

2010-01-05-05 Prion disease update 2009 (11)
To: (06) Transmissible spongiform encephalopathies

PRION DISEASE UPDATE 2009 (11)

A ProMED-mail post

[With the continuing decline of the number of cases of variant Creutzfeldt-Jakob disease (abbreviated previously as vCJD or CJD (new var.) in ProMED-mail) in the human population, it has been decided to broaden the scope of the occasional ProMED mail reports to include other prion-related diseases. Data on vCJD cases from any part of the world are now included in these updates where appropriate, and other forms of CJD (sporadic, iatrogenic, familial, and GSS/Gerstmann-Straussler-Scheinker disease) are included also since they may have some relevance to the incidence and etiology of vCJD. - Mod.CP]

In this update:

[1] UK: National CJD Surveillance Unit - monthly statistics as of 7 Dec 2009 [2] France: Institut de Veille Sanitaire (IVS) - monthly statistics as of 1 Dec 2009 [3] USA: National Prion Disease Center - Sat 7 Nov 2009 [4] UK: National CJD Surveillance Unit (NCJDSU) 17th annual report 2008 [5] Australian CJD cluster [6] Kuru genetic resistance [7] Prion stability

[1] UK: National CJD Surveillance Unit - monthly statistics as of 7 Dec 2009

Date: Mon 7 Dec 2009

Source: UK National CJD Surveillance Unit, monthly statistics [edited]

<<http://www.cjd.ed.ac.uk/figures.htm>>

The number of deaths due to definite or probable vCJD cases remains 166. A total of 4 definite/probable patients are still alive, so that the total number of definite or probable vCJD cases remains 170.

Although 2 new cases vCJD have been recorded this year [2009], the overall picture is still consistent with the view that the vCJD outbreak in the UK is in decline, albeit now with a pronounced tail.

The 1st cases were observed in 1995, and the peak number of deaths was 28 in the year 2000, followed by 20 in 2001, 17 in 2002, 18 in 2003, 9 in 2004, 5 in 2005, 5 in 2006, 5 in 2007, one in 2008, and so far 2 in 2009.

Totals for all types of CJD cases in the UK in 2009

As of Mon 7 Dec 2009 in the UK so far this year [2009], there have been 135 referrals, 55 cases of sporadic CJD, one case of familial CJD, one case of iatrogenic CJD, 3 cases of GSS, and 2 cases of vCJD.

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[2] France: Institut de Veille Sanitaire (IVS) - monthly statistics as of 1 Dec 2009

Date: Tue 1 Dec 2009

Source: IVS - Maladie de Creutzfeldt-Jakob et maladies apparentees [in French, trans. & summ. Mod.CP, edited] <http://www.invs.sante.fr/display/?doc=publications/mcj/donnees_mcj.html>

So far in the 1st 11 months of 2009 there have been 1348 referrals,

77 cases of sporadic CJD, 10 cases of familial CJD 3 case of iatrogenic CJD, and 2 confirmed cases of vCJD.

A total of 25 cases of confirmed or probable vCJD has now been recorded in France since 1997. The 25 confirmed cases comprise 13 females and 12 males. All 25 are now deceased. Their median age is 37 (between 19 and 58). 7 were resident in the Ile-de-France and 18 in the provinces. All the identified cases have been Met-Met homozygotes. No risk factor has been identified. One of the 25 had made frequent visits to the United Kingdom.

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[3] USA: National Prion Disease Center - Sat 7 Nov 2009
Date: Sat 7 Nov 2009
Source: US National Prion Disease Pathology Surveillance Center [edited]
<<http://www.cjdsurveillance.com/pdf/case-table.pdf>>

During the period 1 Jan 2009 to 7 Nov 2009 there were 341 referrals, of which 198 were classified as prion disease, comprising 133 cases of sporadic CJD, 33 of familial CJD, and no cases of iatrogenic CJD or vCJD. (N.B. The prion disease category includes cases where the type determination is pending, but where vCJD has been excluded).

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[Although the population of the United States is approximately 2.5 times the combined population of France and the UK, the total number of cases of sporadic CJD in the USA at 133 matches the combined total in France and the UK of 132. In contrast the number of cases of familial CJD in the USA at 33, compared with the combined total of 11 for France and the UK, more closely corresponds to the difference in population size. - Mod.CP]

[4] UK: National CJD Surveillance Unit (NCJDSU) 17th annual report 2008
Date: Tue 3 Nov 2009
Source: 17th Annual Report 2008 Creutzfeldt-Jakob Disease Surveillance in the UK [edited]
<<http://www.cjd.ed.ac.uk/report17.pdf>>

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 2 care coordinators and a secretary. It is based within the NCJDSU and was formed in response to concerns regarding the care of CJD patients.

The information provided in this Seventeenth Annual Report continues

to indicate that the number of sporadic cases remains relatively stable (the data for 2008 may still be incomplete). Detailed clinical and epidemiological information has been obtained for the great majority of patients. Referrals, having been fewer between 2004 and 2007, increased in 2008, back towards pre-2004 levels. 2008 has seen the highest mortality rate from sporadic CJD in the UK (1.43 per million per year) since 1985; a rate which is comparable with other European countries. Although the post mortem rate for patients with suspected CJD has declined, in line with general autopsy rates in the UK, it remains high (around 60 percent). The number of brain specimens examined for sporadic CJD in the neuropathology laboratory rose from 23 in 2007 to 28 in 2008 (32 in 2006). In 1990-2008 average annual mortality rates from sporadic CJD in England, Wales, Scotland, and Northern Ireland were, respectively, 0.94, 1.08, 0.96, and 0.58/million/year. The differences between these rates are not statistically significant ($p=0.4$). The mortality rates from sporadic CJD in the UK are comparable to those observed in most other European countries and elsewhere in the world, including countries that are free of BSE [bovine spongiform encephalopathy]. The highest and lowest mortality rates from sporadic CJD were observed in the South West (SMR [standardised mortality rate] =122) and Northern Ireland (SMR=74) respectively. The variation in the observed mortality rates between the different regions within the UK is not statistically significant (p greater than 0.1).

Up to 31 Dec 2008, there were 164 deaths from definite or probable variant CJD (vCJD) in the UK. Of these, 115 were confirmed by neuropathology. A further 3 probable cases were alive on 31st Dec 2008. The clinical, neuropathological, and epidemiological features of the cases of vCJD are remarkably uniform and consistent with previous descriptions. Risk factors for the development of vCJD include age, residence in the UK and methionine homozygosity at codon 129 of the prion protein gene -- all 147 clinically affected cases of vCJD with available genetic analysis have been methionine homozygotes.

In 2008 the NCJDSU was referred the 1st case who met the clinical criteria in life for possible vCJD and was heterozygous (methionine/valine) at codon 129 of the PRNP gene (no post-mortem was undertaken). The clinical picture was typical of vCJD seen to date, which is reassuring for surveillance purposes. Although a single case with only a 'possible' classification, this may have implications for the presentation of further clinical cases in codon 129 heterozygotes in the future and for the estimation of prevalence of sub-clinical infection in the population.

Analysis of vCJD diagnoses and deaths from January 1994 to December 2008 indicates that a peak has passed. While this is an encouraging finding, the incidence of vCJD may increase again, particularly if different genetic subgroups with longer incubation periods exist. The identification of an individual of the PRNP-129 MV genotype as a possible case of vCJD and, in a separate case, disease-related prion protein in the spleen of a clinically unaffected blood recipient (reported in 2004) is consistent with such a hypothesis [see footnote]. These cases, along with the report of the prevalence of abnormal prion protein in the large study of appendix and tonsil tissues, suggests the possibility of a greater number of preclinical

or subclinical cases in the population than might be indicated by the present numbers of confirmed clinical cases.

The incidence of vCJD is higher in the north of Britain than in the south and the only statistically significant geographic cluster of vCJD cases in the UK remains that seen in Leicestershire (5 cases occurring between 1996 and 1999).

The NCJDSU continues to collaborate with the Health Protection Agency Centre for Infections and Health Protection Scotland, in relation to a range of activities, including testing of pathological specimens from the National Anonymous Tonsil Archive study through to input into the development and implementation of public health policy, for example, in relation to the follow up of those identified as at increased risk of CJD. This year [2009], the neuropathology laboratory identified a UK adult haemophiliac patient with PrPres in a restricted distribution in the spleen. This patient had been entered into a joint study with the UK Haemophilia Centre Doctors' Organisation and NCJDSU. The patient had no neurological signs or symptoms, and no neuropathological evidence of vCJD. This case raises the possibility of transmission of vCJD infectivity via plasma products, and is the subject of ongoing investigations.

A case of protease-sensitive prionopathy was identified on neuropathological and biochemical grounds, the 1st case of this disorder identified in the UK since its description by Gambetti et al in the USA in 2008.

The activities of the NCJDSU are strengthened by collaboration with other surveillance projects, including the Transfusion Medicine Epidemiology Review and the study of Progressive Intellectual and Neurological Deterioration in Children. The collaboration of our colleagues in these projects is greatly appreciated; the effectiveness of this collaboration allowed the identification in 2003 of a case of vCJD associated with blood transfusion and the identification in 2004 of disease-related PrP in the spleen of a recipient of blood donated by someone incubating vCJD. In 2008, for the 1st time, the Unit prepared a Scientific Report, which is available on the Unit's website (<<http://www.cjd.ed.ac.uk>>). The aim of the Scientific Report is to inform interested parties of details of the current and planned scientific research being undertaken by staff at the NCJDSU, in the context of the Unit's previous research and its on-going core background surveillance. The Scientific Report complements the Annual Report, which provides a description of the clinicopathological epidemiology of CJD in the previous 12 months, reflecting the Unit's core surveillance work. The NCJDSU Business Plan provides financial, structural, and organisational information. The success of the National CJD Surveillance Unit continues to depend on the extraordinary level of co-operation from the neurology and neuropathology communities and other medical and paramedical staff throughout the UK. Ongoing support is provided by the Infectious Disease Epidemiology Unit, London School of Hygiene and Tropical Medicine. We are also particularly grateful to the relatives of patients for their collaboration.

[Footnote: In 2008 the NCJDSU was referred for the 1st time an

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

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[The most significant development has been the identification in 2008 of an individual who met the clinical criteria in life for possible vCJD who was heterozygous (methionine/valine) at codon 129 of the PRNP gene, unlike the 147 clinically confirmed cases of vCJD with available genetic analysis data who have been methionine homozygotes. This case may or may not herald the onset of a category of vCJD cases with prolonged incubation periods. Uncertainty remains because an autopsy could not be carried out and the patient's condition remains classified as probable vCJD. - Mod.CP]

[5] Australian CJD cluster
Date: Fri 18 Sep 2009
Source: Australian Government Department of Health and Ageing,
Communicable Diseases Intelligence 33(2); June 2009
<<http://www.health.gov.au/internet/main/publishing.nsf/Content/cda-cdi3302d.htm>>

Analysis of a potential Creutzfeldt-Jakob disease cluster

During 2008, the ANCDJR [Australian National Creutzfeldt-Jakob Disease Registry] published findings from an investigation conducted assessing an increased number of sporadic CJD cases within a coastal region of New South Wales during the period 1993-2006. Statistical analysis identified a spatially significant cluster in 3 contiguous

statistical local areas, consisting of 13 definite and 1 probable CJD case. An epidemiological review of ANCJDR case data for the 14 cases did not reveal a plausible cross-over or point source transmission event to explain the cluster of cases.

One potential hypothesis for the significant finding related to the region's clinicians and their management of potential CJD cases. To investigate this theory, further evaluation was undertaken comparing the regional area with the entire state, emphasising rates of referrals for 14-3-3 CSF testing, rates of case notification to the ANCJDR and suspect CJD post-mortem rates. These observations were chosen to objectively quantify an intensity of surveillance and how this relates to incidence rates. Our analyses demonstrated that the cluster area maintained a higher level of surveillance and clinical awareness compared with the entire State of New South Wales. The population-based rate of notification of all suspect cases to the ANCJDR was 68 percent greater in the cluster area than for New South Wales (age-adjusted RRMH [Mantel Haenszel relative risk]: 1.68, 95 percent CI [confidence interval] =1.36-2.10) and similarly, the population-based rate of request for CSF testing was 59 percent greater than the state referral rate (age-adjusted RRMH: 1.59, 95 percent CI=1.25-2.02). No difference between the likelihood of a suspect case being confirmed as probable or definite CJD (all types or sporadic only) was observed, suggesting that once CJD was questioned as a diagnosis in a clinical setting, the likelihood of a case being assessed for CJD classification was no different in the circumscribed area to the entire state. In contrast, a difference did exist in the proportion of cases that were assessed by neuropathological examination (biopsy or autopsy), with the cluster area having an almost 2.5 times greater neuropathological examination rate in suspect cases compared with New South Wales (age-adjusted RRMH, 2.34, 95 percent CI=1.56-3.51). Simply stated, approximately double the intensity of surveillance translated to a doubling of the CJD incidence rate.

One of the distinguishing features of the 14 cluster cases provided another key piece of supporting evidence for enhanced surveillance. The cohort displayed a significantly older age at death when compared with sporadic CJD cases from New South Wales and Australia overall. Analysis of autopsy data in Austria, where autopsy of all suspect CJD cases is mandatory, suggests global under-ascertainment of older age CJD cases. Hence, the ability to detect older and less typical cases in this cluster region suggests clinicians manifested a greater than usual suspicion of CJD and atypical presentations. These findings have provided us with a hypothesis that intensity of surveillance for rare disorders can be quantified and this can positively correlate with higher incidence. It further suggests that the true incidence of CJD in Australia may be almost twice the currently observed average rate of 1.18 cases per million per year. A further exploration of this hypothesis is needed within and between individual nations and may give us an improved understanding of methodologies for optimal surveillance for rare conditions such as CJD.

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[This analysis of an apparent cluster of CJD cases in a coastal region of the state of New South Wales in Australia attributes the higher incidence of cases in this region to an increased intensity of surveillance for rare disorders. By extension this suggests that the true incidence of CJD in Australia may be almost twice the currently observed average rate of 1.18 cases per million per year. - Mod.CP]

[6] Kuru genetic resistance

Date: Wed 18 Nov 2009

Source: Reuters News [edited]

<<http://www.reuters.com/article/latestCrisis/idUSN18133830>>

Gene protects brain-eaters from mad cow-type disease

Villagers in the highlands of Papua New Guinea who ritualistically ate human brains but did not die of a brain disease called kuru have a genetic mutation that protects them, researchers said on Wednesday [18 Nov 2009]. Their study of the unusual cannibalistic practice shows evolution in real time in the human population, and might lead to a treatment for similar brain-wasting conditions, the researchers reported in the New England Journal of Medicine. Kuru once wiped out entire generations of women in remote Papuan villages. It was traced to a now-defunct mortuary ceremony in which women and children ate the brains of their dead relatives. Dr Simon Mead of the University College London Institute and colleagues found that women in these communities were more likely to live to an old age if they had the protective gene. Women without the gene died young of kuru.

Kuru is caused by prions, the unusually folded brain proteins that also cause mad cow disease or bovine spongiform encephalopathy, Creutzfeldt-Jakob disease, or CJD, chronic wasting disease in deer and elk, and scrapie in sheep. All are fatal and incurable, creating spongy holes in the brain. They can be transmitted by eating contaminated body parts. BSE devastated British dairy herds in the 1980s and was traced to feeding sheep remains to cattle. Some people developed a rare form of CJD from eating infected beef, and 166 people in Britain and 25 in France have died of it.

Mead's team studied more than 3000 Papuans, including 709 who participated in cannibalistic mortuary feasts. They included 152 who died of kuru. They looked at the genes for prions, ordinary brain proteins that take on a misfolded shape in prion disease such as CJD and kuru. They found a mutation called G127V that protected people from kuru. Only people who ate brains and survived have it, they found. "It is not found in patients with kuru and in unexposed population groups worldwide," they wrote.

They have looked at people who had CJD and who did not have it, and have been unable to find the mutation, Mead said. The gene itself is seen in many animals and almost never mutates. "All the way back to frog there is the same amino acid in exactly this position in the prion protein gene. That tells us it is doing something very

fundamental," Mead said. So the mutation must have evolved because of the selective pressure caused by eating brains, he said.

"It is remarkable how few definite examples there are that we can really link with a clear history of a disease or an event. It was such a devastating disease and well-documented ... and we can now see the effects of this genetically," Mead said. In prion diseases, the misfolded prion attaches to healthy prions, which for unknown reasons take on the misfolded shape. The mutation seems to block this attachment, Mead said, and its discovery points researchers to the precise site. That could lead to treatments for CJD, which occurs randomly in about one in a million people, Mead said.

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[The paper referred to above is the following: Mead S, Whitfield J, Poulter M, Shah P, et al: A Novel Protective Prion Protein Variant that Colocalizes with Kuru Exposure. N Engl J Med. 2009 Nov 19; 361(21): 2056-65 (<<http://content.nejm.org/cgi/content/short/361/21/2056>>).

The authors performed genetic and selected clinical and genealogic assessments of more than 3000 persons from Eastern Highland populations, including 709 who participated in cannibalistic mortuary feasts, 152 of whom subsequently died of kuru. Persons who were exposed to kuru and survived the epidemic in Papua New Guinea are predominantly heterozygotes at the known resistance factor at codon 129 of the prion protein gene (PRNP). The authors report a novel PRNP variant -- G127V -- that was found exclusively in people who lived in the region in which kuru was prevalent and that was present in half of the otherwise susceptible women from the region of highest exposure who were homozygous for methionine at PRNP codon 129. Although this allele is common in the area with the highest incidence of kuru, it is not found in patients with kuru and in unexposed population groups worldwide. Genealogic analysis reveals a significantly lower incidence of kuru in pedigrees that harbor the protective allele than in geographically matched control families. The authors conclude that the 127V polymorphism is an acquired prion disease resistance factor selected during the kuru epidemic, rather than a pathogenic mutation that could have triggered the kuru epidemic. Variants at codons 127 and 129 of PRNP demonstrate the population genetic response to an epidemic of prion disease and represent a powerful episode of recent selection in humans. - Mod.CP]

[7] Prion stability
Date: Fri 13 Nov 2009
Source: Proceedings of the National Academy of Sciences of the USA (PNAS) [edited]
<<http://www.pnas.org/content/early/2009/11/12/0910350106.abstract>>

Design and construction of diverse mammalian prion strains

[Authors: David W. Colby and 6 others. Institute for Neurodegenerative Diseases Departments of Neurology and Pathology, University of California, San Francisco, CA 94143]

Prions are infectious proteins that encipher biological information within their conformations; variations in these conformations dictate different prion strains. Toward elucidating the molecular language of prion protein (PrP) conformations, the authors have produced an array of recombinant PrP amyloids with varying conformational stabilities.

In mice, the most stable amyloids produced the most stable prion strains that exhibited the longest incubation times, whereas more labile amyloids generated less stable strains and shorter incubation times. The direct relationship between stability and incubation time of prion strains suggests that labile prions are more fit, in that they accumulate more rapidly and thus kill the host faster.

Although incubation times can be changed by altering the PrP expression level, PrP sequence, prion dose, or route of inoculation, the authors report the ability to modify the incubation time predictably in mice by modulating the prion conformation.

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[see also:

Prion disease update 2009 (10) 20091103.3784

vCJD - Italy: susp. 20091024.3671

Prion disease update 2009 (09) 20091005.3461

Prion disease update 2009 (08) 20090908.3170

Prion disease update 2009 (07) 20090806.2783

Prion disease update 2009 (06) 20090706.2433

Prion disease update 2009 (05) 20090602.2054

Prion disease update 2009 (04) 20090406.1337

vCJD, 5th death - Spain (Cantabria) 20090307.0953

Prion disease update 2009 (03) 20090305.0918

Prion disease update 2009 (02) 20090202.0463

Prion disease update 2009 (01) 20090108.0076

2008

Prion disease update 2008 (14): new vCJD wave imminent? 20081218.3980

Prion disease update 2008 (13) 20081201.3780

Prion disease update 2008 (12) 20081103.345

Prion disease update 2008 (11) 20081006.3159

vCJD, mother & son - Spain: (Leon) 20080926.3051

Prion disease update 2008 (10) 20080902.2742

vCJD - Spain: susp. 20080410.1311

Prion disease update 2008 (05) 20080408.1285

Prion disease update 2008 (01): correction 20080104.0046

Prion disease update 2008 (01) 20080102.0014

2007

Prion disease update 2007 (08) 20071205.3923
Prion disease update 2007 (07) 20071105.3602
Prion disease update 2007 (06) 20071003.3269
Prion disease update 2007 (05) 20070901.2879
Prion disease update 2007 (04) 20070806.2560
Prion disease update 2007 (03) 20070702.2112
Prion disease update 2007 (02) 20070604.1812
Prion disease update 2007 20070514.1542
CJD (new var.) update 2007 (05) 20070403.1130
CJD (new var.) update 2007 (04) 20070305.0780
CJD (new var.) update 2007 (03) 20070205.0455
CJD (new var.) update 2007 (02): South Korea, susp 20070115.0199

2006

CJD (new var.), blood transfusion risk 20061208.3468
CJD, transmission risk - Canada (ON) 20061207.3457
CJD (new var.) update 2006 (12) 20061205.3431
CJD (new var.) update 2006 (11) 20061106.3190
CJD (new var.) update 2006 (10) 20061002.2820
CJD (new var.) - Netherlands: 2nd case 20060623.1741
CJD (new var.) - UK: 3rd transfusion-related case 20060209.0432
CJD (new var.) update 2006 (02) 20060206.0386
CJD (new var.) update 2006 20060111.0101

2005

CJD (new var.) update 2005 (12) 20051209.3547
CJD (new var.) update 2005 (11) 20051108.3270
CJD (new var.) update 2005 (10) 20051006.2916
CJD (new var.) update 2005 (02) 20050211.0467
CJD (new var.) - UK: update 2005 (01) 20050111.0095

2004

CJD, genetic susceptibility 20041112.3064
CJD (new var.) - UK: update 2004 (14) 20041206.3242
CJD (new var.) - UK: update 2004 (10) 20040909.2518
CJD (new var.) - UK: update 2004 (02) 20040202.0400
CJD (new var.) - UK: update 2004 (01) 20040106.0064
CJD (new var.) - France: 8th case 20041022.2864
CJD (new var.) - France: 9th case 20041123.3138
CJD (new var.), blood supply - UK 20040318.0758
CJD (new var.), carrier frequency study - UK 20040521.1365

2003

CJD (new var.) - UK: update 2003 (13) 20031216.3072
CJD (new var.) - UK: update 2003 (01) 20030108.0057

2002

CJD (new var.) - UK: update Dec 2002 20021207.5997
CJD (new var.) - UK: update Jan 2002 20020111.3223

2001

CJD (new var.), incidence & trends - UK (02) 20011124.2875
CJD (new var.), incidence & trends - UK 20011115.2816
CJD (new var.) - UK: reassessment 20011029.2671

CJD (new var.) - UK: update Oct 2001 20011005.2419
CJD (new var.) - UK: regional variation (02) 20010907.2145
CJD (new var.) - UK: update Sep 2001 20010906.2134
CJD (new var.) - UK: update Aug 2001 20010808.1872
CJD (new var.) - UK: 9th Annual Report 20010628.1231
CJD (new var.) - UK: update June 2001 20010622.1188
CJD (new var.) - UK: update 3 Jan 2001 20010104.0025]