Annual report

Creutzfeldt-Jakob disease surveillance in Australia: update to December 2015

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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 delineation of new disease subtypes, improvements in diagnostic capabilities and the overall heightened awareness of prion diseases in the health care setting. In 2015, 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 2015, and retrospectively to 1970. *Commun Dis Intell* 2016;40(3):E368–E376.

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 cadaveric 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 evolved to encompass the surveillance of all types of CJD, including sporadic, genetic and variant CJD and other transmissible spongiform encephalopathies (TSE) or prion diseases such as Gerstmann-Sträussler-Scheinker 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 but in most countries with long-standing surveillance systems in place such as France and Switzerland, annual incidence rates have been consistently reported above this quoted figure.[4] Incidence rates as high as 2.4 to 2.6 cases per million per year have been reported.[4] Temporally, human prion disease incidence rates have increased in most countries, including Australia, as surveillance mechanisms evolved and diagnostic testing capabilities improved, in parallel with a generally greater awareness of this rare disease in the health care setting.

In 2015, national surveillance of prion disease continued, influenced positively by the restoration of routine autopsy services in New South Wales and Queensland. This has led to increased case classifications in 2015 and overall, a return to more usual annual incidence rates of prion disease in Australia. In this report, updated surveillance figures to 31 December 2015 are provided for all retrospective (to 1970) and prospective (from 1993) cases ascertained, including discussion 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 cer-

ebrospinal fluid (CSF) 14-3-3 protein detection. Other mechanisms include or have included personal communications from clinicians, families, hospitals and CJD-related groups, as well as 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 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 that have been classified as definite or probable cases during 2015.

In conjunction with the ANCJDR's surveillance responsibilities, the registry provides diagnostic platforms 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 more than 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 undertakes Western blot analysis for misfolded, protease-resistant prion protein in tonsil and brain tissue from biopsies or autopsies to supplement immunohistochemical assessment. Previously, the ANCJDR performed prion protein gene testing as appropriate. However from 1 September 2015, this service was ceased and is now undertaken by external, independent providers. The ANCJDR actively promotes all 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 are calculated using direct age-standardisation, based on the Australian Bureau of Statistics 1970 to 2015 estimated resident population for Australia and for each state and territory[5–13] and standardised to 2000 population estimates.[14] Population based rates of post-mortem examination in suspected human prion disease were calculated using the Australian Bureau of Statistics 1993 to 2015 estimated resident population for specific states and territories.[5–12] 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 were approved 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

Sixty-six persons with suspected human prion disease were added to the CJD surveillance register in 2015. Cases were initially notified via request for CSF 14-3-3 protein testing (53 cases), the CJD Support Group network (6 cases), personal communication from clinicians (4 cases), a coronial referral (1 case), funeral director communication (1 case) and the Victorian Brain Bank Network (1 case). The proportions of the initial notification sources of the 66 cases are consistent with those in previous years and the overall trends for all register cases (Table 1).

Of the 66 cases that were added to register in 2015, 3 cases were known to the ANCJDR prior to 2015 via the CSF 14-3-3 protein test. At the time of referral for diagnostic CSF testing, these 3 cases were not added to the register due to a low level of suspicion for prion disease after assessment. Further information ascertained in 2015 increased the likelihood of prion disease resulting in formal notification and addition of the cases to the register. The number of case additions to the register in 2015 is lower than the previous year (76 cases) but consistent with the previous 10-year average for the years 2004 to 2014 (66 cases).

By state and territory, only modest fluctuations in the number of suspected case notifications com-

Table 1: Source of initial notification of suspected prion disease cases ascertained between 1993 and 2015

Method	Register cases* (%)	Cases removed from the register† (%)	Overall
CSF 14-3-3 protein test request (Since September 1997)	54.4	50.4	52.8
Personal communications			
Neurologists	13.0	12.0	12.6
Neurologists (mail-out reply cards)	2.4	1.7	2.2
Neuropathologists	7.6	8.6	8.0
Neuropathologists (mail-out reply cards)	0.6		0.3
Pituitary Hormones Task Force	1.7	3.0	2.2
Family	2.8	2.4	2.7
Funeral directors	0.1		0.1
Molecular biologist	0.1		0.1
Hospital	0.5	1.4	0.9
Hospital and health department searches			
Death certificates	9.0	5.3	7.5
Hospital medical records	3.0	7.5	4.7
Health department search/state morbidity data	1.3	3.4	2.1
Direct health department notification	1.5	0.3	1.0
CJD Support Group	0.7	0.4	0.6
Combined CSF/genetic test request	0.3	0.9	0.5
Genetic test request	0.3	1.6	0.8
CJD Counselling Service	0.2	0.6	0.3
Victorian Brain Bank network	0.2	0.1	0.2
Coroner's post-mortem request	0.1	0.4	0.2
Press	0.1		0.1
UK Surveillance Unit	0.1		0.1
	100.0	100.0	100.0

* 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 including neuropathological investigation.

CSF Cerebrospinal fluid.

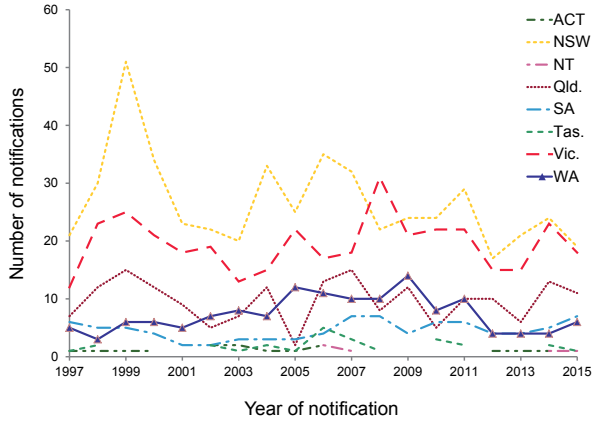
pared with the previous year were observed in 2015 (Figure 1). Since 2012, the number of suspected case notifications from Western Australia was lower than the 1993–2014 long-term average (8 cases per year). This trend continued in 2015, although not as noticeably as in the previous 3 years.

As of 31 December 2015, the majority of the 66 suspected cases added to the register in 2015 were classified as incomplete (43 cases). Eight cases were excluded by either detailed clinical follow-up (1 case) or neuropathological examination (7 cases); 12 cases were classified as definite and 2 as probable prion disease. The remaining suspect case added to the register in 2015 was initially treated in Australia; however, the patient subsequently returned overseas and was therefore unable to be investigated further. This person was thereby excluded from the overall analysis of Australian prion disease cases.

Excluding the prion disease-related post-mortem rate in 2015, wherein figures are still provisional, the average proportion of suspected prion disease cases on the register and who died between 1993 and 2014 and underwent post-mortem examination is 61%. Over this period, this proportion has steadily increased from 38% in 1993 to a peak of 80% in 2008. Since 2008, the proportion has stabilised at around 65%.

Based on the Australian population, the average crude rate of prion disease-related post-mortems between 1993 and 2015 is 1.4 post-mortems per

Figure 1: Prospective notifications of suspected prion disease cases to the Australian National Creutzfeldt-Jakob Disease Registry, 1997 to 2015, by state or territory and year



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 were in the Australian Capital Territory, Tasmania and the Northern Territory (0.7, 1.0 and 0.9 per million per year, respectively) while the highest rates were in Victoria and New South Wales (1.6 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.

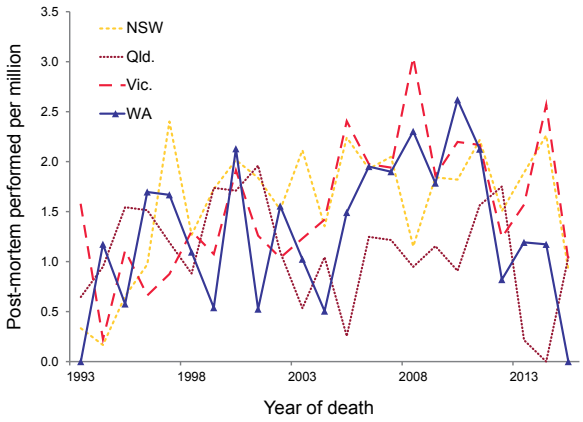
In New South Wales and Victoria, there has been an overall temporal increase in post-mortem rates between 1993 and 2015 (Figure 2a, 2b). Previously, the rate of prion disease-related post-mortems in New South Wales was reported to have declined sharply in 2014, which was related to the deferral of analyses by neuropathological laboratory services during this time. As anticipated, upon completion of these analyses in 2015, post-mortem rates for 2014 returned to an expected level in New South Wales.

In Queensland, South Australia and Western Australia, variability in post-mortem rates has been observed, especially in recent years. In Queensland, the post-mortem rates in 2013 and 2014 were substantially diminished (0.2 and 0.0 post-mortems per million per year respectively) compared with the long-term average of 1.2 post-mortems per million per year between 1993 and 2012. This was directly related to changes to routine autopsy services in this State during 2013 and 2014. In 2015, 5 post-mortems were completed and the post-mortem rate returned to expected levels (1.0 post-mortem per million per year) (Figure 2a). In South Australia and Western Australia, a sustained decrease in the post-mortem examination rate has been observed since 2010–2011. In both states, there were a number of suspected prion disease deaths in 2014 and 2015, where neuropathological examination remains pending. Once finalised, the post-mortem rates for these years is predicted to return to an expected level but will not change the lower rates in 2012 and 2013.

As of 31 December 2015, there were 1,092 cases on the register with 817 of these being classified as probable or definite prion disease cases. An additional definite iatrogenic case who was treated

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

a



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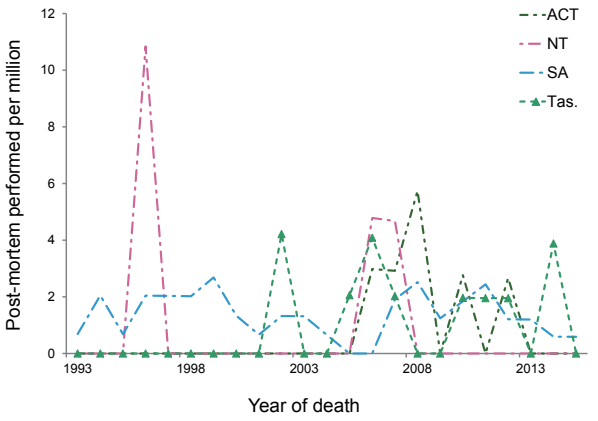


* Post-mortem examination rates were calculated using the Australian Bureau of Statistics 1993 to 2015 estimated resident population for Australia for each state and territory.

† Cases with neuropathology examination results pending are not included in the analyses.

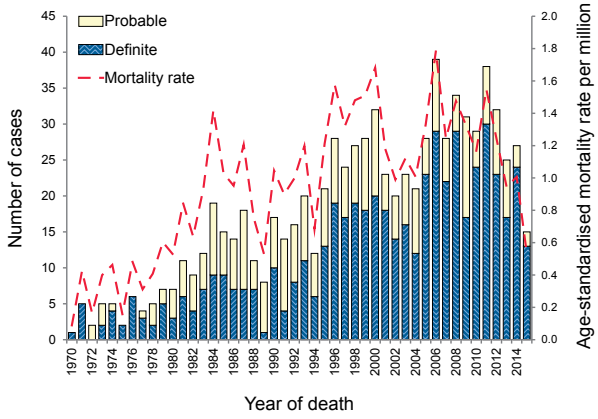
in Australia, and died in the United Kingdom is included in Table 2. However this case is not classified as an Australian case due to the location at death and is thereby excluded from the overall statistical analysis of Australian prion disease cases. Since the start of surveillance, 699 suspected prion disease cases have been excluded from the register after detailed follow-up, with 21 of these being excluded in 2015 (16 after neuropathological examination).

In 2015, 28 cases were re-classified from incomplete to definite prion disease and 8 cases to probable prion disease and there were no further cases of possible prion disease classified. The total number of possible cases remains at 15 of which 14 were sporadic and 1 iatrogenic CJD (Table 2). Of the 259 incomplete cases, 142 are presently alive. In 2015, the total number of incomplete cases (259) under evaluation was only marginally higher than the number in 2014 (251 cases) but still remains significantly higher than the number in 2012 (214 cases) and 2013 (216 cases).

Age-standardised mortality rates show that the rate of human prion disease mortality in Australia during the period of 1970 to 2015 is generally increasing, with the exception of 2015, where case evaluation is pending for the majority of deaths (Figure 3) and incidence is therefore provisional. In 2015, the age-adjusted mortality rate was 0.5 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 2014 was 1.0 death per million (range, 0.1 to 1.8). For the prospective surveillance period of 1993 to 2014, the mean annual rate is 1.2 deaths per million (range, 0.7 to 1.8). By state and territory, the majority of regions in Australia have a mean age-adjusted mortality rate above 1 case per million per year between 1993 and 2014 (range, 1.0 to 1.5). The exceptions are Tasmania and the Northern Territory both with 0.7 deaths per million per year. Restriction of the surveillance data to the period between 2003 and 2014 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 have lower than expected mean mortality rates, while Western Australia and Victoria have 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 have 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

Figure 3: Number of definite and probable prion disease cases and age-standardised mortality rate,* Australia, 1970 to 2015, by classification and year



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

Table 2: Classification of Australian National Creutzfeldt-Jakob Disease Register cases, Australia, 1970 to 2015

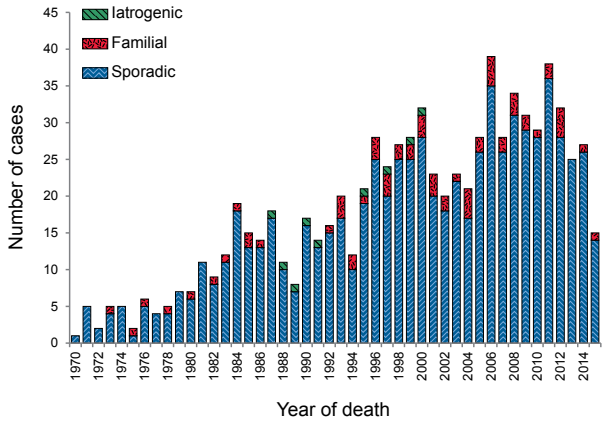
Classification	Sporadic	Familial	Iatrogenic	Variant CJD	Unclassified	Total
Definite	490	51	5*	0	0	546
Probable	256	12	4	0	0	272
Possible	14	0	1	0	0	15
Incomplete					259†	259
Total	760	63	10	0	259	1,092

* 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 142 living cases.

genetic prion disease cases during 2013 and 3 in 2015. Overall, the vast majority of human prion disease cases are sporadic (91%) while genetic and iatrogenic cases represent 8% and 1% respectively, of all definite and probable cases.

Figure 4: Definite and probable human prion disease cases, 1970 to 2015, by aetiology and year



Based on 817 definite and probable human prion disease cases, 54% 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-seven 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 61 years. As there have been no further iatrogenic cases identified since the last reporting period at 31 December 2014, 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 4 months. By aetiology, median duration was found to be 3.7 months for sporadic cases (range, 0.9 to 60 months), 6.3 months for iatrogenic cases (range, 2 to 25 months) and 6 months for genetic cases (range, 1.3 to 192 months). Within 6 months of disease onset, 70% of all prion disease cases were deceased. By aetiology, 72% of sporadic, 51% 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 2015, 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.

Table 3: Prion disease deaths and age-adjusted mortality rates, 2003 to 2015, by year and state or territory

Year	03	04	05	06	07	08	09	10	11	12	13	14	15*	Total	Mean age-adjusted mortality rate† (deaths/million/year)
ACT		1		1		2		1			1			6	1.3
NSW	7	11	10	12	10	6	11	5	14	7	11	11	6	121	1.3
NT				2	1								1	4	0.8
Qld	3			7	2	4	4	2	5	6	3		5	41	0.6
SA	1	2	1	1	3	5	2	4	4	2	2	1	2	30	1.3
Tas.			1	2					1	1		2		7	0.9
Vic.	9	5	11	10	6	13	9	13	9	13	6	11	1	116	1.7
WA	3	2	5	4	6	4	5	4	5	3	2	2		45	1.5
Aus.	23	21	28	39	28	34	31	29	38	32	25	27	15	370	1.3

* Provisional figures.

† Age-standardised mortality rates (2003-2014) were calculated using the Australian Bureau of Statistics 2000 estimated resident population for Australian states and territories.

Discussion

In 2015, the number of suspected prion disease notifications was consistent with the long-term average for the previous 10 years of surveillance (2004 to 2014). This was in contrast to 2012 and 2013, when reduced numbers of notifications were attributed to several possible factors including the temporary changes to the Queensland suspected prion disease autopsy service, changes to the approach to adding cases to the register for investigation by the ANCJDR and natural fluctuations.

By state and territory, only modest fluctuations in the number of suspected case notifications compared with the previous year were observed in 2015. The number of notifications of suspected cases in Western Australia in 2015 continued to be lower than the numbers observed prior to 2012, but not as significantly as the previous 3 years. 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. Previous evidence that elevated CSF referrals correspond with elevated suspected prion disease notifications[15] led to speculation that lower CSF referrals may be influencing this downward trend in suspected case notifications. CSF referrals from Western Australia have increased annually since the test's introduction in 1997 to a peak level in 2012. Since 2012, referrals appeared to be trending downward but overall were consistent with pre-2012 levels. The exception was in 2014 where there was a marked decline in CSF referrals. This may explain the lower notifications of suspected cases in 2014 although it does not explain the lower suspect case notifications that have been observed for the remaining years with lower notifications since 2012. As previously discussed, Western Australian health services are relied upon to manage case investigations following notifications and manage autopsy referrals. Changes to the 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, which may have contributed to a reduced number of formal notifications and subsequently, confirmed cases reported by the ANCJDR. The ANCJDR in partnership with the Western Australian Department of Health will continue working towards optimal prion disease ascertainment in this State.

The proportion of prion disease-related post-mortems being performed in suspected prion disease cases remains high (61% of all case deaths between 1993 and 2014). This contrasts with the findings of an Australian healthcare setting survey where the national hospital post-mortem rate was 12% in 2002 to 2003[16] and more recently, a major Australian tertiary centre audit of hospital autopsy data was published and described an autopsy rate of 6.6% in 2011 to 2013.[17] The high suspected 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 recent years, changes to the routine autopsy services in both New South Wales and Queensland have impacted on the number and timing of post-mortems being completed. In January 2013, the Queensland autopsy service experienced difficulties with a reliable on-call service to perform brain-only autopsies greatly impacting the ability to achieve TSE post-mortem examinations. While the difficulties were temporary, the practical interruption remained in place until September 2014 and as a result, no autopsies were performed in Queensland in 2014. This contributed to significantly lower figures in Queensland compared with the 2 years prior, where 7 to 8 autopsies were completed per year. The routine service is now operational through the Royal Brisbane Hospital and in 2015, 5 post-mortem examinations were completed.

In New South Wales, the closure of the neuropathology laboratory for refurbishment extended the time required for reporting during 2013 and 2014, although this appears to have had little effect on formal suspected case notifications and CSF referrals for 14-3-3 testing during these years. Furthermore, incidence has remained consistent with levels prior to the laboratory closure. As expected, post-mortem rates slowed in 2014 due to reporting delays. These figures have returned to an expected level now that the laboratory is fully operational and there has been a concerted effort to finalise outstanding investigations during 2015.

The number of cases classified as definite and probable prion disease in 2015 (36 cases) was higher than the long-term average classified annually (28 cases) between 2004 and 2014. In comparison with the previous reporting period, more definite cases were classified in 2015 as expected due to the completion of outstanding post-mortem examinations. This has contributed to prion disease incidence in Australia re-aligning with previously observed levels, rather than diminishing. In 2015, the total number of incomplete cases under evaluation was only marginally higher than the number in 2014 but still remains significantly higher than the annual number prior to 2014. Although the high number of incomplete cases is not unprecedented, it does highlight the imbalance of new suspected

cases with fully evaluated cases with an outcome. In 2015, there have been signs of improvement to this imbalance despite the overall high number of incomplete cases. Compared with the longer-term average (2004 to 2014), an equivalent number of cases have been added to and removed from the register in 2015. Furthermore, the number of definite and probable cases classified during 2015 was 28% higher than the long-term average. This was in contrast to 2014, where increased numbers of cases were added to the register (compared with the long-term average) yet fewer cases were classified as either definite or probable prion disease and fewer were removed from the register as non-prion disease cases. This was predominantly attributable to the alteration of routine autopsy services in Queensland and New South Wales respectively during 2013 and 2014. In 2015, the resumption of routine autopsy services in New South Wales and Queensland led to a greater number of suspect cases classified as confirmed TSE or non-TSE within the current reporting period. Continued effort will be made to evaluate incomplete cases in 2016 to minimise the inflation of the incomplete case group.

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