

FOURTEENTH ANNUAL REPORT 2005

# CREUTZFELDT-JAKOB DISEASE SURVEILLANCE IN THE UK

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# Table of Contents

<b>SECTION 1</b>	
Summary	3
<b>SECTION 2</b>	
Clinical Surveillance	5
2.1 Referrals	5
2.2 Sporadic CJD	7
2.3 Variant CJD	14
2.4 Iatrogenic CJD	22
2.5 Transfusion Medicine Epidemiology Review	23
2.6 Study of Progressive Intellectual and Neurological Deterioration (PIND)	25
<b>SECTION 3</b>	
Case-Control Study	26
<b>SECTION 4</b>	
Laboratory Activities	29
4.1 Neuropathology – Statement of Progress and Surveillance Activities	29
4.2 Protein Laboratory	30
4.3 Brain Banking Activities	32
4.4 Molecular Genetics	32
4.5 CSF 14-3-3 and other brain specific proteins	33
<b>SECTION 5</b>	
National Care Team	35
<b>SECTION 6</b>	
Publications	37
<b>SECTION 7</b>	
Staff	40

## SUMMARY

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

The information provided in this fourteenth report continues to provide evidence of a high level of case ascertainment. In last year's report, a decrease in the number of referrals was noted, along with a drop in the number of recorded sporadic CJD deaths in 2004. This raised concerns about the completeness of case ascertainment. Further data are now available. While the decline in the number of referrals has been maintained in 2005, analysis suggests that much, if not all of the decline is due to changes in the number of referrals who turn out not to be CJD cases. The number of sporadic cases in 2005 was higher than in 2004 and the data for 2005 may still be incomplete; thus the present data do not suggest a significant consistent decline in the number of recorded sporadic CJD deaths (discussed in more detail in Section 2). Detailed clinical and epidemiological information has been obtained for the great majority of patients. The case-control study for risk factors of CJD has continued recruitment and initial analysis has been undertaken, with the results with respect to vCJD published in early 2006. Although there is ongoing evidence that the post mortem rate for patients with suspected CJD has declined, in line with general autopsy rates in the UK, it remains high (around 60%). The decline is reflected in the reduced number of brain specimens examined in the neuropathology laboratory; sporadic CJD numbers being 52 in 2003, 32 in 2004 and 32 in 2005.

In 1990-2005 mortality rates from sporadic CJD in England, Wales, Scotland and Northern Ireland were, respectively, 0.89, 1.01, 0.88 and 0.49/million/year. The differences between these rates are not statistically significant ( $p>0.5$ ). The variation in the observed mortality rates between the different regions within the UK is not statistically significant ( $p>0.3$ ). The highest and lowest mortality rates from sporadic CJD were observed in the South West (SMR=131) and Northern Ireland (SMR=67). 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 December 2005, there were 153 deaths from definite or probable variant CJD (vCJD) in the UK. Of these, 110 were confirmed by neuropathology. A further 6 probable cases were alive as at 31<sup>st</sup> December 2005. The clinical, neuropathological and epidemiological features of these cases of vCJD are remarkably uniform and consistent with our previous descriptions. Risk factors for the development of vCJD include age, residence in the UK and methionine homozygosity at

codon 129 of the prion protein gene - all 139 cases (87%) of vCJD with available genetic analysis have been methionine homozygotes. The incidence of vCJD is higher in the north of the UK than in the south. Analysis of the incidence of vCJD onsets and deaths from January 1994 to December 2005 indicates that a peak has been passed. While this is an encouraging finding, the incidence of vCJD may increase again, particularly if different genetic subgroups are found but with longer incubation periods. The identification of disease-related PrP in the spleen of a blood recipient of PRNP-129 MV genotype is not inconsistent with such an hypothesis. In addition, this case along with the report of the prevalence of abnormal PrP in the large study of appendix and tonsil tissues suggests a possibility of a greater number of preclinical or subclinical cases in the population than might be indicated by the present numbers of confirmed clinical cases.

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

The activities of the NCJDSU are strengthened by collaboration in 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 variant CJD associated with blood transfusion and the identification in 2004 of PrP<sup>res</sup> in the spleen of a recipient of blood donated by someone incubating vCJD. In early 2006 a further case of variant CJD associated with blood transfusion was identified.

The success of the National CJD Surveillance Project continues to depend on the extraordinary level of co-operation from the neuroscience community and other medical and paramedical staff throughout the UK. We are particularly grateful to the relatives of patients for their help with this study.

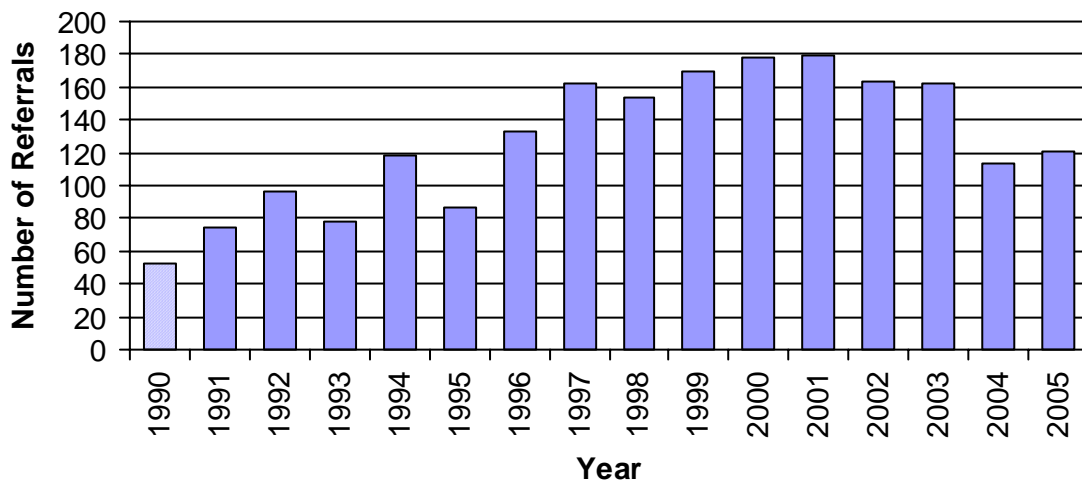
## CLINICAL SURVEILLANCE

The national surveillance of CJD in the UK was initiated in May 1990 in response to a recommendation in the Report of the Working Party on Bovine Spongiform Encephalopathy (Southwood Committee). The surveillance is funded by the Department of Health and by the Scottish Executive Health Department. The initial aim of the NCJDSU was to identify any change in the pattern of CJD that might be attributable to human infection with the agent responsible for the emergence of bovine spongiform encephalopathy (BSE) in cattle. Such a change was recognised in 1996 when vCJD was first described. The NCJDSU now aims to monitor characteristics of CJD, specifically sporadic CJD and variant CJD, to identify trends in incidence rates and to study risk factors for the development of disease. This report documents the findings in relation to UK cases of sporadic, familial, iatrogenic and variant CJD referred up to 31st December 2005 (with data ascertained up to 14<sup>th</sup> February 2006). Mortality data from England and Wales include retrospective data from 1970; for Scotland and Northern Ireland, retrospective mortality data are available from 1985.

### 2.1 Referrals to NCJDSU

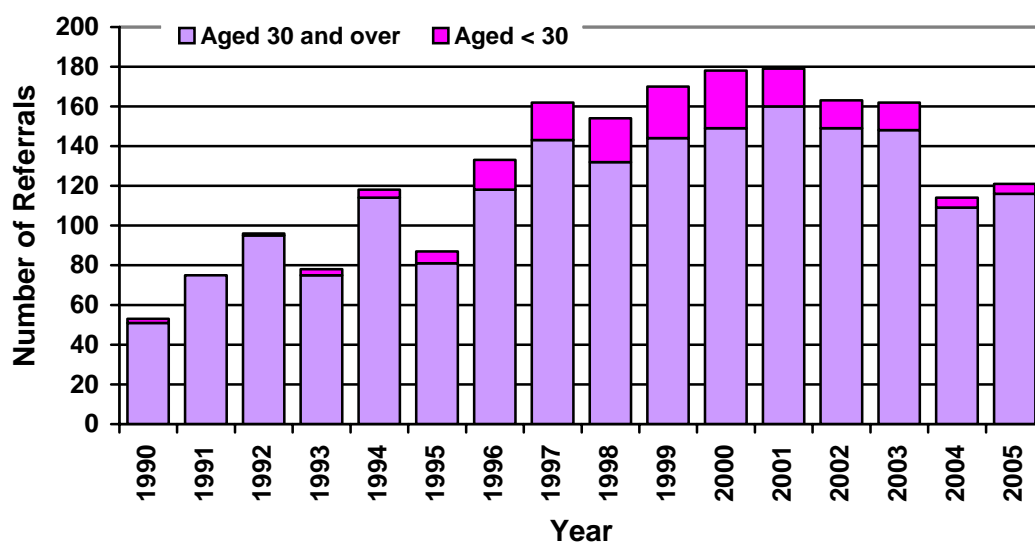
The NCJDSU receives referrals of suspect cases of CJD and a proportion of these will turn out not to have CJD. Referrals of suspect cases increased over the years after the present surveillance system began in 1990, particularly following the description of vCJD in 1996. Over the 1999-2003 period, the annual referral number varied little, between 162 and 179. In 2004, however, there were only 114 referrals, the lowest level since 1996. The number of referrals in 2005 rose slightly to 121 (Figure 1a).

**Figure 1a Referrals to NCJDSU of patients with suspected CJD : 1 May 90 – 31 Dec 05**



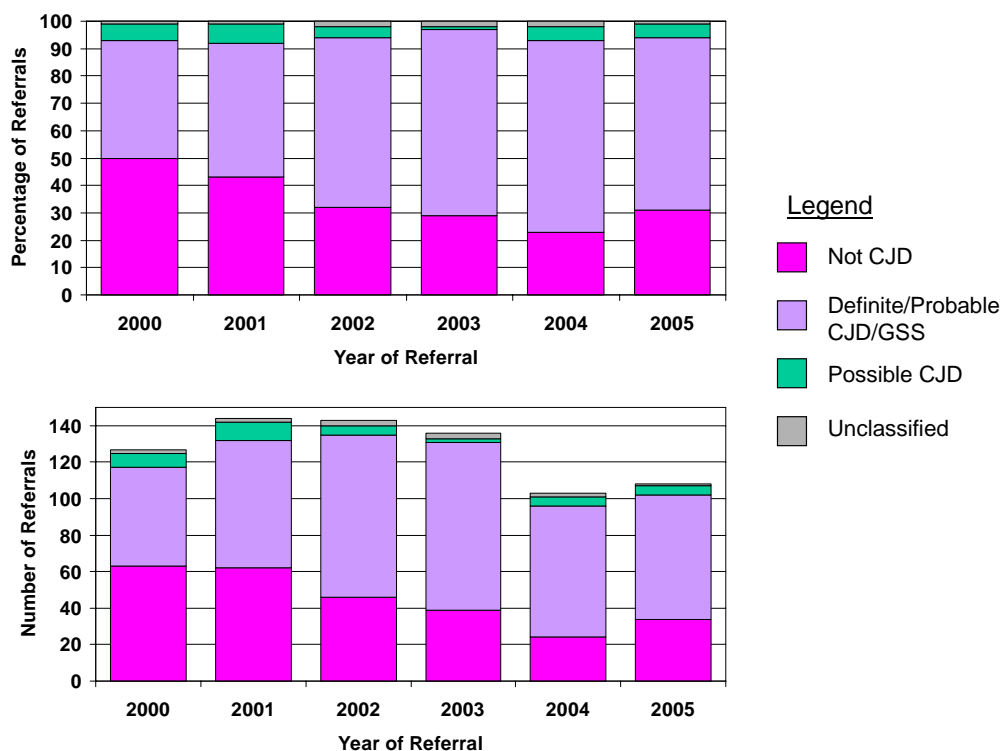
It appears that the pattern of referrals has changed during the period 2000-2004. The number of referrals aged less than 30 has declined since 2000, and can probably be explained by the decline in vCJD cases over that period (Figure 1b). The age group 30-59 shows a fairly constant number of referrals over 2000-2003 (49-54 individuals per year) with a large drop in 2004 and 2005 (35 and 34 individuals respectively). This age range includes more sporadic cases than the younger age group and the observed pattern does not fit particularly with the decline in vCJD cases. However, annual numbers of cases in this age group over the period 2000-2005 appear compatible with random variation (test for extra Poisson variation  $p=0.25$ ). The age group 60 and over show a similar pattern to the 30-59 age group with a fairly constant rate of referrals over 2000-2003 (between 96 and 106 individuals per year) and a drop in 2004 and 2005 (74 and 82 individuals respectively). The annual number of cases over the period 2000-2005 also appear compatible with random variation (test for extra Poisson variation  $p=0.29$ ). However, looking at all referrals aged 30+ during 2000-2005, there is some evidence of extra-Poisson variation ( $p=0.02$ ), suggesting chance is an unlikely explanation for the lower numbers of referrals seen in 2004 and 2005. Performing a comparison of referrals during the period 2000-03 with those in 2004-05, there is very strong evidence of a difference ( $p=0.0001$ ) between the two periods. Figure 1b shows numbers of referrals to NCJDSU split between age groups  $<30$  and  $\geq 30$ .

**Figure 1b Referrals to NCJDSU : 1 May 1990 – 31<sup>st</sup> December 2005: Age  $< 30$  and age  $\geq 30$**



Over the period 2000-2005 the largest drop in referral numbers occurred in those whom eventually turned out not to be cases of CJD (Figure 1c). This suggests that the changes in numbers of referrals in the past couple of years is, at least in part, due to changes in the numbers of non-cases recorded as referrals.

**Figure 1c Diagnostic classification of referrals: 2000-2005\***  
(shown as percentages and absolute numbers)

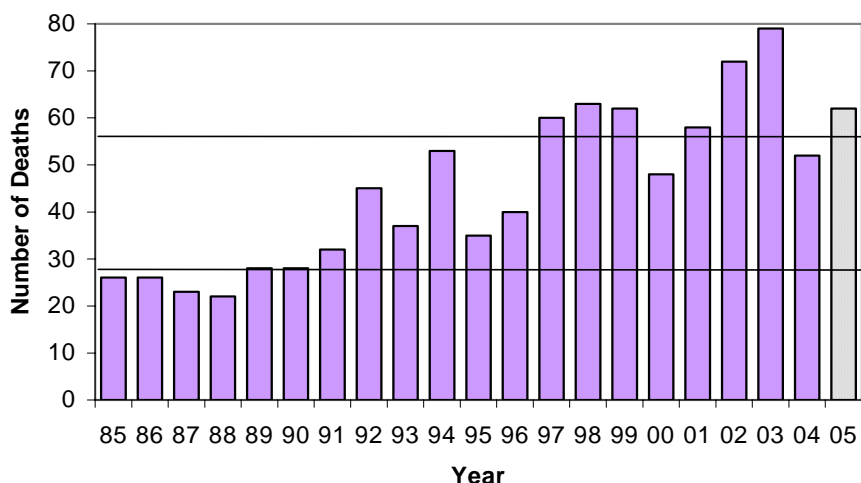


\*excludes suspect vCJD referrals and vCJD cases

## 2.2 Sporadic Creutzfeldt-Jakob Disease

Between 1st January 1970 and 31st December 2005, 1228 cases of sporadic CJD were identified in the UK, of which 9 cases were alive on 31st December 2005. Two further cases were identified in Jersey but they were not included in the following UK analyses. Of these UK cases, 925 (75%) were classified as definite cases with the remainder classed as probable. Figure 2a shows the number of deaths each year from sporadic CJD for the UK between 1985 and 2005, Figure 2b shows similar data for England and Wales between 1970 and 2005 and Figure 2c shows the number of deaths from sporadic CJD in Scotland and Northern Ireland between 1985 and 2005. In England and Wales the number of deaths identified each year increased from an average of about 10 per year at the beginning of the 1970s, and rising from about 30 to 50 per year in the 1990s. A similar phenomenon has been observed in other European countries and this probably largely reflects improved case ascertainment. Over the shorter time period for which data are available for Scotland and Northern Ireland there is no clear secular trend. Over the period 1990-2005 the average crude annual mortality rates from sporadic CJD per million population were 0.89 in England, 1.01 in Wales, 0.88 in Scotland and 0.49 in Northern Ireland (Table 1). When account is taken of age and sex, the variation in recorded mortality between the different countries is not statistically significant ( $p > 0.5$ ).

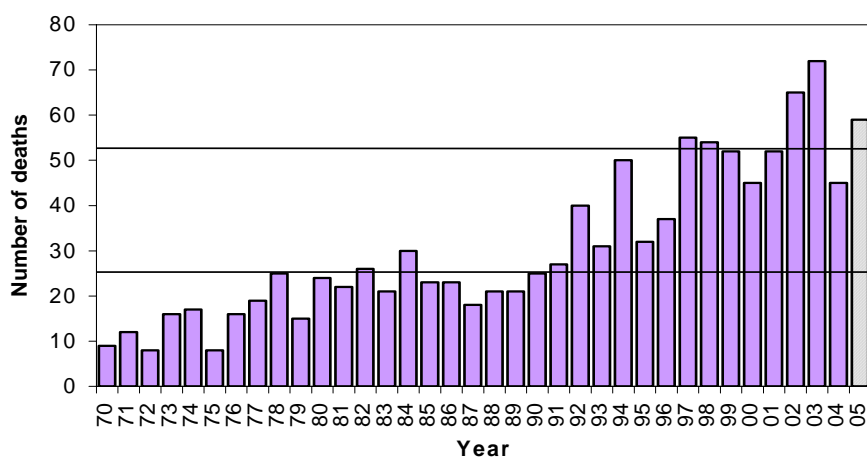
**Figure 2a Deaths from sporadic CJD, UK, 1985-2005**



Note: The horizontal lines indicate the number of deaths approximately equivalent to crude mortality rates of 0.5 and 1 per million per year.

Data for 2005 may be incomplete.

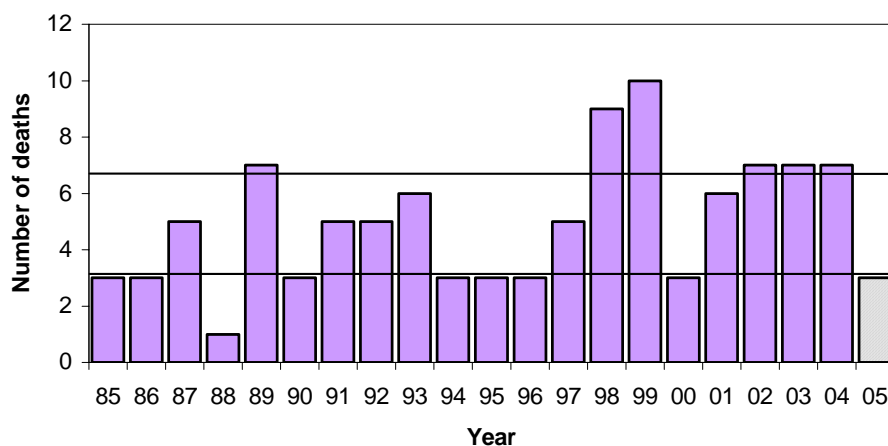
**Figure 2b Deaths from sporadic CJD, England and Wales, 1970-2005**



Note: The horizontal lines indicate the number of deaths approximately equivalent to crude mortality rates of 0.5 and 1 per million per year.

Data for 2005 may be incomplete.

**Figure 2c Deaths from sporadic CJD, Scotland and Northern Ireland 1985-2005 (please note different scale from Figs 1a and 1b)**



Note: The horizontal lines indicate the number of deaths approximately equivalent to crude mortality rates of 0.5 and 1 per million per year.

Data for 2005 may be incomplete.



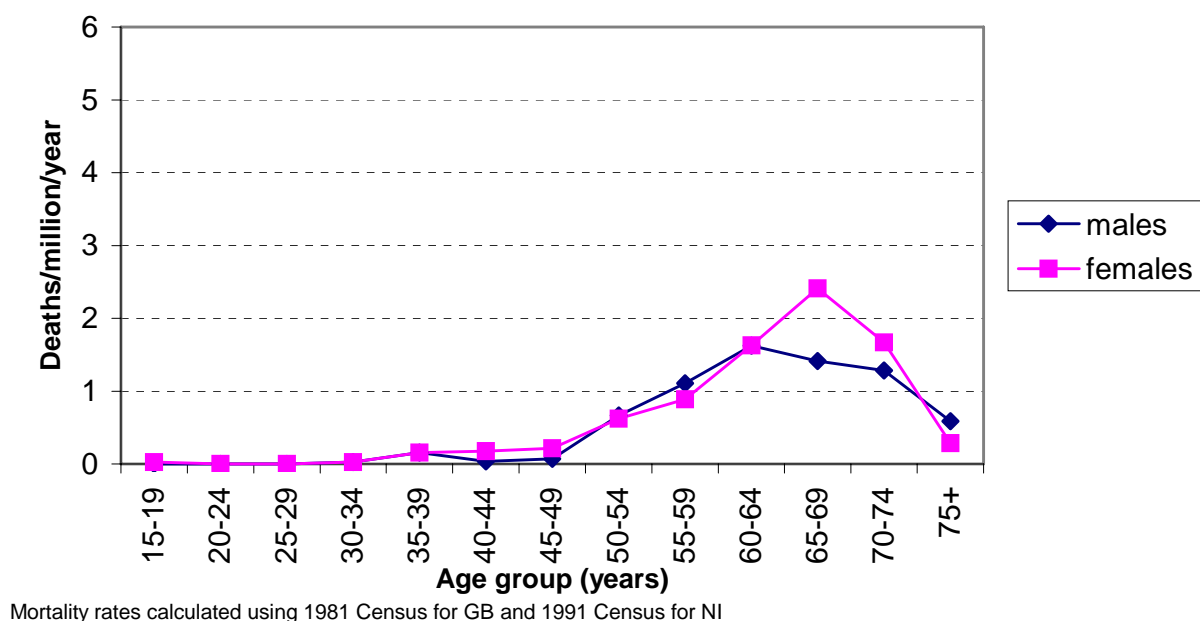
**Table 1 Deaths from definite and probable sporadic CJD by region and county of death: 1<sup>st</sup> January 1990 to 31<sup>st</sup> December 2005**

	No of cases	Total no (mortality rate/million/annum)*		No of cases	Total no (mortality rate/million/annum)*
<b>ENGLAND</b>			<b>ENGLAND</b>		
<u>North</u>			<u>Yorkshire &amp; Humberside</u>		
Cleveland	6		Humberside	8	
Cumbria	12		NorthYorkshire	13	
Durham	6	46 (0.93)	South Yorkshire	24	71 (0.88)
Northumberland	6		West Yorkshire	26	
Tyne & Wear	16				
<u>East Midlands</u>			<u>East Anglia</u>		
Derbyshire	9		Cambridgeshire	6	
Leicestershire	15		Norfolk	15	34 (1.01)
Lincolnshire	9	50 (0.76)	Suffolk	13	
Northamptonshire	2		<u>South West</u>		
Nottinghamshire	15		Avon	19	
<u>South East</u>			Cornwall	13	
Bedfordshire	7		Devon	16	
Berkshire	10		Dorset	17	98 (1.28)
Buckinghamshire	5		Gloucestershire	12	
East Sussex	10		Somerset	11	
Essex	31		Wiltshire	10	
Greater London	82	239 (0.84)	<u>West Midlands</u>		
Hampshire	24		Hereford & Worcs.	8	
Hertfordshire	12		Shropshire	4	
Isle of Wight	2		Staffordshire	19	67 (0.79)
Kent	19		Warwickshire	4	
Oxfordshire	9		West Mids (Met)	32	
Surrey	9		<b>TOTAL FOR ENGLAND</b>		
West Sussex	19		<b>694 (0.89)</b>		
<u>North West</u>					
Cheshire	12				
Greater Manchester	29	89 (0.87)			
Lancashire	23				
Merseyside	25				
<b>WALES</b>			<b>SCOTLAND</b>		
Clwyd	7		Borders	3	
Dyfed	3		Central	5	
Gwent	7		Dumfries & Galloway	0	
Gwynedd	11		Fife	3	
Mid Glamorgan	11		Grampian	11	
Powys	2		Highland	1	
South Glamorgan	3		Lothian	19	
West Glamorgan	3		Strathclyde	25	
<b>TOTAL FOR WALES</b>			Tayside	3	
<b>47 (1.01)</b>			Islands (Shetland)	2	
			Islands (Orkney)	0	
<b>NORTHERN IRELAND</b>			Islands (Western Isles)	0	
13	<b>13 (0.49)</b>		<b>TOTAL FOR SCOTLAND</b>		
			<b>72 (0.88)</b>		

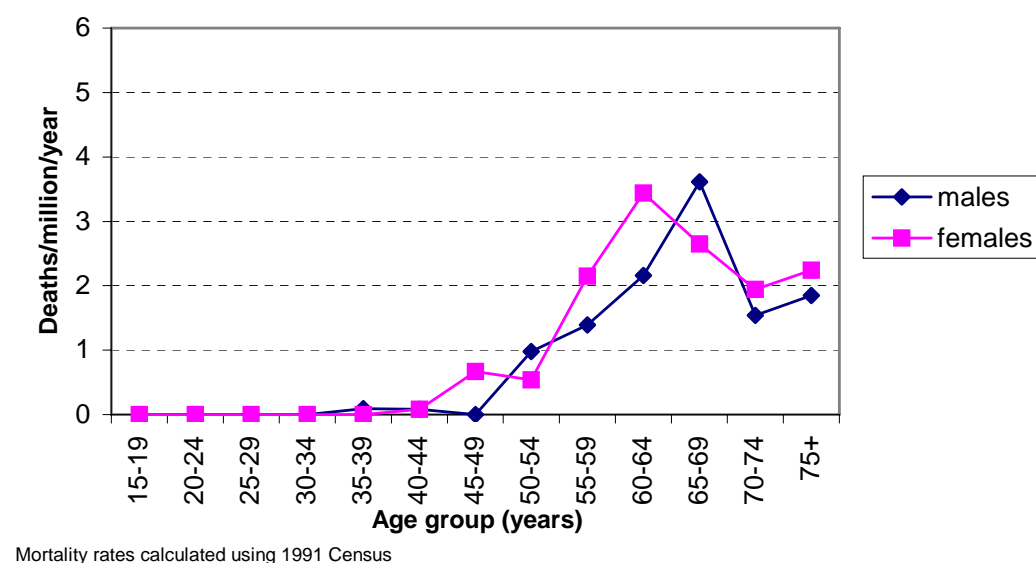
\* based on 1994 population by region (as published in ONS Regional Trends, 1996 edition) over the 16-year period of the study.

Figure 3a, 3b and 3c shows average annual age- and sex-specific mortality rates over the time periods 1970-89, 1990-95 and 1996-05, respectively. The median ages of cases at death during these time periods were 64, 66 and 68 years, respectively. In all three time periods, the mortality rates below 40 years of age were extremely low (< 0.2/million/year). Thereafter, in all three periods, the mortality rates increased until the ages of 60-74 years and then declined. The decline might be explained by an under-ascertainment in the most elderly. The change in the sex ratio, affecting particularly older cases, with a male excess after 1995, was examined in the 2001 annual report. The explanation for this trend remains unclear.

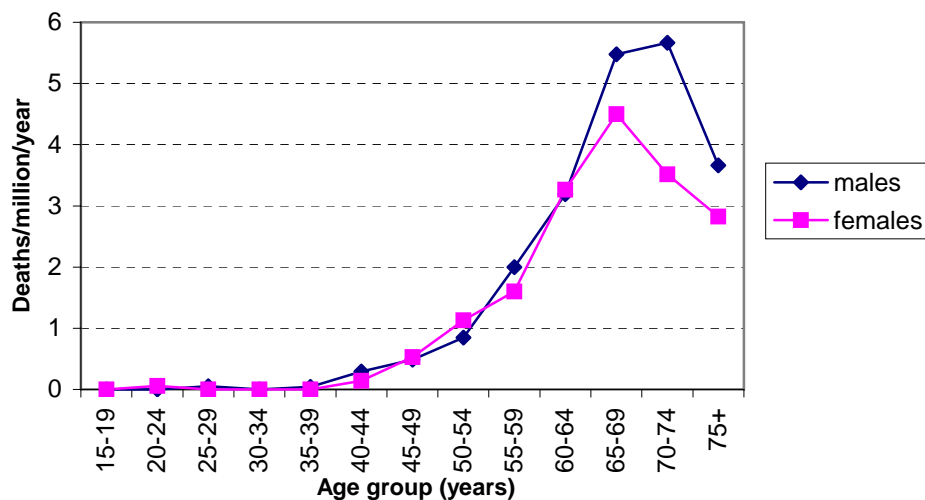
**Figure 3a** Age- and sex-specific mortality rates from sporadic CJD in the UK 1970-1989  
(note: from 1970-1984 only England & Wales, thereafter UK)



**Figure 3b** Age- and sex-specific mortality rates from sporadic CJD in the UK 1990-1995



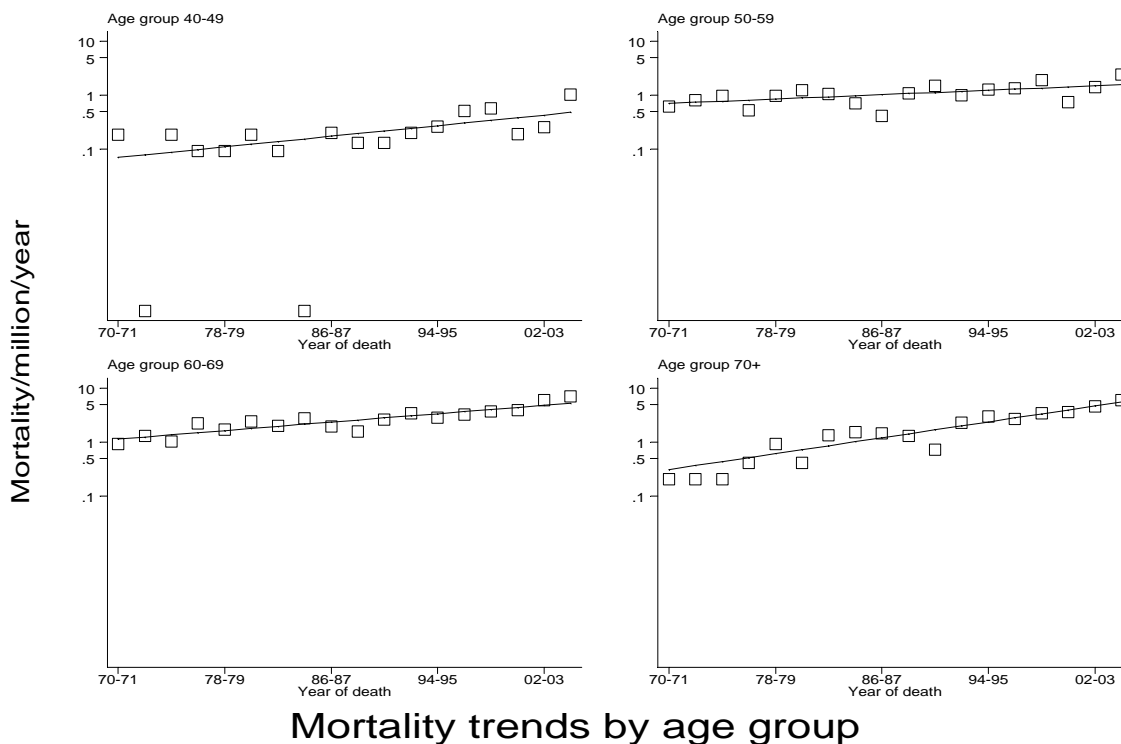
**Figure 3c** Age- and sex-specific mortality rates from sporadic CJD in the UK 1996-2005



Mortality rates calculated using 2001 Census

An analysis of age specific trends from 1970 to 2005 (Figure 4) shows there has been an increase in recorded mortality over time in all age groups, but that the greatest relative increase has occurred in those aged 70 years and above. Currently the mortality rate in this age group is similar to that in the age group 60-69 years. The temporal increases in mortality are statistically significant in all age groups ( $p=0.005$ ,  $p=0.002$ ,  $p<0.001$ ,  $p<0.001$  for age groups 40-49, 50-59, 60-69 and  $\geq 70$  years respectively). These observations are consistent with improved case ascertainment in all ages, but with the greatest increase occurring in the elderly.

**Figure 4** Trends in mortality from sporadic CJD by age: 1970-2005



Mortality rates calculated using 1981, 1991 & 2001 Census for time periods 1970-1985, 1986-1995 and 1996-2005 respectively.

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

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

Age at death (yrs)	Year of death																		Total <sup>2,3</sup>
	70-71	72-73	74-75	76-77	78-79	80-81	82-83	84-85 <sup>1</sup>	86-87	88-89	90-91	92-93	94-95	96-97	98-99	00-01	02-03	04-05 <sup>2</sup>	
10-19	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0 (0)	<b>1 (0)</b>
20-29	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0 (0)	<b>2 (0)</b>
30-39	1	0	0	2	2	1	1	4	1	0	1	0	0	0	1	0	0	0 (0)	<b>14 (0)</b>
40-49	2	0	2	1	1	2	1	0	3	2	2	3	4	8	9	3	4	4 (0)	<b>51 (0)</b>
50-59	7	9	11	6	11	14	12	8	5	13	18	12	15	20	28	11	21	20 (2)	<b>241 (2)</b>
60-69	9	13	10	22	17	24	20	28	22	18	30	39	32	35	40	43	65	39 (4)	<b>506 (4)</b>
70-79	2	2	2	4	9	4	11	16	18	14	7	21	34	30	35	38	51	37 (3)	<b>335 (3)</b>
80-89	0	0	0	0	0	0	2	0	0	2	2	7	3	6	10	11	9	14 (0)	<b>66 (0)</b>
90+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	0 (0)	<b>2 (0)</b>
<b>Total</b>	<b>21</b>	<b>24</b>	<b>25</b>	<b>35</b>	<b>40</b>	<b>46</b>	<b>47</b>	<b>56</b>	<b>49</b>	<b>50<sup>3</sup></b>	<b>60</b>	<b>82</b>	<b>88</b>	<b>100</b>	<b>125</b>	<b>106</b>	<b>151</b>	<b>114 (9)</b>	<b>1219 (9)</b>

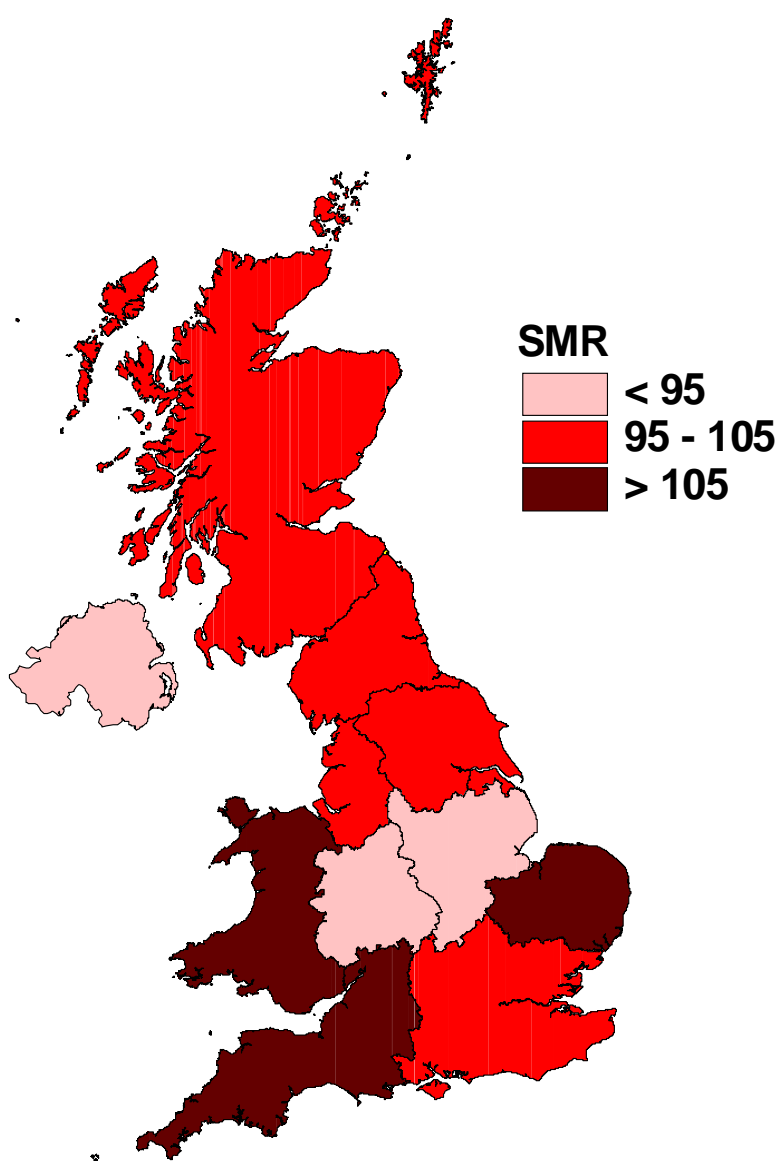
<sup>1</sup> Up to 1984, cases from England and Wales only. From 1985 onwards, cases from Scotland and Northern Ireland are included.

<sup>2</sup> Deaths up to 31st December 2005. Numbers in parentheses indicate additional cases alive on 31st December 2005. Data for 2005 not yet complete.

<sup>3</sup> Total includes one case whose age at death was unknown.

Age- and sex- standardised mortality ratios (SMRs) for the 11 standard regions of the UK for the period 1st January 1990 to 31st December 2005 were calculated (Figure 5). An SMR of 100 equates to average mortality rate. After adjusting for the age/sex distribution of the population, the variation in mortality rates between the different regions is not statistically significant ( $p>0.3$ ). Regions of relatively high mortality are South West (SMR=131), East Anglia (SMR=109) and Wales (SMR=106). Low mortality rates were observed in Northern Ireland (SMR=67), East Midlands (SMR=86) and West Midlands (SMR=90). The highest SMR (131 in South West) arose from 98 cases observed compared with 75 expected, an excess of about 1.5 cases every year compared to the national average. For both East Anglia and Wales the total numbers of excess cases was approximately 3.

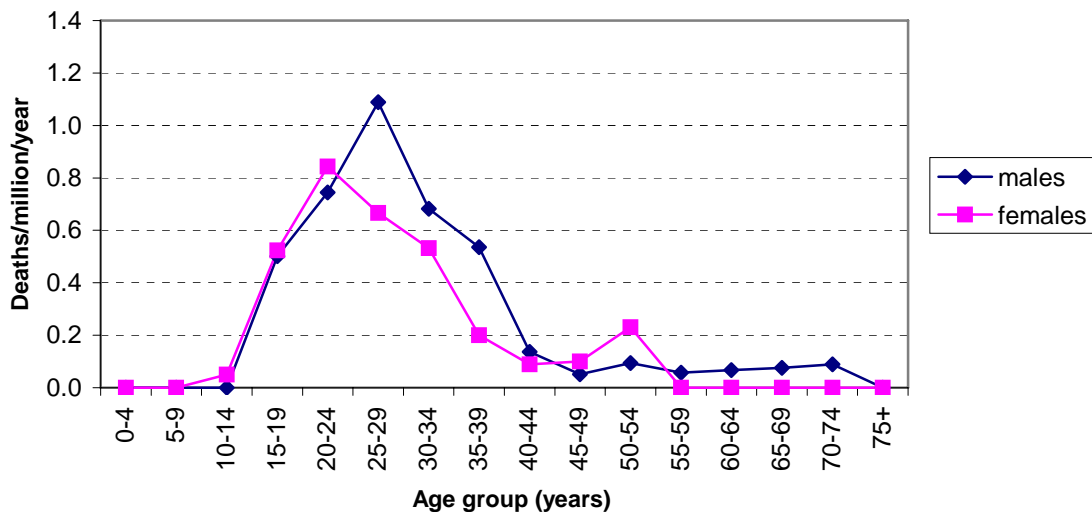
**Figure 5 Standardised mortality ratios (SMRs) by standard region, UK  
1 January 1990 - 31 December 2005**



### 2.3 Variant Creutzfeldt-Jakob Disease

Up to 31st December 2005, 159 cases of definite or probable vCJD had been identified in the UK (110 definite, 43 probable who did not undergo post mortem and 6 probable cases still alive). Seventy-one (45%) of the 159 cases were women. The median age at onset of disease was 26 years and the median age at death 28 years (compared with 66 years for the median age at onset and 67 years for the median age at death for sporadic CJD). The youngest case was aged 12 years at onset while the oldest case was aged 74 years. To date, no case of vCJD has been identified in the UK in individuals born after 1989. The age- and sex-specific mortality rates for vCJD over the time period 1 May 1995 to 31 December 2005 are shown in Figure 6. The median duration of illness from the onset of first symptoms to death was 14 months (range 6-39). The median duration of illness for cases of sporadic CJD was 4 months (range 1 to 74) during the period 1990-2005.

**Figure 6** Age- and sex-specific mortality rates from vCJD in the UK  
1 May 1995 - 31st December 2005



Mortality rates calculated using 2001 Census

#### Incidence of vCJD onsets and deaths from January 1994 - December 2005

Each quarter data on diagnosed cases of variant Creutzfeldt-Jakob disease (vCJD) in the UK are reviewed in order to investigate trends in the underlying rate at which disease onsets and deaths are occurring. The following analysis reviews the data to the end of December 2005.

#### Methods

##### Onsets:

The incidence of onsets by quarter was analysed with Poisson models using polynomial time trends (constant, exponential, quadratic exponential, cubic exponential). When modelling the incidence of onsets over time, delay to diagnosis, and that this delay may be shortening over time because of new diagnostic methods, must be taken into account. Consequently the data were cross-classified by quarter of onset and number of quarters delay from onset to diagnosis, and the delay from onset to diagnosis modelled using a gamma distribution with a mean that can vary over time. A further model looking at a rise to a plateau is also fitted to see if there is evidence that the epidemic has reached a constant level (at least temporarily).

*Deaths:*

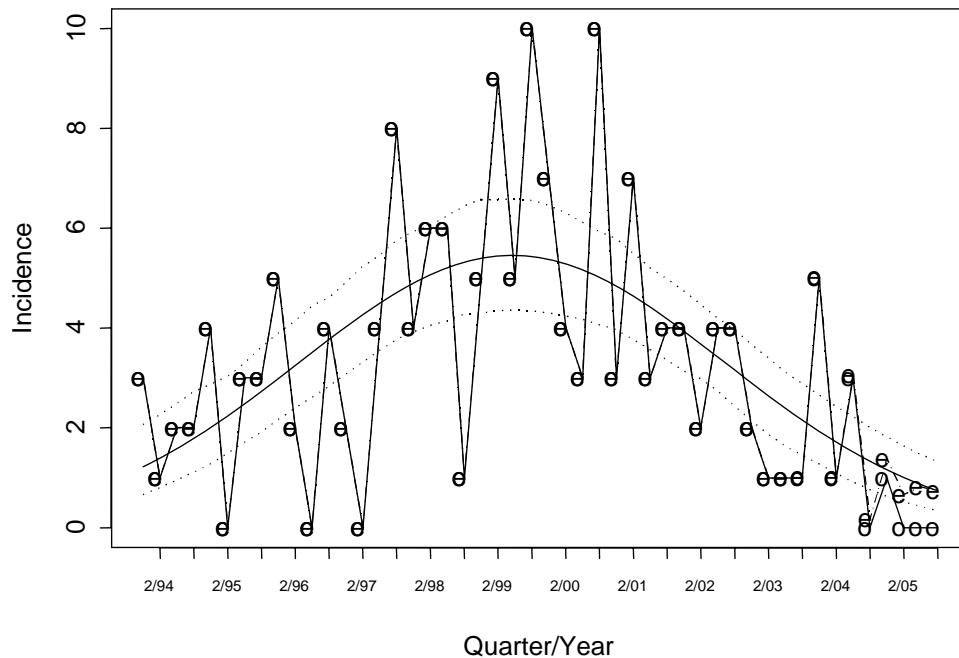
After grouping deaths by quarter the incidence of deaths were modelled by Poisson regression using polynomials. Most deaths are reported quickly so an adjustment for reporting delay is not necessary. With the exception of some increase in 2005, the age at death has not increased as may have been expected, assuming that most exposure to BSE ceased in the early 1990s. In order to examine this further the cases were stratified by quarter of death and birth cohort (pre1970, 1970s and 1980s). Trends in deaths over time were compared between these cohorts. A further model looking at a rise to a plateau was also fitted.

**Results for Onsets**

Since vCJD was first identified, the average interval between the onset of first symptoms and the diagnosis of vCJD has decreased. The mean delay to diagnosis is estimated to have reduced by an average of 4% per year and is currently estimated at 9 months.

The model providing the best fit to the data is shown in Figure 7. This model has a quadratic trend and fits the data better than a simple exponential trend ( $p < 0.001$ ). The quadratic model is consistent with an epidemic that has reached a peak and this model gives an estimated current incidence of 0.7 onsets per quarter. If the quadratic model is assumed to be correct then the peak is estimated to have occurred in mid 1999. A model was also fitted with an increase to a plateau, this model did not fit the data as well as the quadratic model. This provides further evidence that a peak has been passed.

**Figure 7: Observed (-o-) and expected (-e-) quarterly incidence of vCJD onsets  
Fitted exponential trend\* (—) is given with its 95% confidence limits (...)**



\* includes adjustment for delay from onset to diagnosis

### *Predicted onsets by the end of December 2005*

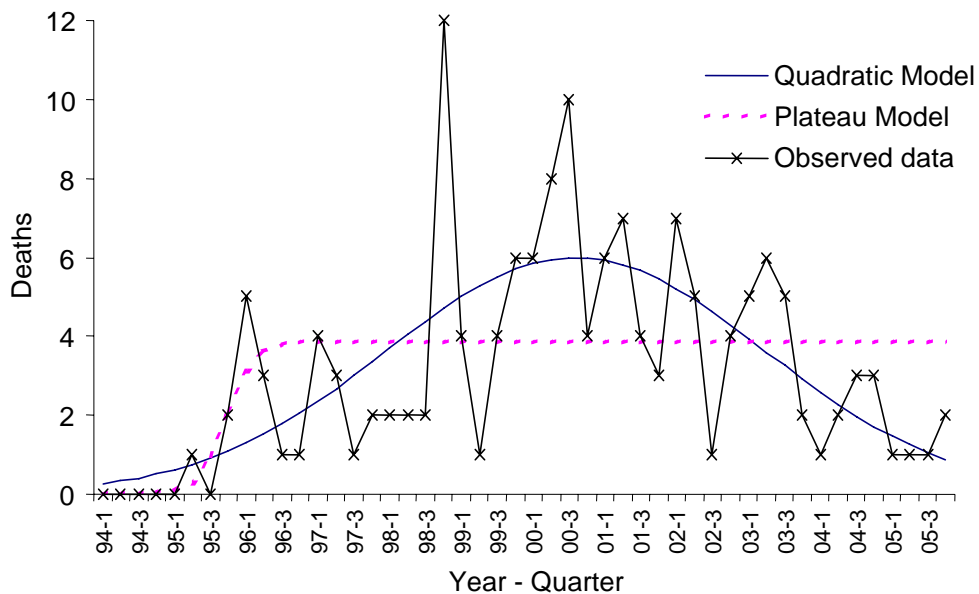
Based on the quadratic model, the estimated total number of cases with onset by December 2005 is 162 (159 already diagnosed + 3 not yet diagnosed) with a 95% prediction interval of 160 to 164.

### **Results for Deaths**

#### *All deaths combined*

As with onsets, the quadratic trend model provided the best fit with a significant improvement on the simple exponential model ( $p < 0.001$ ). This model is shown in Figure 8 and estimates that the current quarterly incidence of deaths is 0.9. If the quadratic model is assumed to be correct then the peak is estimated to have occurred in mid 2000. The model with a rise to a plateau gave significant evidence of a lack of fit ( $p = 0.02$ ), again indicating that a peak has been passed. A model with a cubic term was also fitted but did not provide an improved fit ( $p = 0.60$ ).

**Figure 8** Quadratic-exponential and plateau models for vCJD deaths incidence trend



#### *Predictions for deaths in 2006*

The model with the quadratic term predicts a total of just 2 deaths in 2006 with a 95% prediction interval of 0 to 5. Note that 6 cases are alive so this may be an underestimate.

#### *Assessment of Predictions made at the end of December 2004*

The quadratic model predicted 6 deaths with a 95% prediction interval of 2-13. The observed number was 5, which is consistent with the quadratic model.

### **Deaths by cohort**

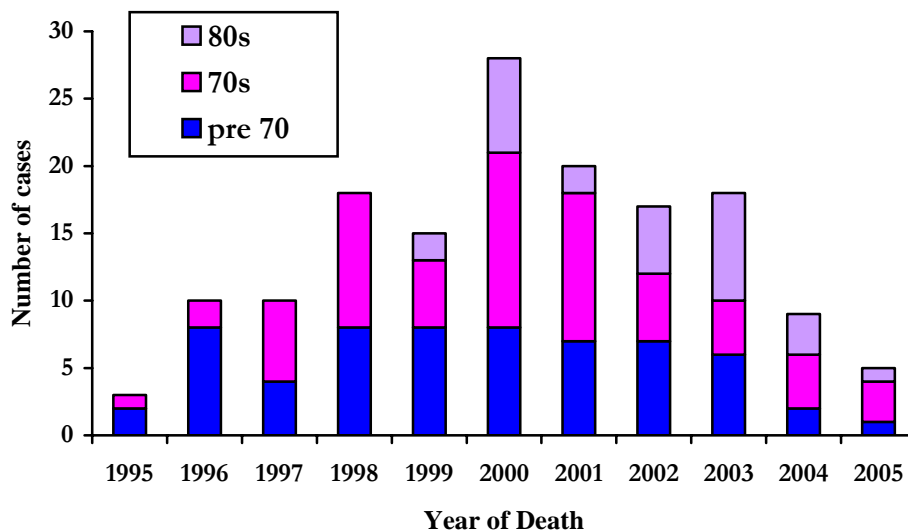
The age at death has so far remained stable, contrary to what might be expected given that most exposure to BSE is presumed to have ceased in the early 1990s. This finding is consistent with a number of possible explanations, for example:



- varying age-specific susceptibility (teenagers and young adults may be more susceptible to infection).
- age-specific exposure (possible different dietary habits in teenagers and young adults compared to older persons).
- different incubation periods by age (teenagers and young adults might have shorter incubation periods).

To examine this in more detail the epidemic curves (quadratic model) are compared in those born before 1970 with those born in the 1970s and the 1980s. This analysis showed significant differences by cohort in the shape of the fitted curves ( $p < 0.001$ ). The main difference is that in the 1980s cohort no deaths were seen prior to 1999 (Figure 9). In all three birth cohorts the quadratic model provides an improved fit compared to an exponential increase model ( $p < 0.001$ ).

**Figure 9 Deaths by year and birth cohort**



### Summary

Results from modelling the underlying incidence of onsets and deaths indicate that the epidemic reached a peak at about 5 or 6 onsets per quarter in mid 1999 and deaths in mid 2000 and has since declined to a current incidence of less than one onset/death per quarter. Extrapolating the best fitting model (the quadratic model) gives an estimate of 2 deaths in the next 12 months (95% prediction interval 0 to 5), however with 6 cases currently alive a prediction of 2 deaths is likely to be a slight underestimate.

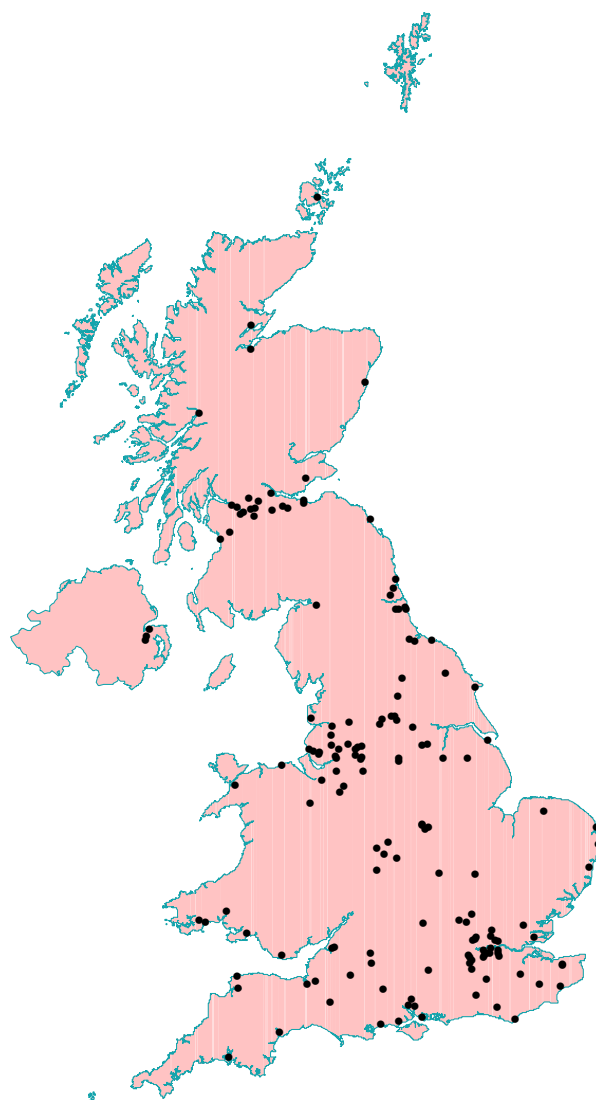
An analysis that looked at deaths by birth cohort (pre 1970, 1970s, 1980s) showed that the shape of the epidemic differs between cohorts, mainly due to the fact that deaths of individuals born in the 1980s were only seen from 1999 onwards.

It is important to note that although a peak has been passed, it is possible that there will be future peaks, possibly in other genetic groups. There is also the possibility of further cases due to person to person spread.

## Geographical distribution of variant CJD

Figure 10 shows the geographical distribution, by place of residence at onset, of 158 cases of vCJD in the UK. For one additional case the address at onset is known only at county level. Cases have been widely spread throughout the UK. Table 3 presents data on the geographical distribution by county of residence at onset (for all 159 vCJD cases) and residence at death (for 150 vCJD cases who had died by 31<sup>st</sup> December 2005 and were resident in the UK at death), along with the crude mortality rate per million population per annum of each standard region.

**Figure 10** Geographical distribution of places of residence at onset of symptoms of vCJD (n=158\*)



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

**Table 3 Cases of definite and probable vCJD shown by region and county of onset (n=159<sup>†</sup>) and region and county of death (n=150<sup>‡</sup>)**

	No of cases resident at onset	No of cases resident at death (mortality rate*)		No of cases resident at onset	No of cases resident at death (mortality rate*)
<b>ENGLAND</b>			<b>ENGLAND</b>		
<u>North</u>			<u>Yorkshire &amp; Humbs</u>		
Cleveland	3	3	Humberside	2	2
Cumbria	1	1	NorthYorkshire	3	2
Durham	1	2	South Yorkshire	4	4
Northumberland	3	4	West Yorkshire	6	7
Tyne & Wear	4	2	<b>Total</b>	<b>15</b>	<b>15 (0.28)</b>
<b>Total</b>	<b>12</b>	<b>12 (0.36)</b>	<u>East Anglia</u>		
<u>East Midlands</u>			Cambridgeshire	1	1
Derbyshire	0	1	Norfolk	2	2
Leicestershire	4	5	Suffolk	2	1
Lincolnshire	2	2	<b>Total</b>	<b>5</b>	<b>4 (0.18)</b>
Northamptonshire	1	1	<u>South West</u>		
Nottinghamshire	0	0	Avon	2	1
<b>Total</b>	<b>7</b>	<b>9 (0.21)</b>	Cornwall	2	1
<u>South East</u>			Devon	3	4
Bedfordshire	0	0	Dorset	1	1
Berkshire	0	1	Gloucestershire	0	0
Buckinghamshire	0	0	Somerset	4	5
East Sussex	2	2	Wiltshire	3	1
Essex	2	1	<b>Total</b>	<b>15</b>	<b>13 (0.25)</b>
Greater London	16	14	<u>West Midlands</u>		
Hampshire	6	3	Hereford & Worcs.	0	1
Hertfordshire	3	3	Shropshire	1	1
Isle of Wight	0	1	Staffordshire	0	0
Kent	5	5	Warwickshire	1	2
Oxfordshire	1	1	West Mids (Met)	4	6
Surrey	6	4	<b>Total</b>	<b>6</b>	<b>10 (0.18)</b>
West Sussex	1	1	<b>ENGLAND</b>	<b>126</b>	<b>122 (0.23)</b>
<b>Total</b>	<b>42</b>	<b>36 (0.19)</b>	<b>TOTAL</b>		
<u>North West</u>			<b>SCOTLAND</b>		
Cheshire	7	8	Borders	0	0
Greater Manchester	9	8	Central	1	1
Lancashire	4	4	Dumfries & Galloway	0	0
Merseyside	4	3	Fife	1	1
<b>Total</b>	<b>24</b>	<b>23 (0.34)</b>	Grampian	1	1
<b>WALES</b>			Highland	3	2
Clwyd	1	0	Lothian	4	4
Dyfed	3	3	Strathclyde	12	12
Gwent	0	0	Tayside	0	0
Gwynedd	1	1	Islands (Shetland)	0	0
Mid Glamorgan	0	0	Islands (Orkney)	1	0
Powys	0	0	Islands (Western Isles)	0	0
South Glamorgan	1	1	<b>SCOTLAND</b>	<b>23</b>	<b>21 (0.38)</b>
West Glamorgan	1	0	<b>TOTAL</b>		
<b>WALES TOTAL</b>	<b>7</b>	<b>5 (0.16)</b>			
<b>NORTHERN IRELAND TOTAL</b>	<b>3</b>	<b>2 (0.11)</b>			

\* mortality rate/million/annum based on 1994 population by region (as published in ONS Regional Trends, 1996 edition) over the period 1<sup>st</sup> May 1995 to 31<sup>st</sup> December 2005.

† includes cases still alive at 31<sup>st</sup> December 2005.

‡ excludes 3 cases who died abroad.

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

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

**Table 4 Distribution of 159 vCJD cases by standard region of residence on 1<sup>st</sup> January 1991**

<b>Standard region (in order of latitude of the centre of the region)</b>	<b>Population aged 10 years and above at the 1991 census</b>	<b>Number (cumulative incidence/million) of vCJD cases by place of residence in 1991</b>
Scotland	4,363,684	18 (4.12)
North	2,635,785	11 (4.17)
Yorkshire & Humberside	4,202,051	15 (3.57)
North-West	5,326,333	24 (4.51)
East Midlands	3,444,391	12 (3.48)
West Midlands	4,464,592	10 (2.24)
East Anglia	1,775,687	6 (3.38)
Wales	2,466,669	5 (2.03)
South-East	15,010,650	42 (2.80)
South-West	4,055,268	13 (3.21)
Northern Ireland	1,320,430	3 (2.27)
Total	49,065,540	159 (3.24)

**Figure 11** Standardised incidence ratios (SIRs) up to 31<sup>st</sup> December 2005 of vCJD by standard region on 1st January 1991

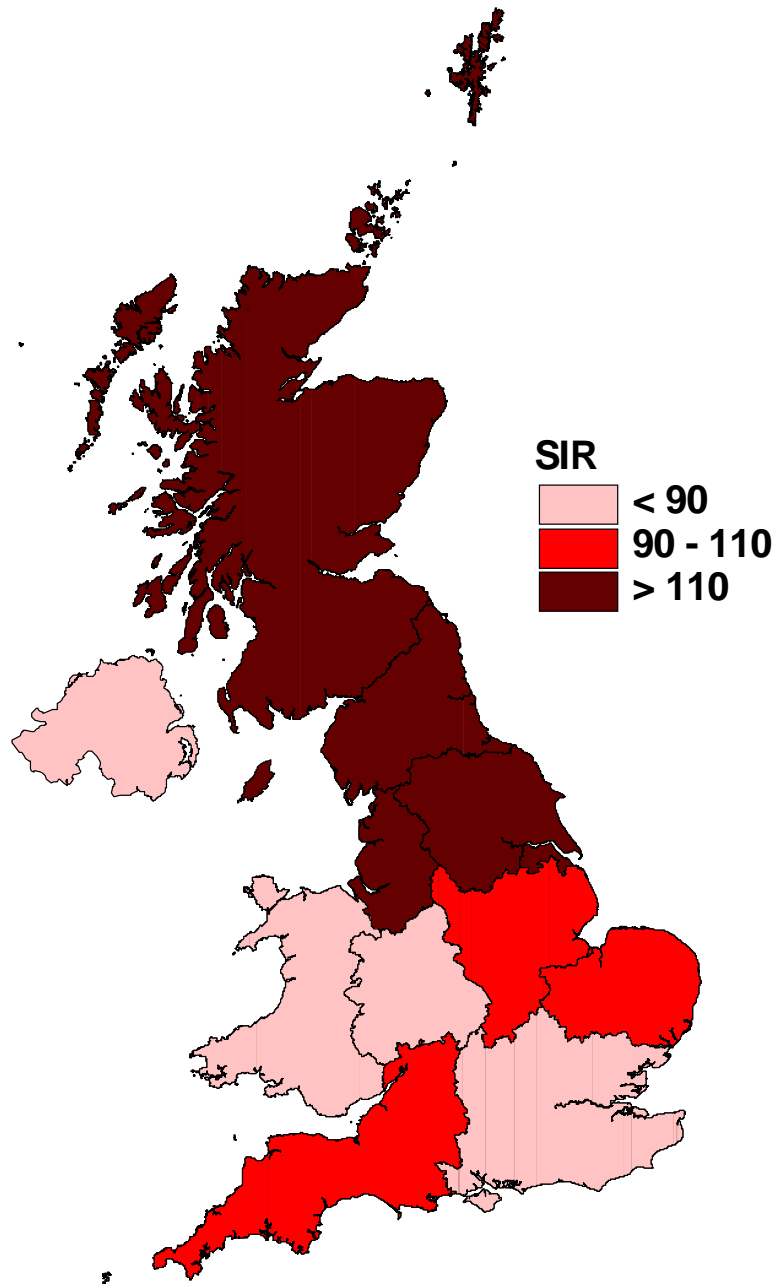


Table 5 shows the distribution of cases between the “North” and the “South” according to place of residence in 1991. We originally performed an analysis of the first 51 cases, distinguishing two areas. The “North” comprised four standard regions: Scotland, North, Yorkshire and Humberside, North West. The “South” comprised the remaining 6 regions: Wales, West Midlands, East Midlands, East Anglia, South West, South East. The excess of cases previously identified in the “North” (rate ratio controlling for age and sex = 1.94; 95% c.i. 1.12, 3.36) has declined somewhat as further cases have accrued, but remains statistically significant. The rate ratio controlling for age and sex is 1.46 (95% c.i., 1.07, 2.01), i.e. individuals living in the “North” in 1991 are about one and a half times more likely to have developed vCJD than individuals who were living in the “South” in 1991.

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

Region	Population aged 10 years and above at the 1991 census	Number (rate/million) of vCJD cases by place of residence at 1 <sup>st</sup> January 1991	
		First 51 cases	Total
“North” (North West, Yorks & Humbs, Northern, Scotland)	16.6 million	26 (1.57)	68 (4.11)
“South” (South West, South East, Wales, West Midlands, East Midlands, East Anglia)	31.2 million	25 (0.80)	88 (2.82)
Total (rate ratio*)	47.8 million	51 (1.94)	156 (1.46)

\*North versus South, adjusted for age and sex

Northern cases were slightly older at onset than southern cases (median of 27 years versus 25.5 years;  $p=0.7$ ), a similar proportion were male (54% versus 55% of southern cases).

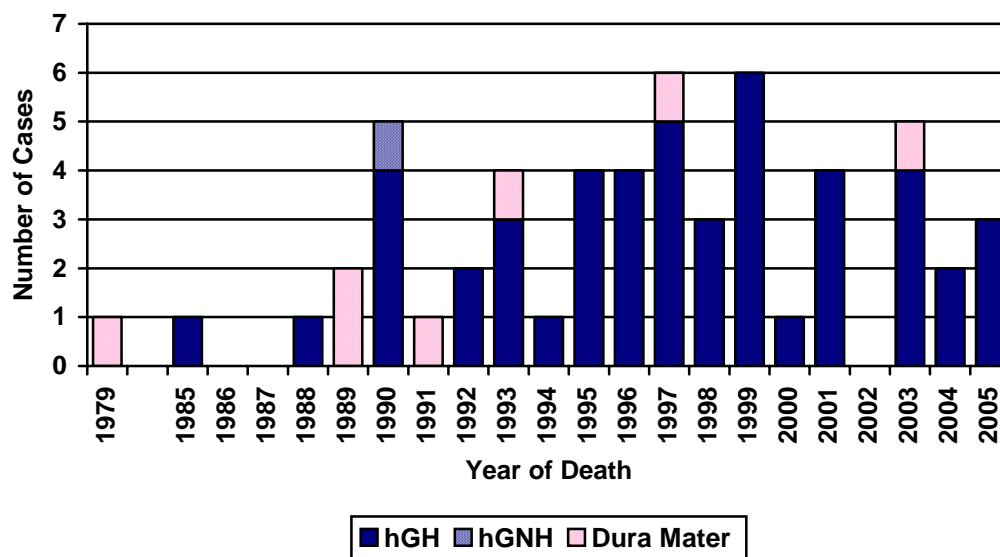
### Geographically Associated Cases of variant CJD

Geographically associated cases of variant CJD are defined to be two or more cases of probable or definite vCJD with a geographical association, either through proximity of residence or through another link with the same location (occupational, educational or social/recreational). By the end of December 2005 a total of thirteen investigations into geographically associated cases of vCJD had been conducted in the UK. The Leicestershire cluster of five cases remains the only statistically significant cluster of cases to date. None of the concluded investigations have revealed any suggestion of possible iatrogenic transmission. No evidence emerged from these investigations in any of the areas apart from Leicestershire of bovine heads being split or brains removed by local butchers in their shops during the relevant time period.

### 2.4 Iatrogenic Creutzfeldt-Jakob disease

Since 1970, up to 31st December 2005, 58 cases of CJD attributable to iatrogenic exposure have been identified, 7 in individuals receiving dura mater implants, 50 in individuals who had received human-derived growth hormone (hGH) and one in a recipient of human gonadotrophin (hGN). Fifty-six of these individuals have died (Figure 12) and 2 were still alive as at 31<sup>st</sup> December 2005.

**Figure 12 Deaths from iatrogenic CJD, 1979-2005**



The mean age at death of the hGH/hGN group was 31 years (with a range of 20-46 years) and for the dura mater cases 42 years (range 27-59 years).

The first identified iatrogenic case was a dura mater recipient who died in 1979. The first hGH-related death occurred in 1985. Since 1985 in the UK, human pituitary-derived hormones have been replaced by synthetic preparations.

A study of the accumulated UK experience with dura mater-related CJD was undertaken and will be published in 2006.

### 2.5 Transfusion Medicine Epidemiology Review

The Transfusion Medicine Epidemiology Review (TMER) is a collaborative project between the UK NCJDSU and UK Blood Services (UKBS). The main purpose is to investigate whether there is any evidence that CJD or vCJD may have been transmitted via the blood supply.

#### Methods

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

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

## Results

The following results are based on vCJD cases who donated or received blood and does not include data on the ongoing study of sporadic CJD.

Thirty-one vCJD cases were reported to have been blood donors. Four additional cases who were not reported to have been blood donors were found to be registered with UKBTS. One of these cases was found to have been a blood donor while the other three cases were registered as a donor but never made any donations. Twenty-four of the cases have been traced at blood centres, including the four additional cases mentioned above. Components derived from donations made by 18 of these individuals were actually issued to hospitals. It has been established that 66 components were transfused to identified recipients. One of these recipients was identified as developing symptoms of vCJD 6½ years after receiving a transfusion of red cells donated 3½ years before the donor developed symptoms of vCJD<sup>1</sup>. In a further recipient who died from a non-neurological disorder 5 years after receiving blood from a donor who subsequently developed vCJD, protease-resistant prion protein (PrP<sup>res</sup>) was detected in the spleen but not in the brain. This is the first recorded case in the UK of autopsy detection of presumed preclinical or subclinical vCJD infection<sup>2</sup>. In early 2006, a further case of probable vCJD was identified in a recipient who developed symptoms of vCJD 7 years, 10 months after receiving a transfusion of red cells from a donor who developed symptoms of vCJD nearly 21 months after donation<sup>3</sup>. The diagnosis of vCJD in this donor was confirmed neuropathologically.

In the reverse study, 11 vCJD cases were reported to have received blood transfusions in the past. A further case received a blood transfusion after onset of illness and is excluded from further discussion. Checks revealed that of these 11 cases, 2 were not transfused, 2 had transfusions which pre-dated available records and 7 had records of transfusion which could be traced. These 7 individuals had received 125 components of blood (with one patient given 103 components), which have been traced to 121 named donors (two of whom had vCJD as described above). The donors of four components are not traceable.

## Conclusion

These findings strongly suggest that vCJD may be transmitted by blood transfusion. The identification of a second case of vCJD in this small cohort of known recipients of blood from persons incubating vCJD establishes beyond reasonable doubt that blood transfusion is a transmission route.

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

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<sup>1</sup> Llewelyn CA, Hewitt PE, 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>2</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>3</sup> Health Protection Agency. New case of transfusion-associated variant-CJD. *CDR Weekly* 2006; 16(6).



## *2.6 Study of Progressive Intellectual & Neurological Deterioration (PIND)*

The aim of this project is to use the mechanism of the British Paediatric Surveillance Unit to identify all cases of progressive intellectual and neurological deterioration in children in the UK, particularly those with features suggestive of vCJD. All cases are discussed by an Expert Neurological Advisory Group of seven paediatric neurologists which allocates the cases to a diagnostic category<sup>4-5</sup>.

As at 31<sup>st</sup> December 2005, after almost 9 years surveillance, 2003 patients with suspected PIND have been reported. The Expert Group has discussed 1415 cases, of which 842 have a confirmed underlying cause other than vCJD, being categorised into 114 known neurodegenerative diseases. Among them were six cases of vCJD; four definite and two probable. Three were reported in 1999, one in 2000 and 2 in mid-2001. One girl was aged 12 at onset - the youngest case of vCJD identified to date.

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

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<sup>4</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>5</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

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

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

1990-1997: For each suspect case, an age- and sex-matched patient at the same hospital was identified as a control.

1998-2002: With the diagnosis of the first cases of variant CJD, it was decided that in addition to hospital controls for variant cases, and instead of hospital controls for sporadic cases, community controls would be recruited, matched for sex and age, through general medical practices. Community controls are more suitable than hospital controls for the investigation of potential medical risk factors. However, major difficulties were encountered arising from the complex process of recruitment that we were required to follow for general practice based controls. Therefore, a revised strategy for control recruitment was devised and recruitment of this group of controls ceased.

2002 to date:

Hospital controls continue to be recruited for variant cases where possible. Seventy-nine hospital controls have been recruited for variant cases to date.

During 2002/03 a one-off recruitment of approximately 900 general population controls throughout the UK was carried out on our behalf by the National Centre for Social Research, which is the largest independent social research institute in Britain. These controls represent a wide age range so that their data can be compared with that from both variant and sporadic cases.

In 2004, we carried out the first analysis of data from variant cases compared with these general population controls. This analysis has been published recently<sup>6</sup>. The findings showed that reported frequent consumption of beef and beef products thought likely to contain mechanically recovered and/or head meat, including burgers and meat pies, was associated with increased risk of vCJD, as was reported frequent chicken consumption. The history of surgical operations were generally similarly reported for cases and controls, with the exception of a small group of minor operations, possibly attributable to under-reporting in controls. Cases and controls had similar reported occupational histories and exposure to animals. These findings are consistent with dietary exposure to contaminated beef products being the main route of infection of vCJD, but recall bias cannot be excluded. There was no convincing evidence of increased risk through medical, surgical or occupational exposure, or exposure to animals.

Analyses are underway to compare cases of sporadic CJD with this group of general population controls.

In addition to the data we have acquired from relatives of cases and controls, we also seek medical and surgical data from medical records. In light of the risk of secondary transmission of vCJD by blood transfusion, it is especially important to investigate medical/surgical risk factors for CJD. The data acquired from primary care records are likely to be more accurate and detailed than that obtained from relatives. For the cases this is done prospectively as they are identified. We also have written consent from three-quarters (approximately 600) of those general population controls to access their primary care medical and dental records. To assemble this information is a huge task and involves visiting practices throughout the UK. This work is in progress for primary care medical records and we have obtained records for 312 individuals to date. We are also in the process of undertaking a pilot project with colleagues at Glasgow Dental School to investigate whether it is possible and feasible to trace dental records.

We are recruiting a second group of controls comprising friends nominated by relatives of cases. That is, relatives of cases are asked to nominate a friend who would agree to be interviewed about a relative of theirs (the control), who is age- and sex-matched to the case. The degree of relative between control and friend is matched to that between the case and their relative. Consent of the control is sought before the friend is interviewed.

The case-control study is a complex, ongoing process, involving relatives of cases at a difficult point in their lives. Often relatives need time (sometimes many months, especially if their relative has recently died) to consider whether they wish to take part in the study and, of course, they can change their mind at any time in the process. Once they have agreed to take part they then are asked to identify a suitable friend. The friend is contacted by the Unit's research nurse to seek agreement to take part in the study. If they agree, a suitable relative of the nominated friend has to be identified, contacted and agree to participate. Finally if both nominated friend and their relative have agreed to take part in the study, the interview can take place between the friend and one of the Unit's research nurses.

Table 6 summarises, to mid February 2006, the progress made in recruiting relative-nominated controls. The table shows that control recruitment has been completed for a third each of variant (14/38) and sporadic (83/240) cases approached. Relatives of 74% (28) of variant cases and 71% (171) of sporadic cases agreed to participate in the study. However, of those agreeing, 6 (21%) of the relatives of variant cases and 34 (20%) of the relatives of sporadic cases were unable to

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<sup>6</sup> Ward HJT, Everington,D, Cousens,SN, Smith-Bathgate,B, Leitch,M, Cooper,S, Heath,C, Knight,RSG, Will,RG. Risk factors for variant Creutzfeldt-Jakob disease: a case-control study. *Annals of Neurology* 2006; 59: 111-120

nominate a friend. This was because either they had not told a suitable friend about the illness or they did not have a friend with a suitable relative. Of those cases for whom control recruitment is ongoing, relatives of 3 variant cases and of 14 sporadic cases are currently undecided as to whether to participate in the study.

**Table 6: Relative nominated controls - recruitment process**

	<b>Variant CJD</b> Number	<b>Sporadic CJD</b> Number
Relatives of cases approached	38	240
<ul style="list-style-type: none"> <li>▪ Relatives of cases agreeing to participate and able to nominate a friend</li> <li>▪ Relatives agreeing to participate but unable to nominate a friend</li> <li>▪ Relatives considering whether to participate</li> <li>▪ Relatives of cases refused</li> </ul>	22 6 3 7	137 34 14 55
Friend of relative contacted	22	109
<ul style="list-style-type: none"> <li>▪ Friend of relative agreeing to participate</li> <li>▪ Friend not replied</li> <li>▪ Friend refused consent</li> </ul>	17 5 0	97 7 5
Control consented	15	97
Friend interviewed regarding control	14	83

## LABORATORY ACTIVITIES

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

### *4.1 Neuropathology – Statement of Progress and Surveillance Activities*

The neuropathology laboratory in the NCJDSU continues to maintain its diagnostic and research activities, including the work of the protein laboratory. The laboratory maintains close links with other neuropathology centres across the UK and overseas with scientific, medical, technical and student visitors over the past year for specialist training purposes. The laboratory has continued to maintain an active research programme both in-house and by collaboration with other research centres in UK, Europe and across the world. The laboratory is part of the NeuroPrion network of centres of excellence across Europe. Since 2001 the autopsy rates for sporadic and variant CJD have declined, in keeping with national trends. This is reflected in the number of cases examined in 2005, although there has been an increase overall in the numbers of cases examined in comparison with 2004, with a corresponding increase in laboratory workload (Tables 7 and 8). This increase is largely accounted for by an increase in the number of GSS cases examined, and in referred cases from the EU. This group of referred cases reflects the spread of variant CJD to countries such as Spain, Portugal and the Netherlands, which experienced their first cases of variant CJD in 2005. In contrast, the number of sporadic CJD cases undergoing autopsy has been maintained. As a result of the Department of Health's guidelines for the examination of brain biopsy specimens, the increased number of cerebral biopsies referred to NCJDSU has continued. These samples require intensive investigation by conventional histology, immunocytochemistry, PET blot and western blot analysis. Many of these biopsy samples do not show any specific histological abnormalities, and so a conclusive diagnosis cannot always be reached, although a descriptive report is issued for each case. In 2005, there was a wider spread of alternative diagnoses in patients who were suspected of suffering CJD, but in whom neuropathological investigations revealed another disease, including a range of cerebrovascular diseases and 2 cases of CNS malignancy.

The laboratory and its staff continue to participate in a range of EQA activities related to both technical and diagnostic neuropathology. The laboratory continues to develop more sensitive techniques for the detection of abnormal PrP in tissues, both within the CNS and in a wide range of non-neural tissues. As before, the laboratory continues to act as a source of information to a wide range of professionals involved in health and safety issues relating to CJD. We are most grateful to all neuropathologists, general pathologists and their technical, secretarial and autopsy

room staff for their continuing support of the NCJDSU. We are also grateful to the relatives of patients with CJD for allowing us to study this group of devastating disorders.

**Table 7 Breakdown of Laboratory Activities 1<sup>st</sup> January 2005 – 31<sup>st</sup> December 2005**

	<b>CURRENT YEAR</b>	<b>PREVIOUS YEAR</b>
<b>REFERRED CASES (UK)</b>		
Sporadic CJD	32	32
Familial CJD	1	0
Variant CJD	4	3
Iatrogenic CJD (growth hormone therapy)	1	2
Iatrogenic CJD (dura mater)	0	1
Gerstmann-Straussler-Scheinker syndrome (GSS)	3	0
Fatal Familial Insomnia	0	0
No evidence of CJD (no alternative diagnosis)*	25	22
Alzheimer's disease	3	8
Dementia with Lewy Bodies	1	0
Other forms of brain disease†	9	3
<b>REFERRED CASES (EUROPEAN UNION)</b>		
Sporadic CJD	2	1
Familial CJD	0	0
Variant CJD	4	1
GSS	0	0
Other forms of brain disease	4	1
<b>REFERRED CASES (REST OF WORLD)</b>		
Sporadic CJD	0	0
Variant CJD	0	2
Familial CJD	0	1
Other forms of brain disease	0	2
<b>TOTAL NUMBER OF CASES</b>	<b>89</b>	<b>79</b>

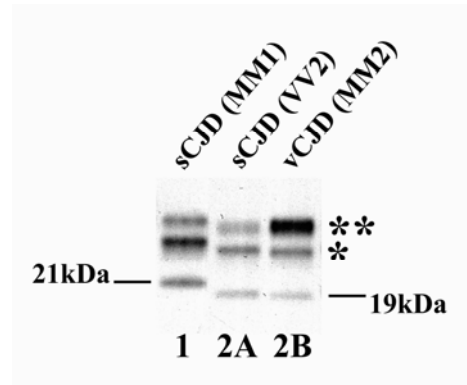
\* Cases with no specific histological or biochemical evidence of CJD, in whom no specific alternative diagnosis can be made. These cases are usually submitted for the exclusion of CJD in the differential diagnosis, and the diagnosis given back to the referring pathologist is the diagnosis submitted at the time of referral. Further histological investigations leading to an alternative diagnosis are the responsibility of the referring pathologist.

† Other forms of brain disease: previous R frontal haematoma (1); arteriosclerosis, lacunar infarction (1); anaplastic astrocytoma (1); small vessel cerebrovascular disease (1); intravascular large B cell lymphoma (1); metastatic carcinoma (1); amyloid angiopathy (1); cord compression – lower cervical (1); Alzheimer pathology/cerebral arteriosclerosis (1).

#### 4.2 Prion Protein Laboratory

Prion protein typing is carried out as a routine diagnostic test on all suspected cases of prion disease where fresh brain tissue is received by the NCJDSU. Small quantities of cerebral cortex are homogenized, treated with proteases and the size and abundance of the three PrP<sup>res</sup> glycoforms determined by Western blot analysis. The prion protein type is classified as type 1 if the nonglycosylated form has a molecular weight of ~21kDa or type 2 if the nonglycosylated form has a molecular weight of ~19kDa. The suffix B is used to denote a PrP<sup>res</sup> isotype where the diglycosylated band predominates. The remaining type 2 cases where the diglycosylated band does not predominate are termed type 2A. The type 2B isotype has previously been found to be characteristic of variant CJD. A typical result is shown in figure 13.

**Figure 13 PrP<sup>res</sup> Types in Sporadic and Variant CJD**



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

A total of 50 UK cases with frozen tissue were received and analysed in 2005, representing an increase of 52% over the previous year. The results of the analysis are shown in Table 8:

**Table 8 Breakdown of UK cases analysed in 2004**

Diagnosis	Type	PrP <sup>res</sup> +ve CNS
CJD	Sporadic	30/30
	Variant	3/3
	Iatrogenic	1/1
	Familial	1/1
GSS		2/2
Alternative final diagnosis or not determined		0/13

The cases that tested positive for PrP<sup>res</sup> are further considered according to the results of PrP<sup>res</sup> typing and genotyping of codon 129 of the prion protein gene (*PRNP*) in Table 9.

**Table 9 PrP<sup>res</sup> type/*PRNP* genotype breakdown of CJD cases received in 2005**

Diagnosis	129	Type 1	Type 2A	Type 1 & Type 2	Type 2B	Total
Sporadic CJD	M/M	17	4 <sup>1</sup>	1	0	22
	M/V	1	3	1	0	5
	V/V	0	3	0	0	3
	<b>Total</b>	<b>18</b>	<b>10</b>	<b>2</b>	<b>0</b>	<b>30</b>
Iatrogenic CJD	M/V	0	0	1 <sup>2</sup>	0	1
Variant CJD	M/M	0	0	0	3	3
Familial CJD	M/M	0	1 <sup>3</sup>	0	0	1
GSS		2 <sup>4</sup> (small PrP <sup>res</sup> fragments only)				2

<sup>1</sup> includes one case typed from a brain biopsy.

<sup>2</sup> growth-hormone therapy-associated iatrogenic CJD.

<sup>3</sup> octapeptide repeat 6X insertion.

<sup>4</sup> genotypes not determined.

## Non-UK Referrals

Four requests for Western blot analysis were received from non-UK referrals. Three of these had a type 2B PrP<sup>res</sup> and were from cases of vCJD in methionine homozygous patients from the Netherlands, Portugal and Spain. The tissue analysed from the Spanish case was a tonsil biopsy. The remaining Dutch case was of the sCJD MM2A sub-type. Twenty-three additional cases were typed as part of the NeuroPrion Tissue Bank Western blot research study bringing the total number of cases received and analysed in 2005 to 77.

### 4.3 Brain banking activities

The bank of fixed and frozen tissues in the surveillance unit was used extensively in 2005 for diagnostic and collaborative research purposes with colleagues in the UK and overseas. A brain bank manager was appointed in 2002, who has primary responsibility for this unique resource. The activities of the Bank comply with current guidelines from MRC and the Royal College of Pathologists. The Bank and its activities are overseen by the Tissue Management Group established by the Department of Health.

### 4.4 Molecular Genetics

#### Familial CJD

Seventy-two cases of familial CJD (excluding cases of GSS) have been identified since 1970 by the NCJDSU (these data are incomplete as formal investigation of familial CJD in the UK is undertaken by the National Prion Clinic in London). Of the 72 cases, 65 were resident in England, 5 were resident in Wales and 2 were resident in Northern Ireland. Eighteen cases are still alive as at 31<sup>st</sup> December 2005. Forty-one of the cases had insertions in the coding region of the PrP gene, 16 carried the mutation at codon 200 (Glu-Lys), 3 at codon 178 (Asp-Asn, both with methionine at codon 129, ie FFI) and one at codon 210 (Val-Ile). The remaining 11 were identified as familial on the basis of relatives known to have had CJD. The mean age at death was 55 years (range 31-77 years).

#### Codon 129 distribution in sporadic CJD

The distribution of codon 129 genotypes in sporadic CJD has been analysed since the inception of the Unit in 1990. The overall distribution of codon 129 genotypes in sporadic CJD is 65% MM, 17% MV, 18% VV (see Table 10). There appears to be evidence ( $p=0.013$ ) of a change in the codon 129 distribution in sporadic CJD between the periods 1990-1995 and 1996-2005. The explanation for this remains unclear and is being investigated further. It should be noted that not all cases are genotyped (data available on 63%) and, therefore, changes in codon 129 distribution may reflect changes in the way in which cases are selected for analysis.

**Table 10 Codon 129 genotypes of cases of sporadic CJD in the UK, 1990-2005**

Deaths from sporadic CJD	MM(%)	MV(%)	VV(%)
Deaths from 1 May 1990 – 31 December 1995	97 (76)	14 (11)	17 (13)
Deaths from 1 January 1996 – 31 December 2005	241 (61)	75 (19)	78 (20)
Total	338 (65)	89 (17)	95 (18)
<b>Genotype distribution for the normal population</b>	(39)	(50)	(11)
<b>Pooling data from five studies</b>			



## Codon 129 distribution in vCJD

All clinical cases for whom genetic data are available (n=139, 87%) were methionine homozygotes at codon 129 of the PrP gene.

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

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

The laboratory received 294 CSF samples from January 2005 – December 2005. Of these, 83 were from patients who were referred to NCJDSU as suspect cases of CJD and 172 were from patients who did not have clinical features to merit formal referral as a suspect case of CJD, but in whom the diagnosis remained a possibility. These are termed CSF only referrals. The remaining CSF samples were sent to the laboratory from hospitals outside the United Kingdom. The origin and numbers of these samples are given in Table 11.

**Table 11 Number and origin of CSF samples received at the NCJDSU: Jan-Dec 2005**

Source	Number of CSF samples (% of total)
CSF from suspect CJD patient referrals	83 (28%)
CSF only referrals	172 (59%)
Non-UK countries	39 (13%)
Total	294

### CSF 14-3-3 results in CSF samples received from suspect CJD patient referrals

Of the 83 CSF samples sent to the NCJDSU from CJD patient referrals, one sample was blood-stained and therefore unsuitable for analysis. The diagnosis and CSF 14-3-3 results from the remaining 82 patients are shown in Table 12.

**Table 12 CSF 14-3-3 results in patients referred to NCJDSU: Jan– Dec 2005**

Type of CJD	Diagnostic group (number of patients)	Positive 14-3-3/ Total number samples tested
Sporadic	Definite	17/19
	Probable	26/28
	Possible	0/1
	Not CJD	12/22
Variant	Definite	1/2
	Probable	1/2
	Unclassified	0/1
	Not CJD	1/2
Genetic	Probable insert mutations	1/2
	Probable FFI	0/1
	Probable GSS	1/1
	Not CJD	0/1

CSF 14-3-3 was negative in two patients with neuropathologically confirmed sCJD. Both of these cases were homozygous for methionine at codon 129 of the PRNP gene. The PrP<sup>res</sup> isotype was 2A in one case but was not analysed in the other case. The disease duration was 8 months for the MM2A case and 9 months for the remaining case.

Four of the 28 patients with probable sporadic CJD are still alive, eight patients have died and are awaiting neuropathological examination and 16 patients have died without neuropathological confirmation of sporadic CJD. Of the patients who died without neuropathological confirmation of sporadic CJD, 5 patients had EEG traces that were considered typical for sporadic CJD whilst 11 had either EEG traces that were not considered typical or EEG traces that were not reviewed by the NCJDSU. Therefore 11 of the 16 patients with probable sporadic CJD who died without neuropathological confirmation have been classified as probable on the basis of the 14-3-3 result without independent EEG support.

There were 12 patients who were referred as suspect cases of CJD who had a positive CSF 14-3-3 but were not diagnosed with sCJD. In nine patients the diagnosis of CJD still remains a possibility. Two of these patients have died without post-mortem examination and the remaining seven cases are still under review. In the remaining three cases a diagnosis of Alzheimer's disease, astrocytoma or intravascular B-cell lymphoma was made at post-mortem.

### **CSF 14-3-3 in CSF only referrals**

One hundred and seventy-two CSF samples were received as CSF only referrals and constituted 59% of the total number of samples received. As six CSF samples were blood-stained only 166 were available for analysis. Eight of the 166 CSF samples analysed for CSF 14-3-3 were positive. Two patients have subsequently died and are undergoing post-mortem neuropathological examination. One patient had several seizures (which can cause 14-3-3 to appear in the CSF) prior to having a lumbar puncture performed. On further examination of the patient, it was felt that the diagnosis was not CJD. The diagnoses in the remaining five patients were paraneoplastic syndrome (3), Hashimoto's encephalitis (1) and cerebrovascular disease (1).

### **Summary**

CSF 14-3-3 was detected in 89% of patients with neuropathologically confirmed sporadic CJD and in 50% of patients with variant CJD. These figures are consistent with those previously obtained by the NCJDSU and agree with those reported in the scientific literature. The presence of CSF 14-3-3 in the CSF of 11 patients with clinical features of sporadic CJD who died without a post-mortem and without typical EEG changes, has enabled these patients to be classified as probable sporadic CJD.

The NCJDSU receives a significant number of CSF samples from patients who do not have enough clinical features to merit a formal referral as a suspect case of CJD, but in whom the diagnosis remained a possibility. In these cases, CSF 14-3-3 analysis is being used to help exclude the diagnosis of CJD and 95% of them had a negative 14-3-3. The remaining 5% of patients had a positive 14-3-3 and further clinical examination in these patients revealed alternative non-CJD diagnoses.

## NATIONAL CJD CARE TEAM

**T**he national CJD Care Team is based within the NCJDSU and was formed in response to concerns regarding the care of patients suffering from CJD. An initial national care coordinator post was established in February 2000 and in September 2001 the National CJD Care Team was formed. Between March 2003 and November 2004 there were two co-ordinators and since November 2004 there has been one co-ordinator. The present team consists of one care co-ordinator and a secretary with clinical neurological support from within the Unit.

When a referral has been made to the NCJDSU of a likely case of CJD, the co-ordinator makes direct contact with the family and offers the opportunity to meet and to assist with care intervention. Referrals are also made to the Care Team from the National Prion Unit in London and Leah Davidson, who co-ordinates the care of iatrogenic CJD cases. Once contact is made, the co-ordinator can meet with the patient and family on a regular basis, depending on need, to provide support and to assist with co-ordination of local health and social care professions. Post bereavement support is offered to the family after the patient dies and assistance given with accessing more specialised counselling.

The National CJD Care Team works in close liaison with the Department of Health and provides access to the CJD Care Package, which is a sum of money available to assist local authorities with the care of patients suffering from all forms of CJD. The Care Fund is available to supplement local care provision for all strains of CJD rather than replace it – health and social services are still required to provide the necessary elements of the individual patient's care package. Care packages for patients will vary according to their individual needs and it is not possible to be prescriptive about what each care package should contain. What is needed is a package that will provide the appropriate level of care at home both for the patient and for their family. The National CJD Care Team is also responsible for the management of the CJD Advice Network. This is a group of health and social service professionals who have had experience of working with patients and families affected by CJD and are available to share their experience and to provide advice to other professionals. Audit is preformed on contacts made to the Network and members are kept up to date with recent developments within CJD with a six monthly newsletter. From the establishment of the first National Care Coordinator post in 2000 until 31<sup>st</sup> December 2005, the care team have been in contact with and/or provided access to care funds to 82 variant cases, 84 sporadic cases, 34 familial cases and 11 iatrogenic cases.

The National Care Coordinator undertook 146 patient visits and case conferences during 2005. In addition, 10 teaching sessions were provided to professionals involved in the provision of care to CJD patients (Table 13).

**Table 13 Patient Visits and Case Conferences  
1<sup>st</sup> January to 31<sup>st</sup> December 2005**

Month	Cases Alive	Patient Visits and Case Conferences
January	40	11
February	37	16
March	40	8
April	40	9
May	40	8
June	39	10
July	37	8
August	35	14
September	39	17
October	36	14
November	37	18
December	34	13

Expenditure from the National CJD Care Fund to the end of December 2005 is £1,236,772 comprising £296,872 in 2005, £311,547 in 2004, £323,722 in 2003 and £304,631 to 2002. A breakdown of expenditure during 2004 is shown in Table 14.

**Table 14 Care Fund Payments  
1<sup>st</sup> January – 31<sup>st</sup> December 2005**

Description	Amount
Adaptations	20,914.71
Alternative Therapy	8,020.56
Car Hire	102,738.08
Counselling	350.00
Equipment	32,121.87
Nursing	121,000.98
Respite	46.50
Social Care	180.32
Transport	11,498.94
<b>TOTAL</b>	<b>£296,871.96</b>

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