# Surveillance of Creutzfeldt-Jakob disease in Australia: 2009 update

Genevieve M Klug, Alison Boyd, Victoria Lewis, Amelia McGlade, Christiane Stehmann, Colin L Masters, Steven J Collins

## Abstract

In Australia, the occurrence of all human transmissible spongiform encephalopathies (TSEs) is surveyed by the Australian National Creutzfeldt-Jakob Disease Registry (ANCJDR). While prospective surveillance commenced in October 1993, the ANCJDR also retrospectively ascertained cases that occurred between 1970 and 1993. During the surveillance period of 1 April 2008 to 31 March 2009, the ANCJDR received 90 suspect TSE case notifications, which is slightly increased from previous annual surveillance periods. Based on the total number of probable and definite CJD cases, ascertained between 1993 and 2009, the Australian age-adjusted mortality rate is 1.18 deaths per million per year. In this short report, we provide updated Australian human TSE figures and discuss a recently published investigation of geographical TSE clustering in regional New South Wales. *Commun Dis Intell* 2009;33:188–191.

Keywords: Creutzfeldt-Jakob disease, transmissible spongiform encephalopathies

## Introduction

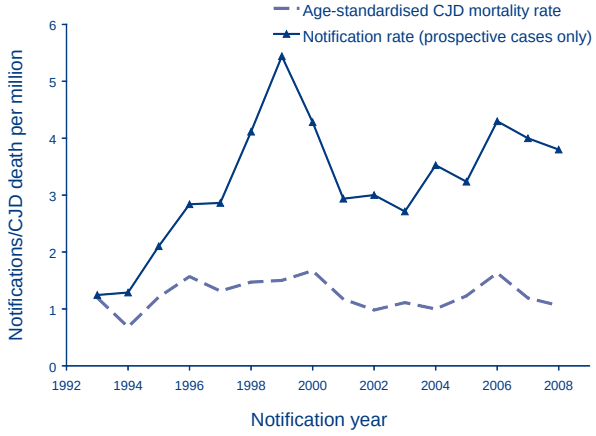
Transmissible spongiform encephalopathies (TSEs) comprise of a group of rare, neurodegenerative diseases with a reported worldwide incidence of approximately 1 case per million per year. TSEs encompass invariably fatal diseases: Creutzfeldt-Jakob disease (CJD), Gerstmann Sträussler-Sheinker syndrome, fatal familial insomnia and variant CJD (vCJD). Although the disease is classified as transmissible, most cases arise sporadically, with no plausible explanation. The remaining cases are related to either a genetic basis or an iatrogenic association through medical intervention. The World Health Organization case definition criteria form the basis for disease classification[1] and include the requirement of neuropathologic assessment of brain tissue for definite cases (either through biopsy or autopsy), while 'probable cases' are classified in accordance with recognised and validated clinical criteria.[2] 'Possible case' classification is based on defined criteria where there is a strong suspicion of CJD, but insufficient investigational evidence to support a probable classification and for this reason these cases are excluded from the following statistical analysis. CJD and vCJD have been notifiable in all Australian states and territories since June 2006 and are two of the 69 communicable diseases under national surveillance as defined by the National Notifiable Diseases List.

The Australian National Creutzfeldt-Jakob Disease Registry (ANCJDR) was established in 1993 to provide nation-wide surveillance for all human TSE regardless of aetiology, and to offer specialised diagnostic services, including cerebrospinal fluid 14-3-3 protein analysis.

## Australian National Creutzfeldt-Jakob Disease Registry surveillance update

Since 1 October 1993, the ANCJDR has been notified of 1,345 suspected cases of CJD, arising in both the prospective and retrospective ascertainment periods. For the prospective period, the average annual rate of suspect cases notified to the ANCJDR was 3.1 per million per year. Fluctuations in these annual notification rates have been observed (Figure 1) and the reasons for these have been discussed previously.[3] More recently, the rate of notifications from 2006 to 2008 has been sustained at a higher level in comparison to the longer term average observed for 1993–2008. The increased number of notifications is most likely underpinned by increased referrals to the ANCJDR of cerebrospinal fluid for 14-3-3 protein testing, particularly for the 2007–2008 period where CSF referrals have increased by 43% in comparison with the previous 6 year average. This sustained increased level of CSF referrals has given the ANCJDR confidence that the introduction of 'fee-for-service' from 1 January 2007 has not detrimentally affected CSF referrals and consequently rates of suspect case notification, as initially speculated.

**Figure 1: Annual age-standardised Creutzfeldt-Jakob disease mortality rates and suspect case* notification rates, 1993 to 2008**



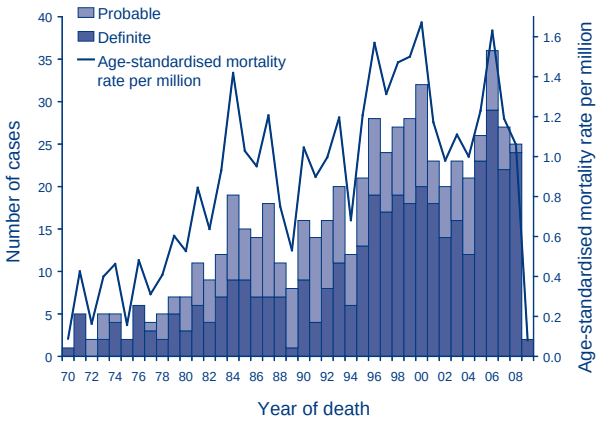

* Prospectively ascertained cases only.

During the 2008–2009 reporting period to 31 March 2009, 90 suspect cases were added to the Register, which is a 17% increase from the previous surveillance year. Of these 90 suspect case notifications, 20 have been reclassified as definite TSE cases. A further 15 cases that were notified prior to 1 April 2008 have also been confirmed as definite (11) or probable (4) TSE since the last update. The Register has a large group of cases still under investigation (184), with the majority of these still alive as at 31 March 2009. Despite active investigation of all suspect cases, the number of incomplete cases continues to expand, although final outcomes for the large majority of all suspect cases have been obtained through detailed investigation. The number of incomplete cases is of concern to the ANCJDR as for many of these cases, a conclusive outcome may not be achievable. Follow-up can be difficult for cases that have been notified several years previously. In 541 cases, CJD has been excluded while 608 cases have been classified as definite (395) or probable (213) CJD and a further 12 cases fulfil the possible case definition (Table 1). A sustained elevation of the annual CJD incidence and the proportions of autopsy-confirmed cases for the surveillance years of 2005–2008 has been observed (Figure 2). As previously discussed, this relates to the growing number of notifications and pro-active approach of the ANCJDR of seeking autopsy in all clinically suspect cases.[3]

The aetiologic proportions of all Australian TSE cases are consistent with previous observations.[3] Cases classified as sporadic CJD comprise 90.5% of all Australian cases, while 8.2% of cases are genetic and the remaining 1.3% are iatrogenic. During the 2008–2009 surveillance period, 4 new cases of familial TSE were classified, while no further iatrogenic CJD and no cases of vCJD were identified in Australia.

Based on the 608 definite and probable cases, TSE incidence peaks at 4.9 cases per million per year in the 65–69 year age group, an incidence almost 5 times the reported global incidence. As sporadic cases comprise the majority of cases, the peak incidence in this group closely aligns with overall TSE rates. Since the last surveillance period, the median age at death for sporadic cases has remained unchanged; 66 years (males, 65 years; females, 67 years), the proportion of female sporadic cases has remained consistent at 53% and their median duration of disease similar at 4 months. A slightly shorter disease duration is observed in males (median, 3 months). Genetically determined TSEs have a younger age at death (medians, overall 59 years; males, 51 years; females, 62 years) and longer illness duration (medians, overall 6 months; males, 4 months; females, 7.5 months) when compared to sporadic cases. The sex ratio for familial cases is slightly biased towards females with 58% of the cases being female.

### Figure 2: Number and age-standardised mortality rate for definite and probable cases of Creutzfeldt-Jakob disease, Australian National Creutzfeldt-Jakob Disease Registry, 1970 to 2009*




* To 31 March 2009.

Age-standardised mortality rates were calculated using the Australian Bureau of Statistics 2000 estimated resident population for Australia.

### Table 1: Classification of cases by the Australian National Creutzfeldt-Jakob Disease Registry, 1 January 1970 to 31 March 2009

| Classification | Sporadic | Familial | Iatrogenic | Variant CJD | Unclassified | Total |
|---|---|---|---|---|---|---|
| Definite | 350 | 40 | 5* | 0 | 0 | 395 |
| Probable | 199 | 10 | 4 | 0 | 0 | 213 |
| Possible | 11 | 0 | 1 | 0 | 0 | 12 |
| Incomplete | 0 | 0 | 0 | 0 | 184† | 184 |
| Total | 560 | 50 | 10 | 0 | 184 | 804 |

* Includes 1 definite iatrogenic case who received pituitary hormone treatment in Australia but disease onset and death occurred while a resident of the United Kingdom. This case is not included in statistical analysis since morbidity and mortality did not occur within Australia.

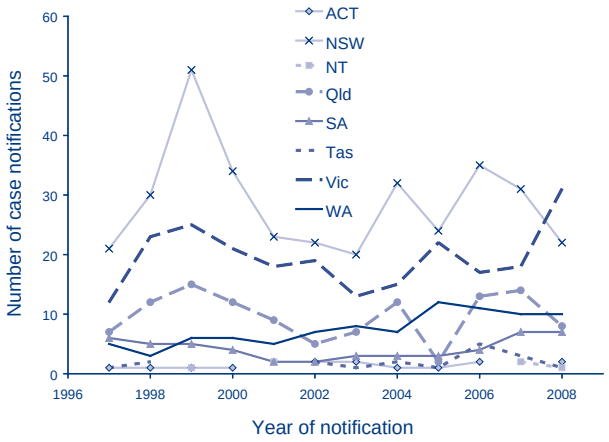
† Includes 128 living cases.

Based on all definite and probable TSE cases, the average, age-adjusted mortality rate in Australia for the 1970–2009 period is 0.88 deaths per million per year. A restriction of the timeframe to the prospective surveillance period of 1993–2009 provides a more reliable representation of the true national figures with a mortality rate of 1.18 deaths per million per year. By individual state and territory, the TSE mortality rates (Table 2) in some jurisdictions have altered since the previous update.[3] Notably, the average age-standardised mortality rates during 1993–2009 have increased in Western Australia, the Australian Capital Territory and the Northern Territory, while in Tasmania, the rate has continued to decline and is currently around half the rate observed in Victoria and Western Australia (Table 2). This strongly suggests case under-ascertainment in Tasmania for this specific period. In the remaining states and territories, no significant changes in the longer-term mortality rate average (1993–2009) have occurred since last reported.

Analysis of incidence rates by state and territory over the last decade highlights the strengths and weaknesses of surveillance in the various regions (Table 2). In Victoria, case numbers have remained constant over this period and have resulted in the highest mortality rate in Australia. In contrast, a lower than expected mortality rate in Queensland, South Australia and Tasmania was observed. This decline was concerning as the 10-year timeframe provided us with a recent snapshot of confirmed cases, excluding the diluting influence of the earlier prospective surveillance years. Broadened surveillance and diagnostic responsibilities, changes to privacy legislation around 2000 and less accessible autopsy services in various regions may have contributed to the lower mortality in the specific states.

Suspect case notification between this and the previous reporting period have remained stable in the Australian Capital Territory, the Northern Territory, South Australia and Western Australia (Figure 3). In contrast, a 70% increase in notifications has been observed in Victoria. While the total number of CSF referrals arising in Victoria has remained unchanged, there has been an increase in the number of clinically suspect TSE cases added to the Register, derived from CSF referrals. Marked declines in notifications in the large populations of New South Wales and Queensland, and to a lesser degree in Tasmania, were observed in 2008. The impact of these lower notifications may be reflected in a reduced number of confirmed CJD cases for this period. A contractual agreement between the ANCJDR and Queensland Health Department was established in May 2008 to evaluate all cases of suspect TSE. The impact of this agreement on TSE incidence in Queensland will be of particular interest.

### Figure 3: Prospective, suspect CJD case notifications to the Australian National Creutzfeldt-Jakob Disease Registry, 1993 to 2008, by state and territory




### Table 2: Transmissible spongiform encephalopathy deaths and mortality rate, by state and territory

| State or territory | TSE cases by year of death | | | | | | | | | | Total TSE deaths | Mean age-adjusted mortality rate (deaths/million/year) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 00 | 01 | 02 | 03 | 04 | 05 | 06 | 07 | 08 | 09 | | 00–09* | 93–09* |
| ACT | | | 1 | | 1 | | 1 | | 2 | | 5 | 1.42 | 1.32 |
| NSW | 12 | 9 | 7 | 7 | 11 | 10 | 11 | 10 | 5 | 1 | 83 | 1.19 | 1.18 |
| NT | | | | | | | 2 | 1 | | | 3 | 0.96 | 0.88 |
| Qld | 7 | 3 | 3 | 3 | | | 6 | 4 | 2 | | 28 | 0.69 | 0.97 |
| SA | 2 | | | 1 | 2 | | 1 | 3 | 3 | | 12 | 0.73 | 1.09 |
| Tas | | | 2 | | | 1 | 2 | | | | 5 | 0.93 | 0.67 |
| Vic | 9 | 10 | 5 | 9 | 5 | 11 | 9 | 5 | 11 | 1 | 75 | 1.45 | 1.37 |
| WA | 2 | 1 | 2 | 3 | 2 | 4 | 4 | 6 | | | 24 | 1.13 | 1.35 |
| Australia | 32 | 23 | 20 | 23 | 21 | 26 | 36 | 27 | 25 | 2 | 235 | 1.11 | 1.18 |

* Includes all deaths occurring between 1 January 1993 or 1 January 2000 and 31 March 2009.

## Analysis of a potential Creutzfeldt-Jakob disease cluster

During 2008, the ANCJDR 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.[4] 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% greater in the cluster area than for New South Wales (age-adjusted $RR_{MH}$: 1.68, 95% CI=1.36–2.10) and similarly, the population-based rate of request for CSF testing was 59% greater than the state referral rate (age-adjusted $RR_{MH}$: 1.59, 95% 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 two and half times greater neuropathological examination rate in suspect cases compared with New South Wales (age-adjusted $RR_{MH}$, 2.34, 95% 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.[5] 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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## Author details

Miss Genevieve M Klug, Research Assistant
Ms Alison Boyd, Registry Co-ordinator
Miss Victoria Lewis, Research Assistant
Miss Amelia McGlade, Research Assistant
Dr Christiane Stehmann– Administrative Assistant
Prof. Colin L Masters, Director
Assoc. Prof. Steven J Collins, Director

Corresponding author: Miss Genevieve Klug, Australian National Creutzfeldt-Jakob Disease Registry, Department of Pathology, The University of Melbourne, Victoria 3010. Telephone: +61 8344 1949. Facsimile: +61 9349 5105. Email: gmjak@unimelb.edu.au

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