Oxfordshire	25	
Rutland UA	1		Surrey	31	
Derbyshire	24		West Sussex	35	
Leicestershire	20		South West	194	1.45
Lincolnshire	20		Bath & North East Somerset UA	6	
Northamptonshire	13		Bournemouth UA	7	
Nottinghamshire	21		Bristol, City of UA	11	
West Midlands	151	1.06	North Somerset UA	11	
Herefordshire, County of UA	6		Plymouth UA	12	
Stoke-on-Trent UA	2		Poole UA	3	
Telford and Wrekin UA	3		South Gloucestershire UA	11	
Shropshire	9		Swindon UA	3	
Staffordshire	34		Torbay UA	4	
Warwickshire	9		Cornwall and Isles of Scilly	23	
West Midlands (Met County)	68		Devon	22	
Worcestershire	20		Dorset	19	
			Gloucestershire	26	
			Somerset	23	
			Wiltshire	13	
TOTAL FOR ENGLAND	1505	1.13			

¹ number of deaths/million/annum based on mid-2001 population estimates in England (source: ONS) over the 27-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 2016

WALES†	No. of cases	WALES†	No. of cases
Isle of Anglesey	5	Neath Port Talbot	1
Gwynedd	6	The Vale of Glamorgan	3
Conwy	6	Cardiff	8
Denbighshire	1	Bridgend	2
Flintshire	3	Rhondda, Cynon, Taff	8
Wrexham	6	Merthyr Tydfil	3
Powys	15	Caerphilly	12
Ceredigion	3	Blaenau Gwent	0
Pembrokeshire	3	Torfaen	4
Carmarthenshire	4	Monmouthshire	3
Swansea	9	Newport	5
TOTAL FOR WALES (MORTALITY RATE*)	110 (1.40)	†unitary authorities	

SCOTLAND†	No. of cases	SCOTLAND†	No. of cases
Aberdeen City	6	Highland	5
Aberdeenshire	10	Inverclyde	3
Angus	2	Midlothian	1
Argyll & Bute	4	Moray	4
Clackmannanshire	2	North Ayrshire	4
Dumfries & Galloway	4	North Lanarkshire	6
Dundee City	7	Orkney Islands	0
East Ayrshire	2	Perth & Kinross	1
East Dunbartonshire	4	Renfrewshire	6
East Lothian	3	Scottish Borders	3
East Renfrewshire	1	Shetland Islands	3
Edinburgh, City of	24	South Ayrshire	4
Eilean Siar	0	South Lanarkshire	8
Falkirk	5	Stirling	5
Fife	10	West Dunbartonshire	2
Glasgow City	14	West Lothian	4
TOTAL FOR SCOTLAND (MORTALITY RATE*)	157 (1.15)	†council areas	

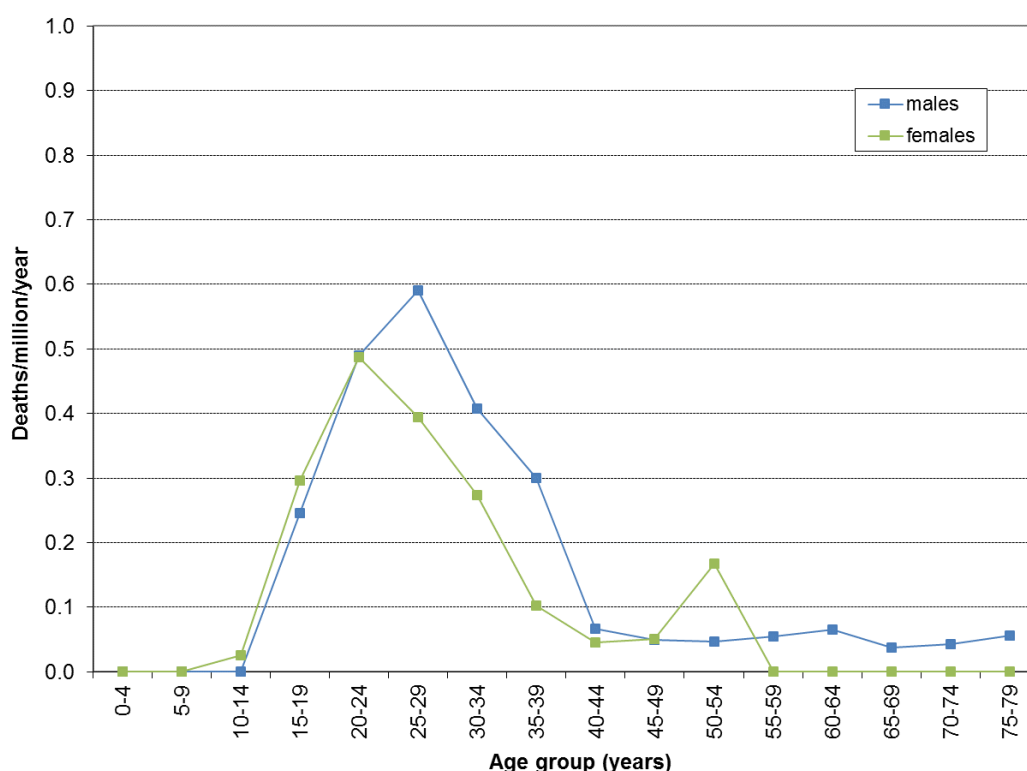
NORTHERN IRELAND†	No. of cases	NORTHERN IRELAND†	No. of cases
Antrim	3	Down	3
Ards	1	Dungannon	0
Armagh	1	Fermanagh	0
Ballymena	0	Larne	1
Ballymoney	1	Limavady	0
Banbridge	1	Lisburn	5
Belfast	10	Magherafelt	0
Carrickfergus	0	Moyle	0
Castlereagh	0	Newry & Mourne	1
Coleraine	2	Newtownabbey	0
Cookstown	1	North Down	0
Craigavon	4	Omagh	1
Derry	2	Strabane	1
TOTAL FOR N IRELAND (MORTALITY RATE*)	38 (0.83)	†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 27-year period of the study. Postcode of residence obtained from AFD Postcode Plus.

2.3 Variant Creutzfeldt-Jakob Disease

Up to 31st December 2016, 178 cases of definite or probable vCJD had been identified in the UK (123 definite and 55 probable cases who did not undergo post mortem). Seventy-five (42%) of the 178 cases were female and 103 (58%) were male. The median age at onset of disease was 26½ 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 sCJD). 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 2016 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 sCJD of 4 months (range 1 to 74) during the period 1990-2016.

Figure 5 Age- and sex-specific mortality rates from variant CJD in the UK
1 May 1995 - 31st December 2016



Mortality rates calculated using ONS mid-2001 population estimates

Of 161 vCJD cases tested, one case of definite vCJD was heterozygous (MV) at codon129 of the *PRNP* gene while the remaining 160 definite or probable vCJD cases were methionine homozygous (MM). A single case of possible vCJD with an MV genotype was described in the Seventeenth Annual Report 2008 (www.cjd.ed.ac.uk/documents/report17.pdf). To date, no case of vCJD has been identified in the UK in individuals born after 1989.

Geographical distribution of variant CJD

Tables 2a and 2b present data on the geographical distribution by residence at onset (for all 178 vCJD cases) and residence at death (for 175 vCJD cases who had died by 31st December 2016 and were resident in the UK at death), along with the crude mortality rate per million population per annum of each standard region.

Table 2a Cases of definite and probable variant CJD shown by residence at onset (n=143) and residence at death (n=144†) in England (region & 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	0.20	East	13	13	0.11
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	0.18	Suffolk	3	3	
Blackburn with Darwen UA	0	0		London	20	18	0.11
Blackpool UA	1	1		Inner London	7	7	
Halton UA	0	0		Outer London	13	11	
Warrington UA	2	2		South East	23	20	0.12
Cheshire	5	6		Bracknell Forest UA	1	1	
Cumbria	1	1		Brighton and Hove UA	0	0	
Greater Manchester	10	9		Isle of Wight UA	0	1	
Lancashire	4	4		Medway UA	0	1	
Merseyside	4	4		Milton Keynes UA	0	0	
Yorkshire and the Humber	17	18	0.17	Portsmouth UA	1	2	
East Riding of Yorkshire UA	1	1		Reading UA	0	0	
Kingston Upon Hull, UA	0	0		Slough UA	0	0	
North East Lincolnshire UA	1	1		Southampton UA	1	0	
North Lincolnshire UA	0	0		West Berkshire UA	0	0	
York UA	0	0		Windsor & Maidenhead UA	0	0	
North Yorkshire	4	4		Wokingham UA	0	0	
South Yorkshire	5	5		Buckinghamshire	0	1	
West Yorkshire	6	7		East Sussex	2	2	
East Midlands	8	10	0.11	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		South West	18	17	0.16
Leicestershire	4	5		Bath & NE Somerset UA	0	0	
Lincolnshire	2	2		Bournemouth UA	1	1	
Northamptonshire	1	1		Bristol, City of UA	1	1	
Nottinghamshire	1	1		North Somerset UA	0	0	
West Midlands	6	10	0.09	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	2	2	
				Somerset	4	5	
				Wiltshire	4	3	
TOTAL FOR ENGLAND	143	144	0.13				

* number of deaths/million/annum based on mid 2001 population estimates (source: ONS): 1 May 1995 to 31 Dec 2016. Postcode of residence obtained from AFD Postcode Plus.

† excludes 3 cases who died abroad.

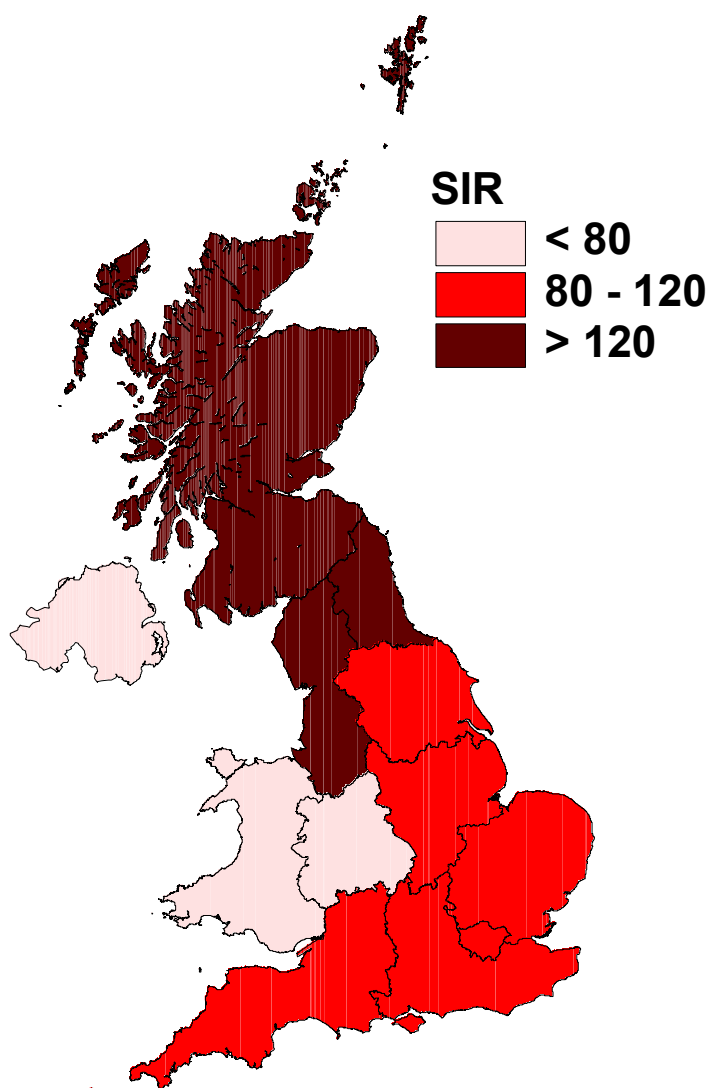
Table 2b Cases of definite and probable variant CJD shown by residence at onset (n=35) and residence at death (n=31): Wales, Scotland and NI

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
Cardiganshire	1	1	Monmouthshire	0	0
Swansea	1	0	Newport	0	0
TOTAL (MORTALITY RATE*)	8	6 (0.10)	†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 (0.20)	†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	1	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	3 (0.08)	†district council areas		

* number of deaths/million/annum based on mid-2001 population estimates (source: ONS): 1 May 1995-31 Dec 2016. Postcode of residence obtained from AFD Postcode Plus.

Cases have been widely spread throughout the UK. 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 6. 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, 100 vCJD cases) of Great Britain in 1991.¹ The rate ratio controlling for age and sex is 1.39 (95% CI 1.03-1.88), 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.

Figure 6 Standardised variant CJD incidence ratios (SIRs) up to 31st December 2016, by region of residence on 1st January 1991

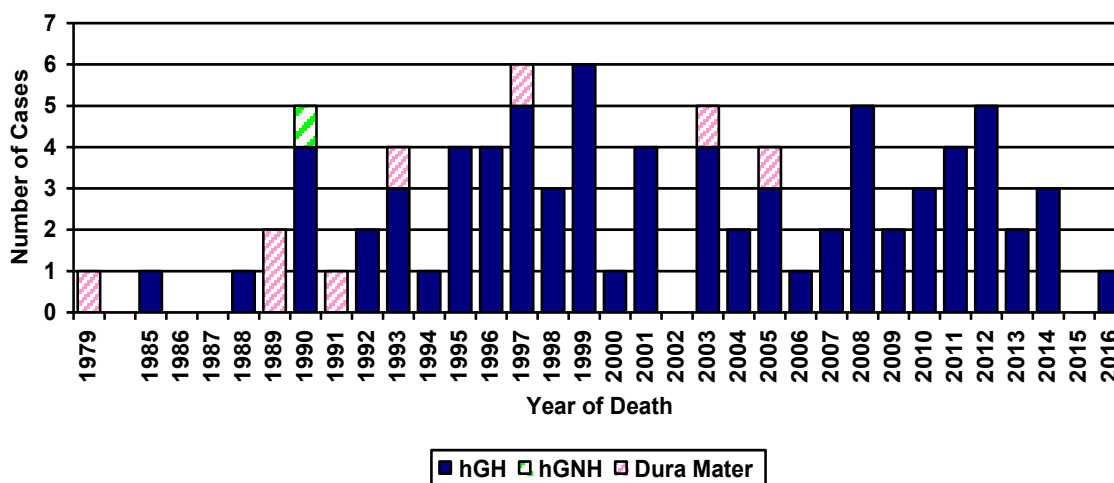


¹ Cousens S, Smith PG, Ward H, Everington D, Knight RSG, Zeidler M, Stewart G, Smith-Bathgate EAB, Macleod MA, Mackenzie J, Will RG. Geographical distribution of variant Creutzfeldt-Jakob disease in Great Britain, 1994-2000. *Lancet* 2001; 357: 1002-1007.

2.4 Iatrogenic Creutzfeldt-Jakob disease

Since 1970, up to 31st December 2016, 85 cases of CJD attributable to iatrogenic exposure have been identified, 8 in individuals receiving dura mater implants, 76 in individuals who had received human-derived growth hormone (hGH) and one in a recipient of human gonadotrophin (hGN) who was treated in Australia. All these individuals have died (Figure 7). The mean age at death of the hGH/hGN group was 35 years (with a range of 20-51 years) and for the dura mater cases 46½ years (range 27-78 years).

Figure 7 Deaths from iatrogenic CJD, 1979-2016



The first identified iatrogenic case was a dura mater recipient who died in 1979. The first hGH-related death occurred in 1985. Since 1985 in the UK, human pituitary-derived hormones have been replaced by synthetic preparations. Details of the UK human pituitary-derived hormone cases, with a discussion of the incubation periods, were published in 2003.² A study of the accumulated UK experience with dura mater-related CJD, including incubation periods, was undertaken and the results published in 2006.³

Iatrogenic transmission of CJD/vCJD is also studied by the Unit through the identification and investigation of surgical or other links between cases. 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.

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 19th Annual Report (www.cjd.ed.ac.uk/documents/report19.pdf)

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

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

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 vCJD⁴. The second recipient (Case 2) died from a non-neurological disorder 5 years after receiving blood from a donor (Donor 2) who subsequently developed vCJD⁵; 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 vCJD⁶. 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 vCJD⁷.

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 PE Hewitt, Dr CA Llewelyn).

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 and allocated to a diagnostic category by an Expert Neurological Advisory Group made up of consultants who have specialised knowledge of paediatric neurology, neurogenetics and metabolic disease, together with representation from the National CJD Research & Surveillance Unit.^{8,9,10}

As of 31st December 2016, after nearly 20 years of surveillance, 4137 patients with suspected PIND had been reported and the Expert Group had discussed 2718 of these. 1752 cases had a confirmed underlying cause other than vCJD, being categorised into over 190 known neurodegenerative diseases. There have been six cases of vCJD: four definite and two probable. Three were reported in 1999, one in 2000 and two 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 A Powell, Ms L Stelitano, Ms AM Winstone)

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

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

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

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

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

⁹ Devereux G, Stelitano 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.

¹⁰ Verity C, Winstone AM, Stelitano L, Will R, Nicoll, A. The epidemiology of progressive intellectual and neurological deterioration in childhood. *Arch Dis Child* 2010; 95:361-364 deterioration in childhood. *Arch Dis Child* 2010; 95:361-364.

2.7 Surveillance of potential occupational exposure to CJD

Public Health England in collaboration with NCJDRSU have set up an occupational surveillance study with two parts: 1) a registry for the prospective long term monitoring of healthcare and laboratory workers who have incurred occupational exposures to prion diseases and 2) the retrospective review of possible occupational exposures of CJD cases who have been healthcare or laboratory workers. By the end of 2016, 2 healthcare workers and one laboratory worker had reported prion-disease exposures as a result of needle stick/sharps injuries. None have subsequently developed prion disease. Retrospective investigations of possible occupational exposures of CJD cases continues to be undertaken to determine if any exposure to prion disease occurred – there is no evidence from the most recent retrospective review to indicate the occurrence of occupational exposure to the prion agent.^{11 12}

(Collaborators on this project: K Sinka)

2.8 Prion surveillance in primary immunodeficiency patients

The study began in 2006 and aims to identify whether there is evidence of abnormal prion protein/vCJD in the blood and/or body tissues of primary immunodeficiency patients exposed to UK sourced immunoglobulin between 1996 and 2000.¹³

By the end of April 2017 a total of 77 patients registered in 16 immunology centres across Great Britain had participated in the study. Of these, 13 had died with a further 6 lost to follow up, leaving 58 participants registered over 12 sites. Participants have now been followed up for approximately 1264 person-years following exposure to UK-sourced immunoglobulin. In this time no participants have shown any clinical or pathological features suggestive of vCJD or evidence of abnormal prion protein in tissues tested.

(Collaborators on this project: M Turner, R McNairney, M Helbert, M Buckland, P Minor, J Cooper, R Herriott, A Huissoon, M Gompels, S Jolles, C Chopra, G Hayman, S Murng, P Wood, M Browning, J Darroch, B Grimbacher, T Garcez, H Alachkar, H Longhurst)

¹¹ Thorpe J, Mackenzie J, Molesworth A, Sinka K, Will R. Occupational exposures to prion diseases in healthcare and laboratory workers. Poster presentation at Prion 2012, 9-12 May, Amsterdam.

¹² Mackenzie JM, Urwin P, Mackenzie G, Knight RSG, Will RG, Molesworth AM. Poster presentation at Prion 2017, 23-26 May, Edinburgh.

¹³ Helbert MR, Bangs C, Bishop M, Molesworth A, Ironside J.(2015). No evidence of asymptomatic variant CJD infection in immunodeficiency patients treated with UK-sourced immunoglobulin. *Vox Sang*. 2015 Nov 3. doi: 10.1111/vox.12358.

2.9 Enhanced surveillance of individuals identified as at increased risk of CJD

The potential for secondary transmission of CJD has led to collaborative studies with the UK Haemophilia Centre Doctors Organisation, Institute of Child Health (London), NHS Blood and Transplant, National Prion Clinic, Public Health England, Health Protection Scotland aimed at identifying whether there is evidence of clinical or sub-clinical infection in those judged to be at increased risk of CJD, such evidence is investigated through review of clinical records and medical histories, and through post-mortem investigations.

As at 31st December 2016, three cases of vCJD and one asymptomatic infection had been identified in recipients of blood from donors who later developed vCJD (see section 2.5 TMER) and one asymptomatic infection in a bleeding-disorder patient who received UK sourced plasma products.¹⁴

(Collaborators on this project: P Adlard, H Ward, L Dewhurst, N Gill, C Hay, P Hewitt, M Makris, S Mead, P Minor, B Palmer, K Sinka)

¹⁴ Peden A, McCardle L, Head MW, Love S, Ward HJT, Cousens SN, Keeling DM, Millar CM, Hill FGH, Ironside JW. Variant CJD infection in the spleen of a neurologically asymptomatic UK adult patient with haemophilia. *Haemophilia* 2010; 16: 296-304.

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 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.

3.1 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 and provides tissues to researchers through the CJD Brain and Tissue Bank, which is part of the MRC-funded Edinburgh Brain Bank.

In the contemporary referrals for 2016, the numbers of cases diagnosed as prion diseases was similar to those in the previous year; the numbers of cases in which there was no evidence of CJD or an alternative diagnosis was made is also very similar. No cases of vCJD were identified in the UK and none were referred from outside the UK. However, one case of vCJD, the first confirmed in an MV individual, was reported by the MRC Prion Unit UCL and referred to the CJDRSU under a shared tissue agreement. One case of variably protease-sensitive prionopathy was identified in 2016, with a further case referred by the MRC Prion Unit UCL under the shared tissue agreement.

In addition to the UK CJD surveillance work, the neuropathology laboratory is involved in CJD screening studies in patients identified as being at increased risk of CJD, including through exposure to vCJD through blood products or plasma products (Table 3). The laboratory is also involved as a reference centre for a PHE 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.

**Table 3 Breakdown of Laboratory Activities:
Period 1st January 2016– 31st December 2016**

	CURRENT YEAR	PREVIOUS YEAR
REFERRED CASES (UK)		
Sporadic CJD	36	29
Genetic CJD	1	1
Variant CJD	0	0
Iatrogenic CJD (GHT)	0	0
Iatrogenic CJD (Lyodura)	0	0
Gerstmann-Straussler-Scheinker Syndrome	0	0
Fatal Familial Insomnia	0	0
Variably protease sensitive prionopathy	1	0
No evidence of CJD	7	13
Alzheimer's disease	1	3
Dementia with Lewy Bodies	0	0
Lewy Body disease	4	1
Other forms of brain disease†	3	2
*MRC PRION UNIT UCL UK REFERRALS (under shared tissue agreement)		
Sporadic CJD	6	-
Genetic CJD	1	-
Variant CJD	1	-
Variably protease sensitive prionopathy	1	-
REFERRED CASES (EU)		
Sporadic CJD	0	2
REFERRED CASES (ROW)		
CJD, probable sporadic	2	2
Other forms of brain disease	0	0
No evidence of CJD	0	1
UK PRION SCREENING STUDIES		
Haemophilia Cases-UKHCDO	0	0
Primary Immune deficiency patients-PIDSUK	0	1
HISTORICAL CASES		
Prion Disorders	6	40
Alzheimer's disease	0	1
No evidence of CJD	3	3
Other forms of brain disease†	1	3
TOTAL NUMBER OF CASES	74	102

NOTES

* Cases referred from the MRC Prion Unit UCL in reporting year 2015 (previous year) were categorised as Prion Disorders under 'HISTORICAL CASES'

† Other: Encephalopathy-2; Huntington's disease -1; Progressive Supranuclear Palsy (PSP) – 1.

Abbreviations:

GHT Growth Hormone Therapy

UKHCDO

UK Haemophilia Centre Doctors' Organisation

ROW Rest of World

PIDSUK

UK Primary Immunodeficiency Screening Project

EU European Union

3.2 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^{res}) fragments determined by Western blot analysis. The recognised PrP^{res} types, their nomenclature and their association with different human prion diseases are shown in Figure 8 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^{res} and increase the sensitivity of the test.

Figure 8

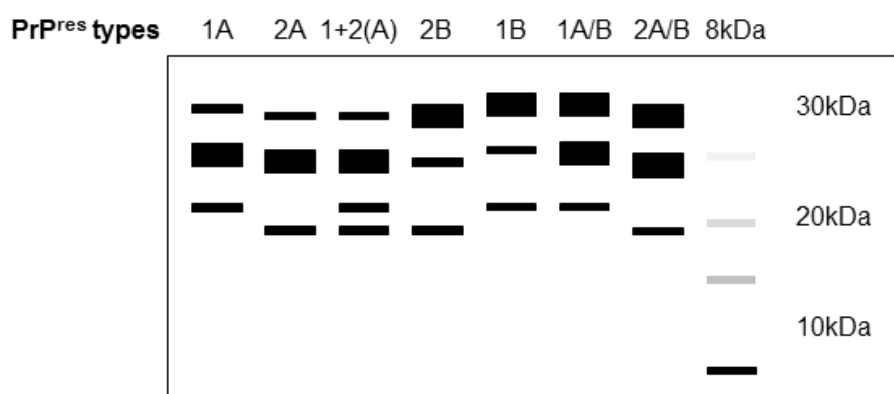


Figure 8 shows the diagrammatic representation of the main protease resistant prion protein (PrP^{res}) types found in the human prion disease brain as determined by proteinase K digestion and Western blot analysis. The classification of the banding pattern has two components, one numerical depending 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 placed 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 42 UK cases with frozen tissue were received and analysed in 2016. The results of the analysis were as follows:

Table 4 Breakdown of cases analysed in 2016

Diagnosis	Type	PrP ^{res} +ve CNS
CJD	Sporadic	34/34
	Genetic	1/1
VPSPr		1/1
Alternative final diagnosis or not determined		0/6 ¹

¹includes one brain biopsy

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

Table 5 PrP^{res} type / *PRNP* genotype breakdown of CJD cases analysed in 2016

Diagnosis	<i>PRNP</i> genotype	Type 1A	Type 2A	Type 1A(+2)	Type 1B	Type 8kDa
Sporadic CJD	MM	19 ^{1,2}		1		
	MV	1	6 ^{3,4}			
	VV		7			
Genetic CJD (E200K)	MM				1	
VPSPr						1

¹includes one case with type 1A, plus a minority 8kDa band

²includes one case with type 1A, plus a previously unrecognised minority intermediate band

³includes one case with a type 2A doublet band characteristic of the kuru plaque variant of sCJD MV2

⁴includes one case with type 2A, plus a minority 8kDa band

MRC Prion Unit UCL UK referrals

Western blot analysis was performed on frozen brain tissue from an additional 19 cases referred to the NCJDRSU by the MRC Prion Unit UCL under a shared agreement and comprised 12 case of sCJD (eight type 1, two type 2 and two type 1+2 PrP^{res} types), one case of VPSPr (8kDa PrP^{res}), one case of vCJD (type 2B in an MV patient) and one case of gCJD with an octapeptide repeat insertion (type 1A PrP^{res}). The remaining four cases did not have a human prion disease.

Non-UK referrals

There were no non-UK referrals for Western blot analysis.

3.3 Brain banking activities

The bank of fixed and frozen tissues in the Research and Surveillance Unit was used extensively in 2016 for diagnostic and collaborative research purposes with colleagues in the UK and overseas. Funding from MRC was renewed in 2013 to support the activities of the CJD bank as part of the Edinburgh Brain Bank (Director – Professor Colin Smith) for a further 5 years. The Edinburgh Brain Bank is a member of the MRC Network of UK Brain Banks, which works to 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.ed.ac.uk/clinical-brain-sciences/research/edinburgh-brain-and-tissue-bank>).

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.

3.4 Molecular Genetics

Genetic CJD

One hundred and fifty-six 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 156 cases, 136 were resident in England, 11 were resident in Wales, 3 were resident in Northern Ireland, 5 were resident in Scotland and one was resident in Guernsey. Twenty-four cases were still alive as at 31st December 2016. Sixty-nine of the cases had insertions in the coding region of the PrP gene, 49 carried the mutation at codon E200K, 15 at codon D178N, 4 at codon V210I, one at codon D167G, 2 at codon V163STOP, one at codon G54S, one at codon E211Q and one at codon E196K. The remaining 13 were identified as genetic on the basis of relatives known to have had CJD. The mean age at death was 55½ years (range 29-95 years).

PRNP Codon 129 distribution in sporadic CJD

The distribution of PRNP codon 129 genotypes in sCJD has been analysed since the inception of the Unit in 1990. The overall distribution of PRNP codon 129 genotypes in sCJD is 61.5% MM, 18.5% MV, 20% VV (see Table 6). There appears to be evidence ($p=0.014$) of a change in the PRNP codon 129 distribution in sCJD between the periods. The explanation for this remains unclear. It should be noted that not all cases are genotyped (data available on 64%) 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 UK, 1990-2016

Deaths from sCJD	Percentage tested	MM (%)	MV (%)	VV (%)
Deaths from 1 January 1990 – 31 December 1999	63%	200 (70)	43 (15)	43 (15)
Deaths from 1 January 2000 – 31 December 2009	65%	255 (59)	90 (21)	87 (20)
Deaths from 1 January 2010 – 31 December 2015	63%	256 (53)	81 (19)	99 (23)
Total	64%	711 (61.5)	214 (18.5)	229 (20)
Genotype distribution for the normal population¹⁵		(44)	(45)	(11)

PRNP codon 129 distribution in variant CJD

In clinical cases for whom genetic data are available ($n=161$, 90%), 160 were methionine homozygotes at PRNP codon 129 of the PrP gene and one case was heterozygous at PRNP codon 129 of the PrP gene.

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

¹⁵ 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.

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

Introduction

During the period January-December 2016, the laboratory received 272 cerebrospinal fluid (CSF) from suspected CJD patients residing in the UK, 58 samples from suspected CJD patients residing outwith the UK and 53 from young onset dementia patients (Table 7)

Table 7 Origin of CSF samples sent to the NCJDRSU for CSF 14-3-3 analysis from January 2016 – December 2016

Patient Group	Number CSF samples received
Young Onset Dementia	53
Suspected CJD (non-UK)	58
Suspected CJD (UK)	272
Total number	383

Results of 14-3-3 and RT-QuIC analysis on the 272 cases of suspected CJD in the UK are shown in Table 8.

Table 8 CSF 14-3-3 and RT-QuIC results in 272 CSF samples from suspected CJD cases in the UK

Patient Group (n)	14-3-3 number positive/total number analysed (% positive)	RT-QuIC number positive/total number analysed (% positive)
Neuropathologically confirmed sporadic CJD (25)	21/25 (84%)	25/25 (100%)
Probable sporadic CJD (62)	42/58 ¹ (72%)	56/60 ² (93%)
Possible sporadic CJD (11)	0/10 ³ (0%)	7/11 (64%)
Neuropathologically confirmed genetic E200K CJD (1)	1/1	1/1
Not CJD (173)	4/169 ⁴ (2%)	0/173 (0%)

¹4 CSF samples were not analysed for CSF 14-3-3 as only RT-QuIC was requested.

²2 CSF samples were insufficient for RT-QuIC analysis.

³1 CSF sample was not analysed for CSF 14-3-3 as only RT-QuIC was requested.

⁴4 CSF samples were not analysed for CSF 14-3-3 as only RT-QuIC was requested.

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Section

5

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Dr AM Molesworth	Senior Epidemiologist
Dr A Green	Reader (CSF analysis)
Dr C Smith	Professor of Clinical Neuropathology
Dr P Urwin	Clinical Research Fellow
Dr B Waddell	Clinical Research Fellow
Dr G Mackenzie	Clinical Research Fellow
Dr A Peden	Postdoctoral Research Fellow
Ms J Mackenzie	Surveillance Co-ordinator
Ms T Lindsay	European Study Co-ordinator
Mrs B Smith-Bathgate	National Care Co-ordinator
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Mr N Attwood	Database Manager
Dr D Ritchie	Postdoctoral Research Fellow
Dr M Barria	Postdoctoral Research Fellow
Dr N McKenzie	Postdoctoral Research Fellow
Mr J Alibhai	Postdoctoral Research Fellow
Ms S Lowrie	Senior Biomedical Scientist
Mrs M Le Grice	Senior Biomedical Scientist
Mrs M Andrews	Senior Biomedical Scientist
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Ms K Burns	Neuropathology Technical Officer
Ms L Banks	Research Technician
Ms A Libori	Research Technician
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