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Creutzfeldt-Jakob disease surveillance in Australia: update to 31 December 2020

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The Abstract to this report, below, contains three numerical errors in the third sentence of its second paragraph.
Please refer to this report's Erratum https://doi.org/10.33321/cdi.2021.45.40 to view the corrected Abstract.

Annual report

Creutzfeldt-Jakob disease surveillance in Australia: update to 31 December 2020

Christiane Stehmann, Matteo Senesi, Shannon Sarros, Amelia McGlade, Victoria Lewis, Marion Simpson, Genevieve Klug, Catriona McLean, Colin L Masters, Steven Collins

Abstract

Nationwide surveillance of Creutzfeldt-Jakob disease and other human prion diseases is performed by the Australian National Creutzfeldt-Jakob Disease Registry (ANCJDR). National surveillance encompasses the period since 1 January 1970, with prospective surveillance occurring from 1 October 1993. Over this prospective surveillance period, considerable developments have occurred in pre-mortem diagnostics; in the delineation of new disease subtypes; and in a heightened awareness of prion diseases in healthcare settings. Surveillance practices of the ANCJDR have evolved and adapted accordingly. This report summarises the activities of the ANCJDR during 2020.

Since the ANCJDR began offering diagnostic cerebrospinal fluid (CSF) 14-3-3 protein testing in Australia in September 1997, the annual number of referrals has steadily increased. In 2020, 510 domestic CSF specimens were referred for 14-3-3 protein testing and 85 persons with suspected human prion disease were formally added to the national register. As of 31 December 2020, just over half (44 cases) of the 85 suspect case notifications remain classified as 'incomplete'; 27 cases were excluded through either detailed clinical follow-up (9 cases) or neuropathological examination (18 cases); 18 cases were classified as 'definite' and eleven as 'probable' prion disease. For 2020, sixty percent of all suspected human-prion-disease-related deaths in Australia underwent neuropathological examination. No cases of variant or iatrogenic CJD were identified.

The SARS-CoV-2 pandemic did not affect prion disease surveillance outcomes in Australia.

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

Introduction

Of human prion diseases (also known as transmissible spongiform encephalopathies), the most common is Creutzfeldt-Jakob disease (CJD). The Australian National Creutzfeldt-Jakob Disease Registry (ANCJDR) was established in 1993 as part of the response to four people dying from CJD related to fertility treatment utilising cadaveric pituitary hormones. As described previously,[1] human prion disease mostly arises sporadically but can occur through person-to-person transmission or from a genetic aetiology. In 1993, the Allars inquiry[2] released its findings into the use of cadaver-derived pituitary hormones under the Australian Human Pituitary Hormone Program and the association with four medically-acquired (iatrogenic) CJD (iCJD) deaths, recommending a broadening of the responsibilities of the nascent ANCJDR. In addition to monitoring for further cases of iCJD in Australia, related to cadaveric pituitary hormone treatment for infertility or short stature and contaminated dura mater grafts, the ANCJDR's activities have evolved to encompass the surveillance of all types of CJD, including sporadic, genetic and variant CJD (vCJD, the zoonosis related to

bovine spongiform encephalopathy: BSE), as well as other prion diseases such as Gerstmann-Sträussler-Scheinker syndrome and fatal sporadic or familial insomnia.

Human prion disease became a notifiable disease in all states and territories of Australia in June 2006. Most initial case awareness at the ANCJDR arises through diagnostic testing requests made to the ANCJDR; this occurs prior to Health Department notification. After a preliminary review of referred cases, those deemed to be genuine suspected human prion disease undergo further detailed evaluation and addition to the national surveillance register, to determine whether a case can be excluded from suspicion or can be classified as a 'definite', 'probable' or 'possible' prion disease case according to diagnostic criteria endorsed by the Creutzfeld-Jakob Disease International Surveillance Network (colloquially EUROCJD) and to determine the aetiology of the illness.[3]

The incidence of sporadic CJD (sCJD) is commonly reported to be approximately one case per million per year; however, in most countries with longstanding surveillance systems in place, annual incidence rates have been consistently reported above this quoted figure.[4,5] Multi-national collaborative studies show that intensity of surveillance correlates with reported incidence rates.[6] Temporally, human prion disease incidence rates have increased in most countries, including Australia, as surveillance mechanisms have been optimised and diagnostic testing capabilities improved, in parallel with a generally greater awareness of this rare disease in the healthcare setting.

In this report, updated national surveillance figures to 31 December 2020 are provided for all retrospective (to 1970) and prospective (from 1993) cases ascertained, including a discussion on case notifications, classifications and overall incidence.

Since the ANCJDR began offering cerebrospinal fluid (CSF) 14-3-3 protein testing in Australia in September 1997, the annual number of referrals has steadily increased. A significant increase in CSF diagnostic referrals has been experienced since 2017, coinciding with the introduction of additional CSF biomarker (total-tau protein) testing.

Surveillance methods

Patients with suspected human prion disease have been prospectively notified to the ANCJDR since October 1993. From 1997 onwards, suspected cases have been increasingly notified through referral for CSF 14-3-3 protein western blot testing, which has over time become the predominant source of initial awareness of suspected CJD cases. Other ascertainment mechanisms include, or have included, personal communications from clinicians, families, hospitals and CJD-related groups, as well as health record searches through hospitals and health departments.

Once referred to the ANCJDR, referrals undergo a *prima facie* assessment and, if the suspicion of prion disease is supported, the case is notified to the appropriate health department and added to the ANCJDR register as a formal 'suspected case' for continued surveillance and evaluation with the aim of exclusion or classification according to EUROCJD-endorsed diagnostic criteria. Investigation of registered 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 to facilitate a comprehensive review. 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.

Classification of registered cases remains as 'incomplete' until all known available information is gathered and reviewed, or until a definitive result from neuropathological assessment is obtained. Cases may be excluded from the register based on neuropathological examination or after thorough clinical evaluation. A 'definite' classification requires brain neuropathological examination, including immunochemical

analysis; 'probable' and 'possible' cases are reliant on a specific clinical profile and diagnostic test outcomes being met as previously described.[3] As of 1 January 2017, the diagnostic criteria were amended to include a positive result in the real-time quaking-induced conversion (RT-QuIC) assay using CSF or other tissues in a person with a progressive neurological syndrome. The updated EUROCJD diagnostic criteria for surveillance of sporadic CJD are listed in Appendix A. In keeping with previous reports, the total number of confirmed prion disease cases for 2020, including for statistical analyses, are those that have been classified as 'definite' or 'probable' cases during 2020.

In support of its surveillance responsibilities, the ANCJDR provides diagnostic platforms for ante- and post-mortem testing for human prion diseases. The testing of CSF for the presence of a family of low-molecular-weight proteins (14-3-3) has been performed weekly by the ANCJDR since 1997. This test has been readily utilised by clinicians. In 2017, the ANCJDR formally added estimation of CSF total-tau protein concentrations, which is also National Association of Testing Authorities/International Laboratory Accreditation Cooperation (NATA/ILAC) accredited, for the diagnosis of human prion disease, while continuing to develop and transition to the powerful RT-QuIC assay to detect the presence of misfolded prion protein in CSF. The total-tau enzyme-linked immunosorbent assay (ELISA) test is performed at the National Dementia Diagnostic Laboratory on a fortnightly basis. The RT-QuIC assay is currently performed at the ANCJDR for research purposes in consultation with managing clinicians. The ANCJDR also undertakes western blot analysis for misfolded, protease-resistant prion protein in brain and tonsil tissue from biopsies or autopsies to supplement immunohistochemical assessment, as required for diagnostic and sub-classification purposes. Prion protein gene (*PRNP*) testing for sequence variations in the open reading frame, particularly for proven disease-causing mutations, is performed by an external, independent provider as appropriate. Upon request, the ANCJDR performs DNA extractions from frozen post-mortem brain tissue, which can be used for *PRNP* testing. The ANCJDR actively promotes all diagnostic tests to clinicians and families to achieve the most accurate diagnosis and classification of persons suspected to suffer from prion disease.

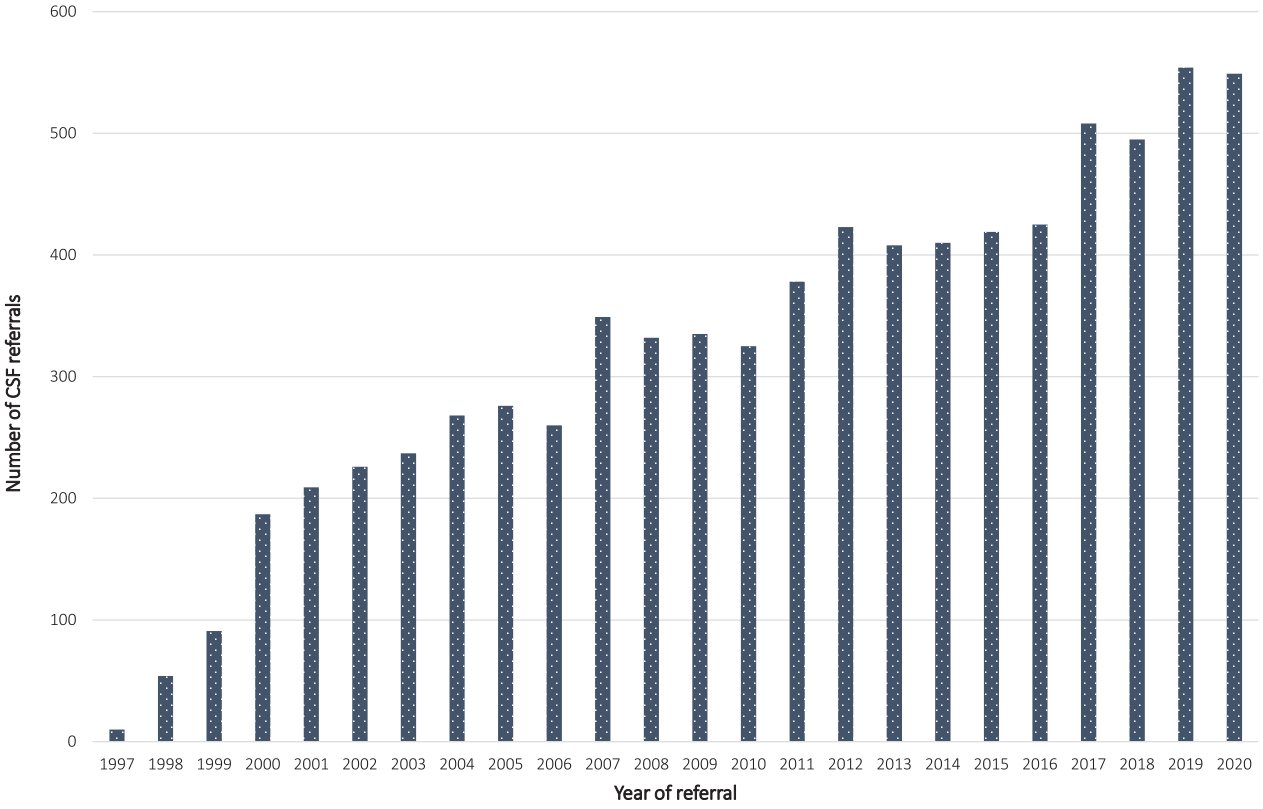
Annual human prion disease incidence rates are calculated using direct age-standardisation, based on the 1970–2020 Australian Bureau of Statistics estimated resident population data for Australia and for each state and territory.[7] Health information is collected through a combination of public health and surveillance responsibilities, based on the national notification of communicable diseases in observance of the *National Health Security Act 2007* and *Privacy Act 1988* (Cth) 16B. ANCJDR surveillance activities for 2020 were approved by The University of Melbourne Human Research Ethics Committee.

Results

In 2020, the ANCJDR received 510 domestic CSF specimens for 14-3-3 protein testing. This number reflects a continuing positive trend in annual CSF referral numbers and represents an increased awareness and perceived utility of 14-3-3 protein diagnostic testing by clinicians (Figure 1). In 2020, non-domestic CSF referrals made up 7% of the total CSF specimens received by the ANCJDR; the total number of non-domestic CSF test referrals has also steadily increased over time.

The majority of domestic CSF referrals come from the most populous states (New South Wales, Victoria, Queensland, Western Australia and South Australia), in which there has been a noticeable steady increase in test referrals, while CSF referrals from the Australian Capital Territory, the Northern Territory and Tasmania have remained relatively unchanged. CSF diagnostic testing resulted in a total of 76 formal suspect case notifications during 2020. The SARS-Cov-2 pandemic did not affect the number of CSF specimens referred for CJD biomarker testing in Australia.

Figure 1: Annual number of CSF specimens referred to the ANCJDR for 14-3-3 protein diagnostic testing, from 1997 to 2020



During 2020, 91 persons with suspected human prion disease were added to the national CJD surveillance register following *prima facie* review. Of these, six cases were known to the ANCJDR prior to 2020 through CSF referrals. At the time of their initial notification in 2018 (2) and 2019 (4), these cases were not added to the register due to a low level of suspicion for prion disease after initial case review. Further information ascertained in 2020 increased the likelihood of prion disease resulting in formal notification and addition of the cases to the register. These six cases therefore contribute to the total numbers of suspect case notifications arising in 2018 and 2019.

The 85 suspected cases for 2020 were initially notified via: request for CSF 14-3-3 protein testing (48 cases); and personal communications from neuropathology services (7 cases); clinicians or hospitals (27 cases); families and the CJD Support Group Network (2 cases); and health departments (1 case). In nine suspected cases, no CSF specimen was received by the ANCJDR for diagnostic testing; these cases were notified by neuropathologists (6 cases) or by the treating doctor or hospital (3 cases). While there is still a predominance of initial case awareness through referrals for CSF diagnostic testing, there has been a noticeable increase, in recent years, in case notifications through treating clinicians, neuropathologists, health departments and families seeking expert advice and guidance from the ANCJDR. Some previous proactive ANCJDR surveillance mechanisms (e.g. mortality database searches and reply-paid mailouts to clinicians) have been discontinued over time due to human resource constraints.

The number of suspected cases added to the ANCJDR register in 2020 follows the trend of increasing rates and was not affected through the SARS-Cov-2 pandemic. The average annual number of suspected prion disease cases notified to the ANCJDR for the period 1997–2020 (i.e. since the introduction of diagnostic testing of CSF) is 73.

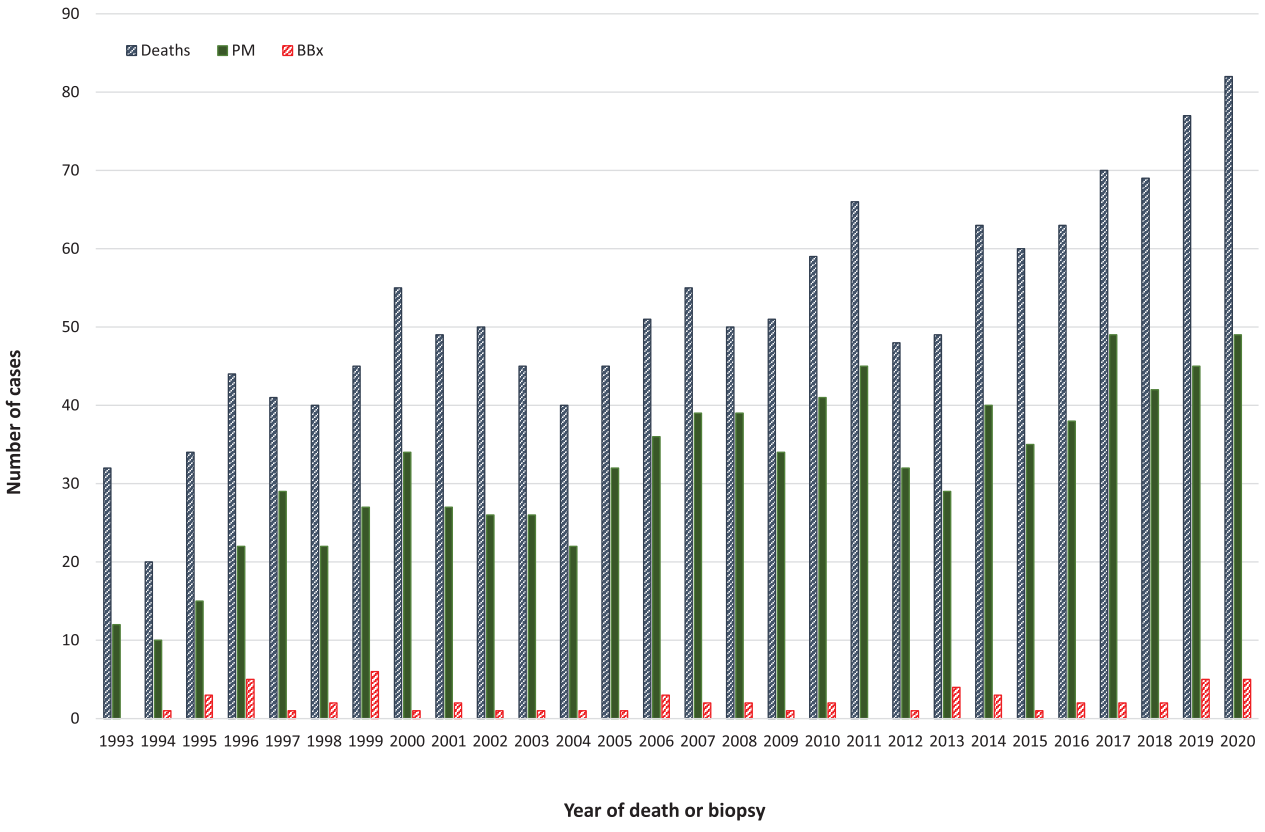
States and territories exhibited modest fluctuations in the annual number of suspect case notifications for 2020, compared to both the previous year and the longer-term average.

Of the 85 formal suspect case notifications received in 2020, 18 cases were confirmed as 'definite' by neuropathological examination and eleven cases were classified as 'probable' following detailed review of clinical information. Four cases were confirmed as non-prion disease following neuropathological assessment and eight following detailed clinical case review, while 17 cases were still alive and considered 'incomplete' at the end of 2020; neuropathology reports were pending for 18 deceased suspected cases. It is routine for several months to elapse between performance of a post-mortem and completion of the neuropathology report. Another nine cases have died without autopsy and remain 'incomplete' pending detailed case investigation.

Since 1993, there has been an increasing trend in the annual number of suspected cases of human prion disease undergoing post-mortem brain examination, or less commonly brain biopsies, albeit with relative plateauing over the last 15 years, beginning with twelve such cases in 1993 to around 30–40 per year for the period from 2005 to 2020 (Figure 2). In 2020, of the 82 suspected CJD case deaths, 49 were referred for a brain post-mortem examination, with five additional patients undergoing pre-mortem brain biopsy.

The average annual proportion of suspected prion disease cases on the register between 1993 and 2019 undergoing post-mortem brain examination is 63% (range 38–78%); the provisional proportion for 2020 is 60%. Annual suspected prion disease brain autopsy referrals by state and territory over the period 1993–2020 display considerable fluctuation in each region. In the more populous states, there has generally been an overall temporal increase in brain autopsy referrals. In regions with smaller populations

Figure 2: Number of brain-only post-mortem (PM) examinations and brain biopsies (BBx) completed relative to suspect case deaths from 1993 to 2020, by year



this increasing trend is also present, but is less robust due to the relative impact of variation in the annual brain autopsy referrals caused by small population sizes and case numbers.

As of 31 December 2020, there were 1,381 cases on the ANCJDR register with 1,099 of these being classified as 'probable' or 'definite' prion disease cases. An additional 'definite' iatrogenic case who was treated in Australia but died in the UK is included in Table 1; this case is not classified as an Australian case due to their location at death and is thereby excluded from the overall statistical analysis of Australian prion disease cases. Since the start of prospective surveillance in 1993, 833 suspected prion disease cases have been excluded from the register after detailed follow-up.

In 2020, 35 cases were re-classified from 'incomplete' to 'definite' prion disease and 31 cases to 'probable' prion disease; no further cases of 'possible' prion disease were classified. The total number of 'possible' cases remains at 15, 14 of which were sporadic and one iCJD (Table 1). In 2020, the total number of 'incomplete' cases under evaluation was slightly lower than in 2019.

The age-standardised mortality rate (ASR) for prion disease for 2020 is 1.24 deaths per million per year. This figure is provisional and almost certainly an underestimate, as 21 neuropathology reports are pending and eleven cases who died in 2020 remain under investigation. Annual ASR values for human prion disease in Australia during the period of 1970 to 2020 have generally increased. The mean annual ASR during the period from 1970 to 2020 is 1.05 death per million (range 0.1–1.8). For the prospective surveillance period of 1993 to 2020, the annual mean ASR is 1.36 deaths per million (range 0.7–1.8). By state and territory, most regions in Australia have an annual mean ASR equivalent to or above one case per million per year between 1993 and 2020 (Table 2). Tasmania and the Northern Territory have recorded 0.9 and 0.7 deaths per million per year, respectively, during this period. Given the small population numbers in these two jurisdictions, the Tasmanian and Northern Territory ASR values are unlikely to represent a significant difference to other states and territories.

A breakdown of annual case numbers and mortality rates is shown in Figure 3 and Table 2. The highest annual number of 'probable' and 'definite' prion disease cases reported, since surveillance commenced in 1993, was 52 and 51 in 2017 and 2019, respectively, resulting in an annual ASR of 1.74 and 1.62 deaths per million. Although this rate is higher than the long-term average of 1.36 deaths per million, similar mortality rates were reported in 2000, 2006, 2011 and 2016.

The proportions of human prion disease aetiologies on the ANCJDR register for 2020 remained similar to previous years (Figure 4); the vast majority of the 1,099 statistical cases of human

Table 1: Overall summary of Australian human prion disease, 1 January 1970 to 31 December 2020

Classification	Sporadic	Familial	Iatrogenic	Variant CJD	Unclassified	Total
Definite	653	61	5[a]	0	0	718
Probable	351	26	4	0	0	381
Possible	14	1	1	0	0	16
Incomplete		5	0	0	261	266
Total	**1,018**	**93**	**9**	**0**	**261**	**1381**

a 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.

Table 2: 'Definite' and 'probable' cases of human prion disease from 1993 to 2020, by year and state or territory

	2020[a]		1993–2020		
Jurisdiction[b]	Cases	ASR[c]	Total cases	Long term average cases	Average ASR[c]
ACT	0	0	14	0.5	1.27
NSW	11	1.19	276	10	1.31
NT	0	0	6	0.2	0.69
Qld.	6	0.85	136	5	1.05
SA	5	2.23	77	3	1.55
Tas.	2	2.60	16	0.6	0.93
Vic.	13	1.66	250	9	1.58
WA	2	0.52	111	4	1.65
Australia	**39**	**1.24**	**886**	**32**	**1.36**

a The figures for 2020 are provisional and almost certainly an underestimate, as 21 neuropathology reports are pending and eleven cases who died in 2020 remain under investigation.

b ACT: Australian Capital Territory; NSW: New South Wales; NT: Northern Territory; Qld: Queensland; SA: South Australia; Tas.: Tasmania; Vic.: Victoria; WA: Western Australia.

c ASR: age-standardised mortality rate, in deaths per million population per year.

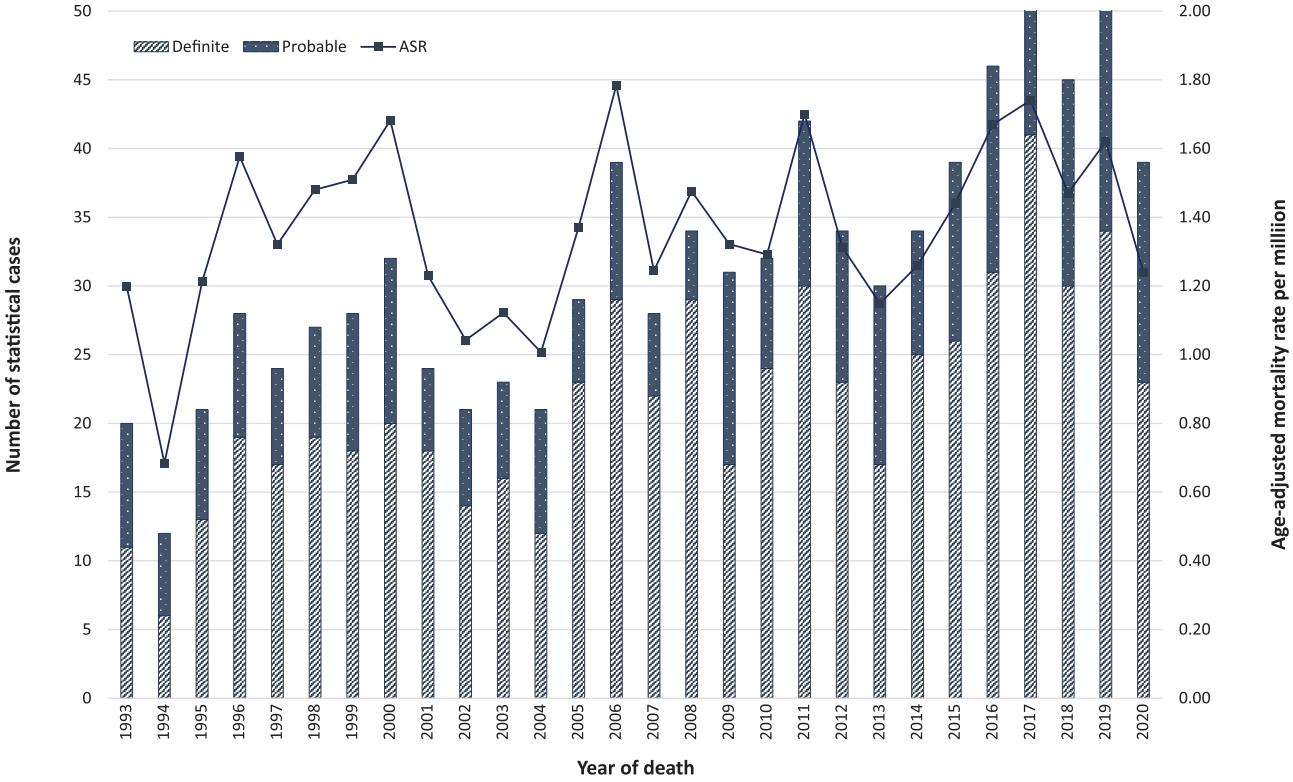
prion disease are 'sporadic' (91%) while genetic and iatrogenic cases represent 8% and < 1%, respectively, of all 'definite' and 'probable' cases.

There are currently 1,004 'definite' and 'probable' sporadic prion disease cases on the ANCJDR register. The distribution is almost equal between males (48%) and females (52%), with the slight predominance in females reflecting their longer life expectancy. The average age at death is 67 years, with a median of 68 years, ranging in age from 19 to 91 years. The average duration of illness is 6.3 months, with a median of 3.8 months, ranging from 0.9 to 60 months.

Genetic prion disease has been confirmed in 87 individuals, 56% of whom were female. The average age at death for genetic prion disease is 58.1 years, with the average duration of disease 13.7 months. The average age at death in females is 59.3 years, with a median of 62 years, ranging in age from 18 to 82 years. The average age at death in males is 56.4 years, with a median of 59 years, ranging in age from 20 to 83 years. The average duration of illness is 12.4 months, with a median of 4.1 months, ranging from 1.3 to 108 months.

There are currently 55 families affected by genetic prion disease on the ANCJDR register, comprising 87 individuals (61 'definite' and 26 'probable' cases); the range of *PRNP* mutations in Australian genetic prion disease cases is shown in Table 3. Three prion protein gene (*PRNP*) mutation carriers were removed from the register after brain autopsies excluded evidence of prion disease. These three E200K mutation carriers died aged 70 or older; the mean age at death for the E200K mutation is 63 years. Five cases on the register remain under investigation without a neuropathological or case classification outcome; however, there is a documented concern for genetic prion disease. Five families are of unspecified *PRNP* status although there is a recorded family history of prion disease.

Figure 3: Human prion disease in Australia from 1993 to 2020; number of definite and probable cases and age-standardised mortality rates (ASR), by year



Discussion

In 2020, the number of suspected prion disease referrals and confirmed cases broadly matched the long-term average (1997–2019). Australia continued to be free of vCJD and no further cases of iCJD were detected. By state and territory, the numbers of suspected case referrals showed generally only modest fluctuations during 2020 compared to the previous year; fluctuations seen in 2020 are within previously-observed ranges.

Long-term national surveillance units report differing annual prion disease mortality rates, ranging from 0.24 to 4.56 per million population.[4,5] Higher rates of human prion disease over short time frames have also been recognised and investigated in various global settings with inconclusive outcomes.[8] The underlying basis for fluctuations and differences in national mortality rates is uncertain, although variation in case ascertainment is one potentially contributing factor.[6]

Spatio-temporal clustering of CJD has previously been recognised in New South Wales and Victoria.[9,10] Detailed epidemiological assessment by the ANCJDR did not disclose any likely horizontal transmission event, but instead uncovered a heightened intensity of surveillance.[9] This more intense level of surveillance was reflected by the significantly higher rates of referrals of suspect prion disease cases for evaluation and diagnostic testing to the ANCJDR, as well as higher neuropathological examination rates in suspected patients.[6,9,10] Monitoring of the geographical distribution of suspected case referrals and confirmed cases remains an important facet of ANCJDR national surveillance.

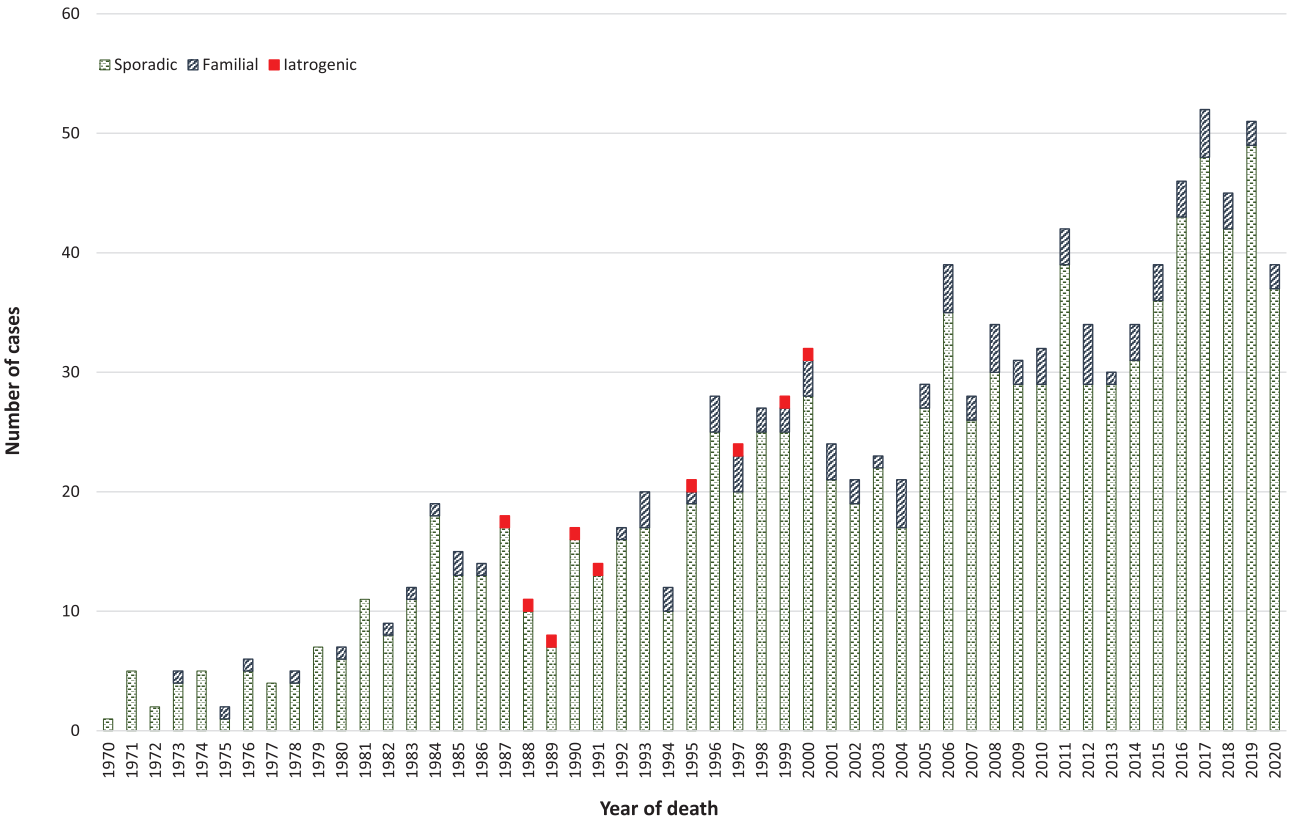
An overall increase in sporadic CJD cases has also been observed in Australia and is most likely due to a combination of an ageing population, improved case ascertainment and diagnostic methodologies, and greater awareness of prion disease in the healthcare sector.[5,11] The gradual but notable increase in the incidence of sCJD, but not that of genetic

CJD, has also been reported in other countries with longstanding prion disease surveillance and supports the notion that it is a result of the globally ageing population.[5,11]

Ascertainment mechanisms in 2020 were unchanged compared to recent years, with the majority of initial referrals coming through requests for diagnostic CSF 14-3-3 protein testing. Some proactive ascertainment mechanisms (such as state health department and tertiary hospital mortality data base searches) have ceased, while other case detection methods have increased. The number of CSF referrals to the ANCJDR for diagnostic (14-3-3 protein) testing remained high for 2020. A 20% increase in diagnostic test referrals coincided with the introduction of CSF total-tau protein estimation in 2017. Estimation of total-tau protein in CSF is NATA/ILAC accredited and complementary to 14-3-3 protein testing to support a pre-mortem diagnosis of sporadic CJD. The identification of misfolded prion protein in CSF by RT-QuIC continues to be developed by the ANCJDR as a diagnostic test and is currently selectively performed for cases after discussion with clinicians. The addition of CSF total-tau protein estimation to 14-3-3 protein detection as a biomarker for the pre-mortem evaluation of suspected sCJD offers modestly enhanced diagnostic capacity while the ANCJDR completes imminent transition to clearly superior protein amplification techniques such as RT-QuIC.

The proportion of post-mortems being performed in suspect prion disease cases remains high and aligns with the long-term mean brain autopsy percentage of approximately 63% (of suspected case deaths) between 1993 and 2019. This contrasts with the findings of an Australian healthcare setting survey where the national hospital post-mortem rate was 12% in 2002–2003;[12] more recently, a major Australian tertiary centre audit of hospital autopsy data has described an autopsy rate of 6.6% in 2011–2013.[13]

Figure 4: 'Definite' and 'probable' human prion disease cases 1970 to 2020,[a] by year and aetiology



a 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.

Table 3: Prion protein gene (*PRNP*) sequence variations/mutations identified in Australian cases

Mutation/polymorphism	Definite/probable cases
E200K	40
D178N	13
V210I	8
P105T	5
P102L	5
Other[a]	11
Not determined	5
Total	**87**

a 2,4,7OPRI - abbreviation for octapeptide repeat insertion; A133V; E200D; G131V; T188A; V176G; V180I; V189I.

The high suspected prion-disease-related post-mortem rate underpins the high and consistent number of confirmed Australian human prion disease cases recorded over the more recent prospective surveillance time period, and provides confident understanding of the cause of death in suspected cases ultimately determined as non-prion disease.

A recent study by the ANCJDR of prion disease in Aboriginal and Torres Strait Islander people has confirmed that sporadic CJD occurs in Aboriginal and Torres Strait Islander people throughout Australia with a phenotype and incidence rate equivalent to non-Indigenous Australians, supporting the adequacy of national human prion disease surveillance.[14]

No vCJD or further iCJD cases were confirmed in Australia during 2020. The most recent human cadaveric pituitary gonadotrophin-related CJD death occurred in 1991, while the most recent Lyodura-related CJD death occurred in 2000. In 2020, the USA and UK both reported one case of iatrogenic CJD associated with pituitary growth hormone. Germany and Italy reported one case of iCJD each, associated with dura mater transplants.

Since vCJD was first reported in 1996, a total of 232 patients, from 12 countries, have been identified with this disease. The most recent vCJD case died in France in 2019. A recent vCJD case (death occurred in 2016) from the UK was the first to be reported as methionine-valine heterozygous at codon 129 of the *PRNP* gene;[15] all cases previously had been methionine homozygous. The patient was 36 years old when he presented with psychiatric symptoms prior to onset of neurological features that included cognitive decline, ataxia and myoclonus, dying after an illness of 20 months. CSF 14-3-3 and RT-QuIC were negative. Brain magnetic resonance imaging (MRI) revealed features more typical of sporadic CJD (bilateral high signal in basal ganglia) without any posterior thalamic high signal ('pulvinar sign'). The patient did not meet the epidemiologic diagnostic surveillance criteria for 'probable' or 'possible' vCJD, although fulfilled criteria for 'probable' sporadic CJD; neuropathology, including western blot glycotyping, was typical of vCJD. It remains uncertain whether this case marks the start of a second wave of vCJD affecting those heterozygous for methionine-valine at codon 129. This case also underscores the importance of performing suspect CJD brain autopsy examinations and the benefits of maintaining high-level surveillance within Australia.

Although the horizontal transmission of amyloid beta (Aβ) peptides associated with Alzheimer's disease through contaminated pituitary hormone treatments and dura mater grafts is essentially proven,[16-18] it remains contentious, but possible, that such inadvertent inoculation can also eventuate in a disease phenotype.[19] Prion protein and Aβ protein share similar properties, such as prion-like mechanisms of template-directed protein propagation, as well as inter-cellular spread of the misfolded protein isoforms and formation of larger fibrils. The long incubation periods of these proteins can result in clinical and pathological evidence of disease becoming apparent only decades after inoculation. Further studies are required to resolve this important issue and the risk of Aβ peptide transmission during routine surgical procedures. History of neurosurgery, embolization procedures with the use of dura in infant or youth age and any other therapeutic procedures involving the use of dura mater or

cadaver-derived pituitary hormones should be searched for in patients who develop early-onset and cerebral amyloid angiopathy (CAA).

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Appendix A

EUROCJD diagnostic criteria for surveillance of sporadic CJD from 1 January 2017

Definite:

Progressive neurological syndrome AND Neuropathologically or immunohistochemically or biochemically confirmed

Probable:

I + two of II and typical EEG[a]

OR

1.2.2 I + two of II and typical MRI brain scan[b]

OR

1.2.3 I + two of II and positive CSF 14-3-3

OR

1.2.4 Progressive neurological syndrome and positive RT-QuIC in CSF or other tissues

Possible:

I + two of II + duration < 2 years

I Rapid progressive cognitive impairment

II A Myoclonus

B Visual or cerebellar problems

C Pyramidal or extrapyramidal features

D Akinetic mutism

a Generalised periodic complexes

b High signal in caudate/putamen and MRI brain scan or at least two cortical regions (temporal, parietal, occipital) either on DWI or FLAIR