Evaluation of the Australian CJD Surveillance System

Monica Robotin[1]

Abstract

An evaluation of the surveillance capacity of the Australian National Creutzfeldt-Jakob Disease Registry (ANCJDR) was undertaken. It focused on the ability of the Registry to detect CJD in Australia and, in particular, to identify cases that require public health responses. The Registry relies on a complex reporting system and staff with expertise to accurately identify and classify cases of CJD. The Registry satisfies the criteria of flexibility and acceptability and has a high positive predictive value and representativeness. The sensitivity of the system could not be evaluated, as the rarity of the condition precludes an independent assessment of the incidence of CJD, but the incidence of CJD is comparable to that found in other countries. The time required to establish a definite diagnosis of CJD is approximately 2 months, impacting negatively on the timeliness of the system. In order to maximise the likelihood of detecting all cases of CJD in Australia in a timely fashion, suggestions are made for improving the system's sensitivity and timeliness of reporting as well as for using methods that allow meaningful comparisons of incidence between populations with different age structures. *Commun Dis Intell* 2002;26:265–272.

Keywords: CJD, evaluation, surveillance

Introduction

Classical Creutzfeldt-Jakob disease (CJD) is a rare degenerative disease of the central nervous system, with an annual incidence of about one in a million people worldwide.[1] It is invariably fatal, with a median duration of illness of 4 months.[2]

CJD is the most common human form of a group of diseases, transmissible spongiform encephalopathies (TSEs), pathologically characterised by a loss of neurons, proliferation of astrocytes and the development of microscopic vacuoles in the brain.[1,2] Animal TSEs include scrapie in sheep and bovine spongiform encephalopathy (BSE) in cattle, popularly known as 'mad cow disease'.[2]

The transmissibility of the TSEs has, in general terms, been demonstrated through inoculation experiments in animals, but for over 85 per cent of human cases the specific cause is unknown.[1,2] Inherited syndromes account for a small proportion of cases and an iatrogenic aetiology has been proven for a further group of cases.[3,4,5,6] In one part of Papua New Guinea, a human TSE known as kuru was transmitted through ritual cannibalism.[7,3]

Concerns about iatrogenic CJD transmission led to the establishment of Australia's National CJD Registry in 1993. More recently, the discovery in the United Kingdom (UK) of a new form of CJD linked to consumption of BSE-contaminated beef has stimulated heightened interest in surveillance for human TSEs.[8]

Public health surveillance for CJD in Australia has therefore been largely motivated by the need to have a mechanism for early detection of cases that may reflect transmission either by iatrogenic means or by consumption of contaminated food products. The occurrence of any such case may have major public health consequences and should be notified to health authorities in a timely fashion.

In order to assess the surveillance capacity of the ANCJDR, an evaluation was undertaken by the author, as part of the course requirements for the Master of Applied Epidemiology degree at the National Centre for Epidemiology and Population Health (NCEPH). The evaluation focused on the ability of the Registry to detect all cases of CJD in Australia, and in particular, to identify cases that may have public health importance.

1. National Centre in HIV Epidemiology and Clinical Research, Sydney, NSW
2. National Centre for Epidemiology and Population Health, Australian National University, Canberra, ACT

Correspondence: Dr Monica Robotin, The National Centre in HIV Epidemiology and Clinical Research, St Vincent's Medical Centre, Level 2, 376 Victoria Street, Sydney NSW 2010, Australia. Telephone: +61 2 9332 4648. Facsimile: 61 2 9332 1837.
E-mail: mrobotin@nchecr.unsw.edu.au.

Evaluation methods

The evaluation of the CJD surveillance system was carried out using guidelines published by the Centers for Disease Control and Prevention (CDC), Atlanta and the World Health Organization (WHO).[9,10,11] (Data from the ANCJDR has recently been published in this journal.[12])

CJD case definition

The Registry uses published criteria to define CJD cases, which are classified as definite, probable or incomplete.[13,14,15]

A definite CJD case has a clinical picture of progressive dementia, with spongiform encephalopathy confirmed by histopathologic examination.

A probable CJD case has similar clinical features, but no pathological confirmation.[13] Probable cases include people alive and some who are deceased and did not have a post-mortem pathological examination. Therefore, the figures for definite and probable cases are subject to retrospective adjustment.[15] If a post mortem examination does not take place (for example if the relatives of the patient refuse consent), the case remains permanently in the probable category.

Incomplete CJD cases are cases for which a clinical suspicion of CJD exists, but further information is needed to enable final classification. For example, cases of progressive dementia where CJD is suspected due to the finding of characteristic proteins in the CSF, may be later classified as definite or probable cases depending on results of further investigations becoming available (for example, post-mortem examination results).

Variant CJD was first reported by the UK National CJD Surveillance Unit in 1996.[8] The case definition for vCJD was developed by the UK Registry and includes clinical and investigational criteria. This case definition was adopted by the World Health Organization and by the ANCJDR.

In addition to clinical history and ancillary investigations such as EEG and MRI of the brain, several laboratory tests are being used to assist in the diagnosis and classification of CJD subtypes.[4,16] Since 1997, the Registry has made available a Western Blot assay for the detection of 14-3-4 proteins in the CSF, as they act as markers of neuronal injury in some forms of CJD.[16,17] The utility of the test is limited in cases with a slower progression of the disease, such as most vCJD cases and some iatrogenic and sporadic cases.[18,19] Other tests used to distinguish subtypes of CJD are glycoform typing of prion proteins and tests for genetic susceptibility.[19,20,21,22]

Description of the CJD surveillance system

Surveillance for CJD in Australia is conducted through the ANCJDR. The Registry is located in the Department of Pathology at the University of Melbourne.

CJD has never been notifiable in any State or Territory in Australia. The Registry collects information directly from clinicians and pathologists and conducts searches of death certificates and hospital separation records (Figure).

Figure. The Australian national CJD surveillance information flow chart

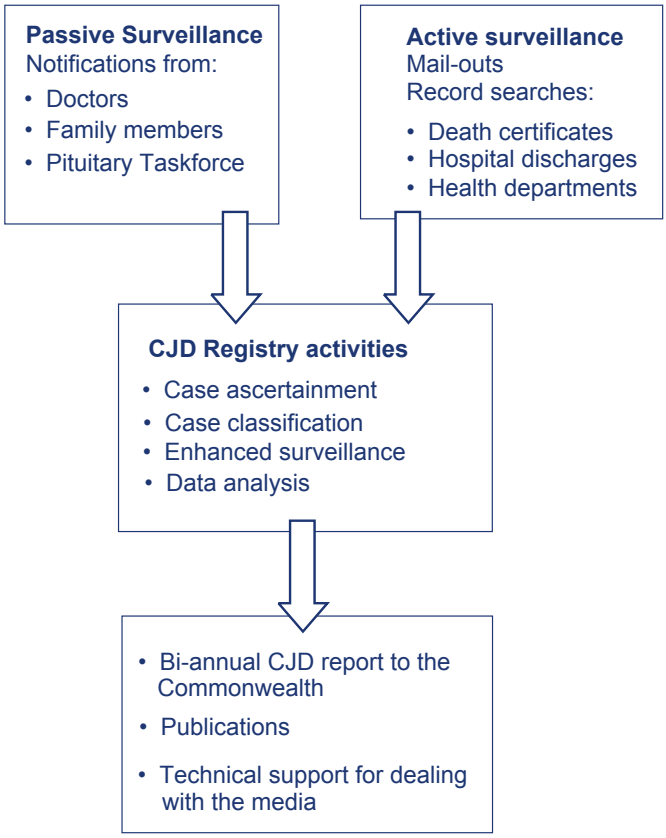

Table 1. The objectives of the CJD Registry

1. Collation and analysis of all cases of CJD identified in Australia since 1970.
2. Monitoring trends in incidence of CJD in Australia and overseas.
3. Identification of clinical features, possible risk factors and geographic distribution of CJD in Australia.
4. Establishment of diagnostic expertise in the pathological diagnosis of CJD in suspected cases.
5. Collaboration with CJD registries overseas.
6. Providing specialist advice to expert committees relating to infection control procedures.
7. Providing advice to the Commonwealth Government on scientific and medical developments relating to CJD.
8. Monitoring vCJD case diagnoses worldwide.

Objectives of the system

When first established in 1993, the Registry's brief was to record all suspected cases of CJD identified in Australia so that iatrogenic cases could be identified. In 1994, the Allars report on the use of pituitary-derived hormones in Australia recommended the expansion of the Registry's activities to include case ascertainment retrospectively from 1970 and prospectively to 2010.[23] Soon after its inception, the Registry's brief was extended to encompass monitoring of all forms of transmissible spongiform encephalopathies. The aim of the Registry was to identify all incident cases of TSEs, obtain detailed clinical information and study possible risk factors for disease development. The stated objectives of the CJD Registry are listed in Table 1.

Population under surveillance

The Registry collects data from all Australian States and Territories; it therefore covers the entire population of Australia. Prospective surveillance has been undertaken since 1993 and cases were sought retrospectively for the period between 1970 and 1992.

Data sources

As CJD is so rare, multiple and overlapping sources are used for the reporting of cases, in order to maximise the likelihood of case detection.[12] They include: personal communications with neurologists and pathologists; regular mail-outs of reminder cards to all these medical specialists; hospital medical records searches; death certificates searches; and referrals from the Pituitary Taskforce and the CJD Counseling Service. The system combines features of a passive surveillance system (e.g. personal communications by neurologists) and an active system (case ascertainment through searches of hospital records and death certificates).

For just over half of the cases reported to the Registry since its inception, the first report has come directly from neurologists and neuropathologists. Of these cases, a relatively small proportion (an additional 7%) was reported as a result of the reminder cards sent to medical specialists twice a year. The mailing list includes all practising neurologists and neuropathologists registered with the respective professional bodies in Australia. On average, 70 per cent of these specialists return the cards whether they see a case or not.

An annual search for CJD-related codes in the National Death Index maintained by the Australian Institute for Health and Welfare has been used for retrospective case finding. This was carried out by the Registry for the period from 1980 to 1994 and retrieved 21 per cent of all cases included in the Register. In the last 5 years, as more cases were notified by clinicians, the contribution of other sources to case ascertainment has proportionally decreased.[12]

Information collected

Upon notification of a possible case, a Registry member contacts the referring source and obtains detailed clinical information. The patient's family is then contacted and informed consent is sought for the completion of a questionnaire, which collates all relevant information obtained from interviewing

families and from patients' medical records. Since the Registry's inception, 936 questionnaires have been completed, with a response rate of 89 per cent. Information collected pertains to possible risk factors for CJD, socio-demographic information, as well as symptoms, clinical signs and results of relevant ancillary and laboratory investigations.

Data storage

A customised database is used to enter this information and for many fields, the Registry's comments are included as free text, which is essential for the documentation of unusual or as yet unclassified cases. Data entry errors are corrected on an informal basis each time new information becomes available and/or changes in classification are made.

Data analysis

Data are analysed twice a year by a full-time Registry member and the following calculations are carried out: the number of TSE-related deaths in Australia; the crude incidence rates of TSE; age-adjusted incidence rates for the Australian population over 45; and tabulations of cases by age, sex and aetiology (Table 2).

Dissemination of results

The information is disseminated through semi-annual reports, publications in peer-reviewed journals and presentations at scientific meetings in Australia and overseas. The semi-annual reports are sent to the Department of Health and Ageing, the National Health and Medical Research Council Special Expert Committee on TSEs, to 15 overseas collaborative TSE research units and to other organisations, on a need to know basis.

Performance of the surveillance system

Qualitative attributes

Simplicity

The Registry is recognised as the sole national repository of surveillance data on CJD. Through personal contact and regular mail-outs, the potential providers of data for the Registry can be reminded of the reporting protocols to the ANCJDR.

The ANCJDR relies on a complex network of reporting sources and conducts regular searches of hospital and death records to ensure complete case ascertainment. The Registry staff are required to have a thorough understanding of CJD pathology and of the diagnostic algorithms used for case classification. Additionally, experience with laboratory techniques involved in making the diagnosis of CJD and special skills in family counselling and interviewing are also needed. This means that although the system is simple in design, it has inherent operational complexities.

Flexibility

A surveillance system should have the ability to adapt to changing needs and/or objectives. The recent discovery of vCJD has provided a potential test of this ability. The Registry incorporated the vCJD case definition and introduced corresponding new data collection elements relating to the diagnosis and possible aetiology of vCJD, proving that the system was able to rapidly adapt to changes. The occurrence of one or more vCJD cases in Australia will be the only practical way to formally test the flexibility of the system in this new role.

Table 2. Data tabulation

Annual incidence in the general Australian population (per million inhabitants).
Annual incidence adjusted for age over 45 years (the population at highest risk).
Annual incidence by State.
Number of cases by age at onset and at death (tabulated by sex and aetiology).
Average age at death (tabulated by sex and aetiology).
Average duration of illness (tabulated by aetiology).
Tabulation of cases by occupation.
Tabulation of cases by country of birth.

Acceptability

A surveillance system depends crucially on the willingness of health professionals and those affected by the disease of interest to contribute relevant and accurate information.

Evidence for the support received by the Registry from targeted specialist doctors comes from the high proportion of cases (over half) that are received as unprompted communications. The response rate to the annual mail-outs to neurologists and neuropathologists has stabilised in the 60–70 per cent range for the last 3 or 4 years.

The acceptability of the surveillance system to patients and their families can be measured to some extent by the completion rates of questionnaires seeking information on personal, professional and medical histories. For the cases reported since surveillance was implemented prospectively in 1993, questionnaires have been completed for some 90 per cent of referred cases. According to staff, no complaints have been brought to the attention of the Registry specifically about its procedures, or the nature of the information sought.

Quantitative attributes

Sensitivity

The proportion of cases detected by a surveillance system is affected by several factors, including: the likelihood that the disease requires medical attention and is correctly diagnosed; the availability of a diagnostic test; and the chance that the case is then reported to the surveillance system.

Due to the severity of the condition, a case of CJD would come to the attention of the health system and would be referred to a specialist medical practitioner. Nevertheless, there is no information available on whether all such cases would actually be referred. It is conceivable that dementia occurring in an older person will not be fully investigated, particularly if the person dies soon after the onset of dementia.

Similarly, there has been no quantitative assessment of the proportion of potential CJD cases seen by different categories of medical specialists. It may be possible that some cases are seen by psychiatrists and general physicians who are not contacted by the Registry card system and may be unaware of the Registry's procedures or existence.

Ideally, assessment of the sensitivity of the surveillance system would require information on the true occurrence of CJD in Australia to compare with the rates being reported by the Registry. Given the rarity of CJD, it is not possible to measure its incidence independent of the Registry. However, Davanipour found that rates of sporadic CJD vary little across populations, so the sensitivity of the Australian reporting system can to some extent be assessed by comparisons with the incidence reported from other countries.[1] An increase in the notification of cases to the Registry has been observed since 1997, when diagnostic testing for CSF 14-3-3 proteins became available.[12] The annual recorded incidence of CJD has approximately doubled since the mid-1980s, from 0.564 cases per million prior to 1988, to 1.092 cases per million in 1999. Similarly, in France the annual incidence rate was 0.68 per million for 1992 to 1994 and 1.19 per million during 1995 to 1997.[24] The European Union Collaborative study found that the overall incidence rate for 1993 to 1995 in the 6 European participating countries was 0.69 per million, with rates by year and country ranging from 0.37 in 1995 in Slovakia to 1.18 cases per million in 1994 in the Netherlands.[25] The United States (US) figures for the annual age-adjusted mortality rates for CJD for 1979 to 1990 was 0.9 deaths per million; the rate remained stable through to 1994.[26,27] With the exception of the US, all other surveillance systems reported an increase in CJD incidence in the last 10 years, and attributed it to improved recognition and reporting of cases rather than an increase in the number of affected individuals.[24,25]

Positive Predictive Value

As the criteria required for diagnosis are very specific, the number of reported cases that are incorrectly labelled as CJD is very small. Through good communication between the Registry and its reporting sources, information relevant to the diagnosis of CJD is updated and the Positive Predictable Value of the Registry is likely to be high.

Representativeness

Similar to the assessment of sensitivity, the representativeness of the surveillance system can only be measured with reference to the real occurrence of CJD in different Australian subpopulations. Assessment of representativeness can be made indirectly by comparing reported rates across Australian jurisdictions, under the assumption that there is little variation in the true rate of sporadic CJD.[1] Table 3 shows little variation in reported rates across Australian States and Territories.

Table 3. Reported rates of sporadic CJD, 1990 to 1999, by jurisdictions

	ACT	NSW	NT	Qld	SA	Tas	Vic	WA
Number of cases 1990-1999	1	64	1	38	19	2	50	23
Incidence/million	1.00	1.03	0.52	1.18	1.29	0.42	1.09	1.30
95% CI	0.025, 5.57	0.793, 1.339	0.013, 2.896	0.837, 1.14	0.776, 2.01	0.0508, 1.516	0.80, 1.438	0.824, 1.95

Confidence intervals are calculated using Poisson regression.[28]

Timeliness

Delays in CJD reporting may occur between the time it takes to report a case to the Registry (which is dependent on the time elapsed between the onset of symptoms and the time a provisional diagnosis of CJD is made) and the time it takes for the Registry to confirm the diagnosis. From a public health perspective, timeliness is important if specific actions are required to stop routes of transmission indicated by new cases.

The timeliness of reporting a case to the Registry has been improved by the introduction of the 14-3-3 assay, although this investigation is most useful in supporting the diagnosis of sporadic CJD, which does not carry public health implications. The time required for neuropathologic confirmation of a case is on average 2 months. However, if the reporting source communicates a clinical suspicion of vCJD or raises a public health concern, the Registry's prioritising of the investigations can reduce this duration to a few weeks. At the time of referral, detailed information on possible exposures that could be implicated in the transmissibility of TSEs (including surgery, hormone administration, farm work, reception/donation of transplanted organs, country of birth and occupational history) is sought from the referring doctors and families to determine whether a case has public health implications.

The usefulness of the system

The usefulness of the system can be judged by the extent to which it is supporting public health policies and interventions related to the prevention of TSEs. Since the inception of the surveillance system, the monitoring of CJD has resulted in the identification of 10 iatrogenic cases (the last one in 1999), half of them related to the use of dura mater grafts. The use of these grafts was discontinued in 1987, prior to the establishment of the Registry.[6] Half the cases were associated with the administration of human-derived growth hormone or human pituitary gonadotrophins, which ceased in 1985.[6,23] The biannual Registry reports are used to inform decision-making in the area of TSEs, primarily in confirming the absence for the moment of iatrogenic CJD or vCJD in Australia.

Discussion

The ANCJDR is detecting sporadic CJD cases at rates that are comparable to those detected in other countries with comprehensive surveillance systems. It is using sophisticated diagnostic techniques and generally benefits from a high degree of cooperation from reporting physicians and the families of people diagnosed with CJD.

By using qualitative criteria of evaluation, the CJD surveillance system was found to have high degrees of flexibility and acceptability. Although simple in design, the system relies on a complex reporting system and experienced staff, to accurately identify and classify cases of CJD and recognise those of public health importance. Evaluating the system against quantitative criteria, the PPV and representativeness were also found to be high. An independent evaluation of the system's sensitivity could not be made due to the rarity of the condition, but as the incidence of CJD is comparable to that in other countries, the sensitivity is likely to be high and some suggestions are made to validate this further. The timeliness of reporting is not high for sporadic cases, but for suspected cases of vCJD the time to diagnosis has been reduced by 75 per cent, as a result of improved lines of communication with the reporting sources and prioritisation of cases. It is unlikely that the time to diagnosis can be reduced for all referred cases with the current level of staffing, due to the high workload involved in case ascertainment and classification.

To ensure the sensitivity of the system, repeat mail-outs, or personal contact with non-responding practitioners may prove useful. An initiative of this kind would serve to assess the system's sensitivity even if it does not contribute additional cases. Another approach could be the broadening of search terms for dementia when checking hospital discharge records or death certificates to increase the yield of potential cases.

Including psycho-geriatricians and psychiatrists in the biannual mail-out may help identify possible CJD cases occurring in the elderly and improve the timeliness of reporting of possible vCJD cases, as they will most likely first present with psychiatric symptoms.

Using age standardised rates for reporting, rather than crude rates, will allow comparisons between different populations and may help differentiate whether the incidence of CJD does indeed fall with advancing age, or whether this is just under-ascertainment in some areas. To assess age-specific trends, consideration could be given to the use of age-specific rates for the entire Australian population, as applying them to the individual States and Territories would result in numbers too small to reach statistical significance.

The Australian National CJD surveillance system is designed as a stand-alone system, which contrasts with the UK system, based on a more formal collaboration between the National CJD Surveillance Unit, the Public Health Medicine Environmental Group, the Public Health Laboratory Service and the UK Health Departments.[15] The higher level of integration in the UK system was prompted by the specific requirements imposed by the vCJD epidemic, which called for a local response for the prevention of potential secondary transmission and the protection of the entire community in the context of an evolving public health threat.[15] The implementation of a formal cooperation program with health authorities, similar to the UK model, may be beneficial in the light of possible vCJD cases being detected by the Registry, to provide technical support for a national response to a suspected or confirmed case and to provide specialised information to the health sector and the wider community.

When the ANCJDR was established, the issue of whether CJD should be notifiable was debated. This issue may need to be revisited in the light of the public health implications of vCJD, which became apparent only after the Registry's inception. It can be argued that making CJD notifiable under State and Territory legislation would not improve the completeness or the timeliness of reporting, as diagnosis would still require the input of a specialist unit, due to the complex diagnostic process entailed. It can be argued that it would be best for the notifying sources to continue to report directly to the ANCJDR, rather than to the State and Territory health departments. Another option would be for reporting to continue in the present form, but that the confirmed cases be notified to a coordinating national health agency, leading to a higher degree of integration of the system and an increased awareness of TSEs for all interested parties.

Acknowledgements

I would like thank Colin Masters, Steven Collins, Alison Boyd, James Lee and Vicki Lewis from the Australian CJD Case Registry who offered me their time and expertise, which I found invaluable for the preparation of this report, John Kaldor, my NCHECR supervisor who guided my writing of the manuscript and Mahomed Patel and Linda Halliday, my NCEPH supervisors, for their useful comments.

References

1. Davanipour Z, Alter M, Sobel E. Creutzfeldt-Jakob disease. *Neurology Clinics* 1986;4:415–426.
2. Collins S, Masters CL. Transmissibility of Creutzfeldt-Jakob disease and related disorders. *Sci Prog* 1995;78:217–227.
3. Alter M. How is Creutzfeldt-Jacob disease acquired? *Neuroepidemiology* 2000;19:55–61.
4. Brown P, Preece M, Brandel J, Sato T, McShane L, Zerr I, et al. Iatrogenic Creutzfeldt-Jakob disease at the Millennium. *Neurology* 2000;55:1075–1081.
5. Collins S, Masters CL. Iatrogenic and zoonotic Creutzfeldt-Jakob disease; the Australian perspective. *Med J Aust* 1996;164:598–602.
6. Newcombe RL. Neurosurgery and iatrogenic transmission of Creutzfeldt-Jakob disease. *Med J Aust* 1996;164:603–604.
7. Hornabrook RW. Kuru. *Med J Aust* 1968;2:35–36.
8. Will RG, Ironside JW, Zeidler M, Cousens SN, Estibeiro K, Alperovitch A, et al. A new variant of Creutzfeldt-Jakob disease in the UK. *Lancet* 1996;347:921–925.
9. Klaucke DN, Buehler JW, Thacker SB, Gibson Parrish R, Trowbridge FL, Berkelman RL. Guidelines for evaluating surveillance systems. Atlanta: US Centers for Disease Control, 1988.
10. World Health Organization. Protocol for the Assessment of National Communicable Disease Surveillance and Response Systems. WHO/CDS/ISR/2001.2.

11. Centers for Disease Control and Prevention. Updated guidelines for evaluating public health surveillance systems: recommendations from the guidelines working group. *MMWR* 2001;50 (no RR–13):1–35.

12. Boyd A, Fletcher A, Lee JS, Lewis V, Masters CL, Collins SJ. Transmissible spongiform encephalopathies in Australia. *Commun Dis Intell* 2001;25:248–52.

13. Brandel JP, Delasniere-Laupretre N, Laplanche JL, Hauw JJ, Alperovitch A. Diagnosis of Creutzfeldt-Jakob disease: effect of clinical criteria on incidence estimates. *Neurology* 2000;322:841–844.

14. Hauw JJ, Sazdovitch V, Laplanche JL, Peoc'h K, Kopp N, Kemeny J, et al. Neuropathologic variants of sporadic Creutzfeldt-Jakob disease and codon 129 of PrP gene. *Neurology* 2000;54:1641–1646.

15. UK Department of Health. Monthly Creutzfeldt-Jakob disease figures. http://www.doh.gov.UK/cjd/stats, 2001.

16. Collins S, Boyd A, Fletcher A, Gonzales MF, McLean CA, Masters CL. Recent advances in the pre-mortem diagnosis of Creutzfeldt-Jakob disease. *J Clin Neurosci* 2000;7:195–202.

17. Collins S, Boyd A, Fletcher A, Gonzales M, McLean CA, Byron K, Masters CL. Creutzfeldt-Jakob disease: diagnostic utility of 14.3.3 Protein immunodetection in cerebrospinal fluid. *J Clin Neurosci* 2000;7:203–208.

18. Chapman T, McKeel DW, Morris JC. Misleading results with the 14-3-3 assay for the diagnosis of Creutzfeldt-Jakob disease. *Neurology* 2000;57:1058–1063.

19. Hill AF, Butterworth RJ, Joiner S, Jackson G, Rossor MN, Thomas DJ, et al. Investigation of variant Creutzfeldt-Jakob disease and other human prion diseases with tonsil biopsy samples. *Lancet* 1999;353:183–189.

20. Cohen FE. Protein misfolding and prion diseases. *J Mol Biol* 1999;293:317–320.

21. Alperovitch A, Zerr I, Pocchiari M, Mitrova E, Cuesta JD, Hegyi I, et al. Codon 129 prion protein genotype and sporadic Creutzfeldt-Jakob disease. *Lancet* 1999;353:1673–1674.

22. Parchi P, Peterson RB, Gambetti P. New topics in familial prion diseases. *Seminars in virology* 1996;181–187.

23. Australian Government Publishing Service. Report of the inquiry into the use of pituitary-derived hormones in Australia and Creutzfeldt-Jakob disease. Australian Government Publishing Service, Canberra, June 1994.

24. D'Aignaux JH, Laplanche JL, Delasnerie-Laupretre N, Brandel JP, Peoc'h K, Salomon D, et al. Trends in mortality from sporadic Creutzfeldt-Jakob disease in France 1992–1997. *J Neurol Neurosurg Psychiatry* 2000;68:787–789.

25. Will RG, Alperovitch A, Poser S, Pocchiari M, Hofman A, Mitrova E, et al. Descriptive epidemiology of Creutzfeldt-Jakob disease in six European countries, 1993–1995. *Ann Neurol* 1998;43:763–767.

26. Holman RC, Khan AS, Kent J, Strine TW, Schonberger LB. Epidemiology of Creutzfeldt-Jakob disease in the United States, 1979–1990 — analysis of national mortality data. *Neuroepidemiology* 1995; 14:174–181.

27. Holman RC, Khan AS, Belay ED, Schonberger LB. Creutzfeldt-Jakob disease in the United States, 1979–1994 — using national mortality data to assess the possible occurrence of variant cases. *Emerg Infect Dis* 1996,2:333–337.

28. Breslow NE, Day NE. Statistical methods in cancer research. Vol. 2. Lyon: WHO, 1987.