Annual reports

Creutzfeldt-Jakob disease surveillance in Australia: update to December 2014

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Abstract

Nation-wide surveillance of human transmissible spongiform encephalopathies (also known as prion diseases), the most common being Creutzfeldt-Jakob disease, is performed by the Australian National Creutzfeldt-Jakob Disease Registry, based at the University of Melbourne. Prospective surveillance has been undertaken since 1993 and over this dynamic period in transmissible spongiform encephalopathy research and understanding, the unit has evolved and adapted to changes in surveillance practices and requirements concomitant with the emergence of new disease subtypes, improvements in diagnostic capabilities and the overall heightened awareness of prion diseases in the health care setting. In 2014, routine national surveillance continued and this brief report provides an update of the cumulative surveillance data collected by the Australian National Creutzfeldt-Jakob Disease Registry prospectively from 1993 to December 2014, and retrospectively to 1970. *Commun Dis Intell* 2016;40(2):E207–E215.

Keywords: Creutzfeldt-Jakob disease, prion disease, transmissible spongiform encephalopathy, disease surveillance

Introduction

In 1993, the Allars' inquiry[1] into the use of cadaver-derived pituitary hormones under The Australian Human Pituitary Hormone Program and the association with 4 medically acquired (iatrogenic) Creutzfeldt-Jakob disease (CJD) deaths recommended broadening of the responsibilities of the nascent Australian surveillance unit while monitoring for further cases of iatrogenic CJD in Australia. The Australian National Creutzfeldt-Jakob Disease Registry (ANCJDR) was established in October 1993 at the University of Melbourne. The monitoring of further Australian iatrogenic CJD cases related to pituitary hormone treatment for infertility or short stature and contaminated dura mater grafts remains one of the core objectives of the ANCJDR. However, the ANCJDR's activities have changed to encompass the surveillance of all types of CJD, including sporadic, genetic and variant CJD and other transmissible spongiform encephalopathies such as Gerstmann-Sträussler-Sheinker syndrome and fatal familial insomnia.

As described previously,[2] human prion disease can arise sporadically or from genetic or iatrogenic aetiologies. Detailed evaluation of each suspected case added to the register is undertaken to determine whether a case can be excluded from suspicion or classified as a definite, probable or possible prion disease case according to World Health Organization (WHO) diagnostic criteria.[3] CJD was made a notifiable disease in all states and territories of Australia as of June 2006. Most initial notifications to the ANCJDR arise through diagnostic testing available through the registry and this occurs prior to Health department notification.

The global incidence of CJD is commonly reported to be 1 case per million per year. However, in most countries with long-standing surveillance systems in place such as France and Switzerland, annual incidence has been reported above this quoted figure.[4] Incidence rates as high as 1.2 to 2.4 cases per million per year have been reported.[4] Temporally, human prion disease incidence increased in most countries, including Australia, as surveillance mechanisms have evolved and diagnostic testing capabilities improved. This was associated with a generally greater awareness of this rare disease in the health care setting.

In 2014 changes occurred that have or will have an influence on the incidence rates of CJD in Australia. These include: difficulties in achieving suspected prion disease autopsies in Queensland between January 2013 and September 2014; and the closure of the New South Wales neuropathology laboratories between December 2012 and March 2015 due to laboratory facility upgrading. In this report, updated surveillance figures to 31 December 2014 are provided for all retrospective (to 1970) and prospective (from 1993) cases ascertained, including discussion of the potential impact in relation to these changes on case notifications, classifications and overall incidence.

Methods

Patients with a suspected human prion disease are prospectively notified to the ANCJDR predominantly through referral for diagnostic cerebrospinal fluid (CSF) 14-3-3 protein detection. Other mechanisms include or have included personal communication with clinicians, families, hospitals and CJD-related groups, health record searches through hospitals or health departments. Once notified to the ANCJDR, referrals are assessed and if the suspicion of prion disease is supported, the case will be added to the register as a formally notified suspected case for continued investigation with the aim of exclusion or classification according to the WHO diagnostic criteria. Investigation of register cases can be prolonged as the ANCJDR requires next-of-kin consent to access and compile the appropriate clinical information from various health information sources for comprehensive evaluation. Response times can vary as the information can be extensive or sources numerous. Medico-demographic questionnaires are offered and forwarded to families if they are willing to contribute, providing valuable information for analysis and evaluation.

The classification of register cases remains as 'incomplete' until all known available information is gathered and reviewed or a definitive result from neuropathological assessment is obtained. Cases may be excluded from the register on the basis of neuropathological examination or after thorough clinical evaluation. A 'definite' classification requires brain tissue examination, including immunohistochemically and 'probable' and 'possible' cases are reliant on specific clinical profile and diagnostic test outcomes being met as previously described.[3] In this report, the total number of confirmed prion disease cases includes those who have been classified as definite or probable cases during 2014.

In conjunction with the ANCJDR's surveillance responsibilities, the registry provides a diagnostic platform for ante– and post-mortem diagnostic testing for human prion diseases. The testing of CSF for the presence of a family of low molecular weight proteins called '14-3-3' is performed weekly by the ANCJDR. This test, first introduced in 1997, has been readily utilised by the health community and referrals have increased substantially since its introduction to around 400 referrals each year. As described previously, the test provides an increasingly larger proportion of initial notifications of suspected human prion disease to the ANCJDR each year. The ANCJDR also facilitates prion protein gene testing as appropriate, and Western blot analysis of tonsil and brain tissue from biopsies or autopsies to supplement immunohistochemical assessment. The ANCJDR actively promotes these diagnostic tests so that these options are available to clinicians and families to achieve the most accurate diagnosis and classification of persons suspected to have prion disease.

Annual human prion disease incidence rates were calculated using direct age-standardisation, based on the Australian Bureau of Statistics 2000 estimated resident population for Australia and for each state and territory.[5] Population based rates of post-mortem examination in suspected human prion disease were calculated using the Australian Bureau of Statistics 1993–2014 Australia demographic statistics for specific states and territories.[6–12] Health information is collected through a combination of public health and surveillance responsibilities, based on the national notification of communicable diseases. ANCJDR surveillance activities for the period reported has been under ethical approval by The University of Melbourne Human Research Ethics Committee.

Statistical analysis (Log-Rank test) was performed using Stata (Intercooled Stata 7, Stata Corporation, College Station, TX).

Results

Seventy-six persons with suspected human prion disease were added to the CJD surveillance register in 2014. Cases were initially notified via a request for the 14-3-3 CSF test (55 cases), personal communication from clinicians (11 cases), hospitals (3 cases), direct health department notifications (2 cases), the CJD Support group network (1 case), a Coronial referral (1 case), family communication (1 case), the Victorian Brain Bank Network (1 case) and the CJD counselling service (1 case). Two of these cases had previously been added to the register and excluded after evaluation. In 2014, these two cases were re-added to the register after further information was provided by the CJD Support group network and after a request for autopsy. One of these cases has again been excluded from the register after clinical advice, while the other remains under investigation. The proportions of the initial notification sources of the 76 cases are consistent with those in previous years and the overall trends for all register cases (Table 1).

Of the 76 cases that were added to register in 2014, five cases were known to the ANCJDR prior to 2014 via the CSF 14-3-3 protein test (3 cases), the CJD support group network (1 case) and the CJD counselling service (1 case). At the time of initial notification, these 5 cases were not added to the register due to a low level of suspicion of prion disease after assessment. In 2014, the provision of

Table 1: Source of initial notification of suspected prion disease cases ascertained between 1993 and 2014

Method	Register cases* (%)	Cases removed from the register† (%)	Overall
CSF 14-3-3 protein test request (Since September 1997)	53.0	49.9	51.8
Personal communications			
Neurologists	13.4	12.2	13.0
Neurologists (mail-out reply cards)	2.6	1.8	2.3
Neuropathologists	7.9	8.6	8.2
Neuropathologists (mail-out reply cards)	0.6		0.3
Pituitary Hormones Task Force	1.7	3.1	2.3
Family	3.0	2.5	2.8
Molecular biologist	0.1		0.05
Hospital	0.6	1.5	0.9
Death certificates	9.4	5.5	7.8
Hospital and health department searches			
Hospital medical records	3.2	7.7	4.9
Health department search/state morbidity data	1.3	3.5	2.2
Direct health department notification	1.5	0.3	1.0
CJD Support Group	0.4	0.1	0.3
CJD counselling service	0.3	0.4	0.3
Combined CSF/genetic test request	0.3	0.9	0.6
Genetic test request	0.3	1.6	0.8
Victorian Brain Bank Network	0.1	0.1	0.2
Coroner's post-mortem request	0.1	0.3	0.1
Press	0.1		0.05
UK surveillance unit	0.1		0.05
Total	100	100	100

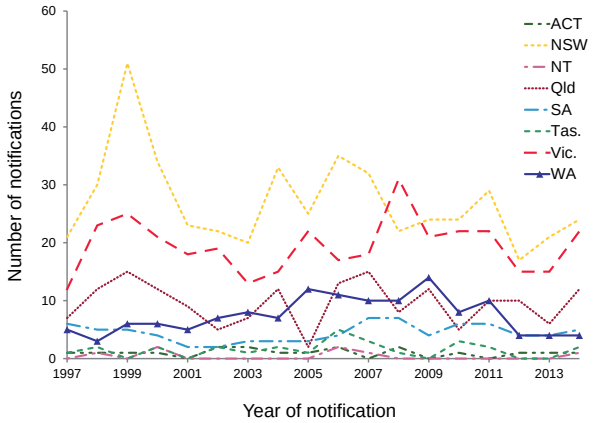
* Registry cases; includes all cases currently on the register as classified cases or cases still under investigation

† Cases removed by the registry; includes all suspected cases excluded from the register after detailed investigation.

further information increased the likelihood of prion disease resulting in formal notification and addition of the cases to the register. The number of case notifications in 2014 was greater than the previous 2 calendar years where lower than expected numbers were observed (53 cases in 2012 and 52 in 2013). In 2013, it was noted that these lower numbers were most likely a reflection of a more clinically discerning approach adopted by the ANCJDR when adding cases to the register.[13]

Excluding the 5 cases added to the register in 2014 but initially notified prior to this time, the number of new suspected cases notified to the ANCJDR in 2014 was 9% lower (71 cases) than the long-term average annual number based on data from 1993 to 2014 (78 cases). This is in sharp contrast to the lower numbers of notifications observed in 2012 and 2013 where 33% to 34% reductions were observed (Figure 1).

Figure 1: Prospective notifications of suspected prion disease cases notified to the ANCJDR, 1997 to 2014, by state or territory and year



By state and territory, there was an increase in the number of suspected case notifications in New South Wales, Queensland, Tasmania and Victoria compared with 2012 and 2013, returning to previously observed levels. The Australian Capital Territory, South Australia and the Northern Territory were unchanged from the previous year. Western Australia continued to have less than half the number of suspected case notifications in 2014 compared with the 1993–2014 long-term average (8 cases per year). This observation was similar to 2012 and 2013. Sizeable relative fluctuations are not surprising with annual CJD notifications given the small absolute case numbers involved. However, it should be noted that since 2009, notifications have been consistently declining in Western Australia. Since 2012, CSF 14-3-3 protein testing referrals from Western Australia have declined and there have been fewer cases within this referral group where the suspicion for prion disease warrants formal addition to the register and therefore case notifications for addition to the register are lower. This is in contrast with previous evidence that elevated CSF referrals correspond with elevated suspected prion disease notifications.[4]

As of 31 December 2014, the majority of the 76 suspected cases added to the register in 2014 were classified as incomplete (59 cases). Nine cases were excluded after detailed clinical follow-up (3 cases) or neuropathological examination (6 cases); 7 cases were classified as definite and 1 as probable prion disease.

Excluding the prion disease-related post-mortem rate in 2014, wherein figures are still provisional, the average proportion of suspected prion disease cases on the register who died between 1993 and 2013 and underwent post-mortem examination is 62%. Over this period, this proportion has steadily increased from an average of 45% during 1993 to 1995 to 71% between 2005 and 2012. This contrasts with the findings of an Australian healthcare setting survey where the national hospital post-mortem rate was 12% in 2002 to 2003.[15] The high prion disease-related post-mortem proportion underpins the high and consistent number of confirmed Australian human prion disease cases recorded over the more recent time period and provides confident understanding of the cause of death in suspected cases ultimately determined as non-prion disease. In contrast to the 2005 to 2012 period, the proportion of suspected prion disease case deaths in 2013 where a post-mortem examination was performed declined by 14% and this was a reflection of a reduced number of autopsies being performed and completed in 2013 in New South Wales and Queensland.

Based on the Australian population, the average crude rate of prion disease-related post-mortems between 1993 and 2014 was 1.4 post-mortems per million per year (range, 0.6 to 2.0), which is considerable given prion disease is particularly rare. By state and territory and for the same period, the lowest rates of suspected prion disease post-mortems performed annually are in the Australian Capital Territory, Tasmania and the Northern Territory (0.8, 1.0 and 0.9 per million per year, respectively), while the highest rates are in Victoria and New South Wales (1.5 per million per year). Despite the smaller populations in Tasmania, the Northern Territory and the Australian Capital Territory, the post-mortem rates are not substantially lower than the rates of more populous states and provide a level of confidence that suspected case deaths in these states and territories have a similar likelihood of undergoing post-mortem examination. In Queensland, where the suspected prion disease autopsy service was interrupted between January 2013 and September 2014, the post-mortem rate in 2013–2014 was substantially diminished (0.2 and 0.0 post-mortems per million per year respectively) compared with the long-term average for Queensland of 1.2 post-mortems per million per year between 1993 and 2012.

In the more populous states and territories, there has been an overall temporal increase in rates between 1993 and 2014 with the exception of South Australia where rates have been variable over this period (Figure 2a, 2b). In the smaller population regions, this positive trend was also present but less robust due to the considerable variation in the annual rates due to small population sizes and case numbers.

Since 2011, a sustained decrease in the post-mortem examination rate in South Australia and Western Australia was observed. In both states, there were a number of suspected prion disease deaths in 2014 where neuropathological examination is pending. Once finalised, the 2014 post-mortem rate is predicted to return to an expected level but clearly will not change the lower rates in 2012 and 2013. In Queensland, the influence of the interrupted autopsy service is demonstrated in Figure 2a with the sharp decline in the annual rate since 2012.

In New South Wales and Victoria, the respective 2013 post-mortem rates returned closer to levels observed prior to the reduced rates of 2012. While this stabilisation has continued in 2014 in Victoria, the rate in New South Wales has again decreased sharply. This is most likely due to a decrease in the completion of neuropathological analysis of post-mortem tissue as a result of the New South Wales neuropathology laboratory service being temporarily closed, rather than a decrease in

post-mortem procedures being performed in New South Wales in 2014. The closure commenced in December 2012 due to the requirement to upgrade the existing neuropathology laboratory facilities. The New South Wales neuropathology service resumed operations in March 2015.

Figure 2a: Rate of post-mortem examination in suspected prion disease case deaths per million population, by state and territory and year

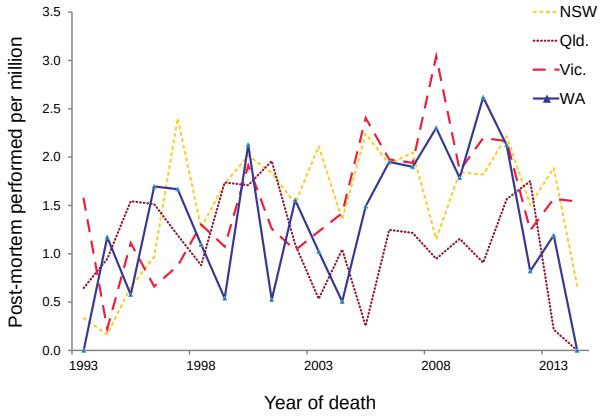
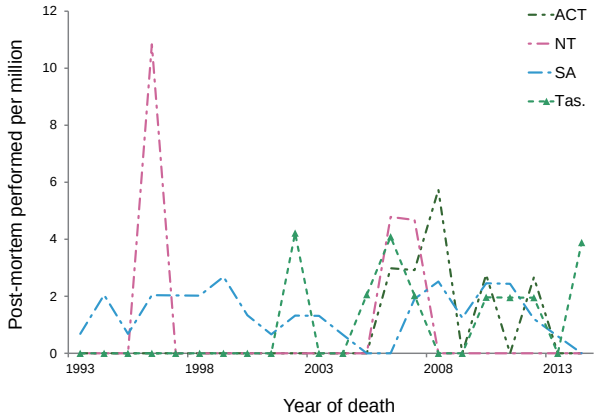


Figure 2b



In total, 11 suspected cases died in New South Wales in 2014 and subsequently underwent a post-mortem procedure to remove tissue for analysis. The immunohistochemical analysis of these 11 tissues is currently pending. Once these examinations have been completed, the post-mortem rate in suspected case deaths in New South Wales should return to expected levels in line with previous years.

As of 31 December 2014, there were 1,048 cases on the register with 781 of these being classified as probable or definite prion disease cases. An additional definite iatrogenic case who was treated in Australia, and died in the United Kingdom is included in Table 2. However this case is not classified as an Australian case due to the location at death and is thereby excluded from the overall statistical analysis of Australian prion disease cases. Since the start of surveillance, 678 suspected prion disease cases have been excluded from the register after detailed follow-up, with 17 of these being excluded in 2014 (13 after neuropathological examination).

In 2014, 16 cases were re-classified from incomplete to definite prion disease and 8 cases to probable prion disease. There were no further cases of possible prion disease classified in 2014 and the total number of possible cases remains at 15 of which 14 cases were sporadic and 1 was iatrogenic CJD (Table 2). Of the 251 incomplete cases, 145 are presently alive. In 2014, the total number of incomplete cases under evaluation has increased from the number observed in 2013 (216 cases). Although the higher number of incomplete cases is not unprecedented, it does highlight the imbalance of new suspected cases with fully evaluated cases with an outcome. Compared with the long-term average (2004–2013) figures, there have been 17% more cases added to the register but 14% fewer cases confirmed as definite or probable and 26% fewer cases excluded in 2014. In particular, the number of definite case classifications has

Table 2: Classification of Australian National Creutzfeldt-Jakob Disease Register cases, Australia, 1970 to 2014

Classification	Sporadic	Familial	Iatrogenic	Variant CJD	Unclassified	Total
Definite	464	49	5*	0	0	518
Probable	249	11	4	0	0	264
Possible	14	0	1	0	0	15
Incomplete					251†	251
Total	727	60	10	0	251	1,048

* 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.

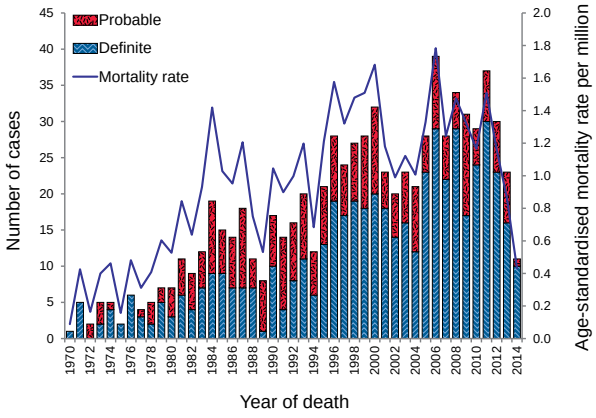
† Includes 145 living cases.

continued to decline (30% decrease compared with the 2004–2013 average), whereas the number of probable cases confirmed has been equivalent with the long-term average (2004–2013). Lower levels of classifications and exclusion of suspected cases is in part due to the inflation of the number of cases classified or excluded in 2012 due to concerted efforts by the ANCJDR to classify outstanding cases but also reflects the impact of the suspension and deferral of autopsy services in Queensland and New South Wales respectively during 2013 and 2014.

Age-standardised mortality rates show that the rate of human prion disease mortality in Australia during the period of 1970 to 2014 is generally increasing, with the exception of 2014, where case evaluation is pending for the majority of deaths (Figure 3) and incidence is therefore provisional. In 2014, the age-adjusted mortality rate was 0.4 deaths per million per year and this would be expected to increase after further investigation and classification of incomplete cases. The mean annual age-adjusted mortality rate during the period from 1970 to 2013 was 1.0 death per million (range, 0.1 to 1.8). For the prospective surveillance period of 1993 to 2013, the mean annual rate was 1.3 deaths per million (range, 0.7 to 1.8). By state and territory, the majority of regions in Australia had a mean age-adjusted mortality rate above 1 case per million per year between 1993 and 2013 (range, 1.0 to 1.5). The exceptions were Tasmania and the Northern Territory with 0.6 and 0.7 deaths per million respectively. Restriction of the surveillance data to the period between 2003 and 2013 allows comparisons between states and territories during a time-frame of relatively consistent surveillance practices, diagnostic capabilities and utility with the exception of MRI diagnostics (Table 3). During this period, Tasmania, the Northern Territory and Queensland had lower than expected mean mortality rates, while Western Australia and Victoria had the highest prion disease mortality in Australia.

The proportions of human prion disease aetiologies represented on the register have remained similar to previous years (Figure 4). Previously we

Figure 3: Number of definite and probable prion disease cases and age-standardised mortality rate*, Australia, 1970 to 2014, by classification and year



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

Table 3: Definite and probable human prion disease deaths and age-adjusted mortality rates, 2003 to 2013, by year and state or territory

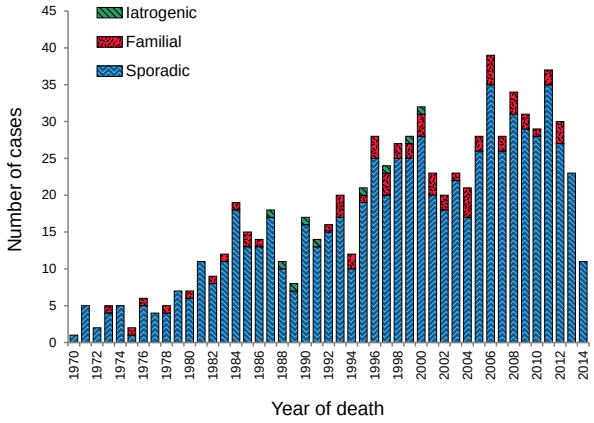
Year	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014*	Total	Mean age-adjusted mortality rate† (deaths/million/year)
ACT		1		1		2		1			1		6	1.4
NSW	7	11	10	12	10	6	11	5	14	6	10	3	105	1.2
NT				2	1								3	0.9
Qld	3			7	2	4	4	2	5	6	3		36	0.7
SA	1	2	1	1	3	5	2	4	4	2	1		26	1.4
Tas.			1	2						1		2	66	0.6
Vic.	9	5	11	10	6	13	9	13	9	12	6	6	109	1.7
WA	3	2	5	4	6	4	5	4	5	3	2		43	1.7
Aus.	23	21	28	39	28	34	31	29	37	30	23	11	334	1.3

* Provisional figures.

† Age-standardised mortality rates (2003–2013) were calculated using the Australian Bureau of Statistics 2000 estimated resident population for Australian states and territories.

reported that the annual number of genetic prion disease cases had declined in recent years[2] although this changed with the classification of 6 confirmed genetic prion disease cases during 2013. In 2014, there were no further cases classified as definite or probable genetic prion disease. Overall, the vast majority of human prion disease cases were sporadic (91%) while genetic and iatrogenic cases represented 8% and 1% respectively of all definite and probable cases.

Figure 4: Definite and probable human prion disease cases, 1970 to 2014, by aetiology and year



Based on 781 definite and probable human prion disease cases, 53% per cent were female. Similar proportions for gender exist for all human prion disease aetiologies. Median ages at death for the overall case group or by specific aetiology are largely unchanged from the previous reporting period. Sixty-six years is the median age at death for all cases overall and only a single year difference between males (66 years) and females (67 years). For sporadic cases, 67 years is the median age at death both overall and for both males and females. For genetic prion disease, there is a 4 year age difference between males (58 years) and females (62 years) and overall the median age of death from genetic prion disease is 60 years. As there have been no further iatrogenic cases identified since the last reporting period at 31 December 2013, there has been no change to the previously reported median age at death for iatrogenic cases.[2]

Duration of illness is typically short for human prion disease, especially sporadic CJD, with the median length of illness duration for all cases combined being 3.9 months. By aetiology, median duration was found to be 3.5 months for sporadic cases (range, 0.9 to 60 months), 6.3 months for iatrogenic cases (range, 2 to 25 months) and 5.8 months for genetic cases (range, 1.5 to 192 months). Within 6 months of disease onset, 70% of all prion disease cases were deceased. By aetiology, 72% of sporadic, 53% of genetic and 56% of iatrogenic human prion disease were deceased 6 months after the onset of symptoms. Survival is significantly shorter in sporadic CJD than the genetic form ($P < 0.0001$ by Log Rank Test).

Between 1 January and 31 December 2014, no variant CJD or further iatrogenic prion disease cases were identified in Australia. The most recent human-derived pituitary gonadotrophin-related CJD death occurred in 1991, while the most recent Lyodura-related CJD death occurred in 2000.

Discussion

In 2014, the number of suspected prion disease notifications returned to levels similar to the long-term average for the 1993 to 2014 surveillance years. This was in contrast to the previous 2 years, when reduced numbers of notifications were attributed to several possible factors including the temporary interruption of the Queensland suspected prion disease autopsy service and changes to the approach to adding cases to the register for investigation by the ANCJDR. However, although these factors were largely unchanged for the majority of 2014, notifications of suspected cases for most jurisdictions (including Queensland) were increased compared with 2012 and 2013, and closer to previous years. This suggests that natural fluctuation strongly contributed to the reduced notifications during 2012 and 2013.

Notifications of suspected cases in Western Australia continued to be lower than expected in 2014, as was observed in 2012 and 2013. As previously discussed, Western Australian health services are relied upon to manage case investigations following notifications and manage autopsy referrals. Changes to the functional role of the ANCJDR in Western Australia during these years may limit the ANCJDR's capacity to ascertain the true level of clinical suspicion for CJD, and may have contributed to a reduced number of formal notifications and subsequently, confirmed cases reported by the ANCJDR. A further contributing factor may be the decrease in CSF testing referrals from Western Australia since 2012, particularly in 2014. The ANCJDR will continue working towards improving ascertainment in Western Australia with the Western Australian Department of Health.

The temporary interruption of the Queensland suspected prion disease autopsy service in 2013 and the majority of 2014 has undoubtedly and, as expected, reduced the number of confirmed prion disease cases in that State during this period. A lower population-based post-mortem rate has con-

tributed to the marked decline in the overall crude numbers and corresponding incidence within these years. Furthermore, this has contributed to an overall lower incidence in Australia in 2013. It would be expected that the finalised 2014 incidence will be similarly influenced. Interestingly, formal case notifications in Queensland returned to expected levels in 2014 after a decline in 2013 and CSF referrals were consistent with previous years, suggesting that the lower Queensland notification number in 2013 was an isolated occurrence rather than a direct consequence of the service interruption.

In New South Wales, the closure of the neuropathology laboratories for refurbishment has extended the time required for reporting, although this appears to have had little effect on formal suspected case notifications and CSF referrals for 14-3-3 testing in 2013 and 2014. Furthermore, incidence has remained consistent with levels prior to the laboratory closure. Post-mortem rates slowed for 2014 as would be expected due to reporting delays. However, it is expected that these figures should improve now that the laboratory is fully operational.

The number of cases classified as definite and probable prion disease in 2014 (24 cases) was equivalent to the number classified in 2013 although lower than the long-term average number classified annually (29 cases) between 2004 and 2013. In comparison with the previous reporting period, fewer definite cases were classified in 2014 as expected due to the reduced autopsy or neuropathology services although this was compensated for by a 2-fold increase in probable case classifications. The concerted effort by the ANCJDR to garner as much clinical information on suspected CJD cases that have not had post-mortem examination to try to achieve an accurate clinical diagnosis will be maintained in the future.

With this continued focus and the resumption of routine autopsy and diagnostic neuropathology services in two of the most populous Australian states, it is expected that the surveillance parameters of CSF referrals, formal suspected case notifications with addition to the register, post-mortem examinations and prion disease incidence, should re-align with previous findings.

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