The importance of ongoing international surveillance for Creutzfeldt–Jakob disease

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Abstract | Creutzfeldt–Jakob disease (CJD) is a rapidly progressive, fatal and transmissible neurodegenerative disease associated with the accumulation of misfolded prion protein in the CNS. International CJD surveillance programmes have been active since the emergence, in the mid-1990s, of variant CJD (vCJD), a disease linked to bovine spongiform encephalopathy. Control measures have now successfully contained bovine spongiform encephalopathy and the incidence of vCJD has declined, leading to questions about the requirement for ongoing surveillance. However, several lines of evidence have raised concerns that further cases of vCJD could emerge as a result of prolonged incubation and/or secondary transmission. Emerging evidence from peripheral tissue distribution studies employing high-sensitivity assays suggests that all forms of human prion disease carry a theoretical risk of iatrogenic transmission. Finally, emerging diseases, such as chronic wasting disease and camel prion disease, pose further risks to public health. In this Review, we provide an up-to-date overview of the transmission of prion diseases in human populations and argue that CJD surveillance remains vital both from a public health perspective and to support essential research into disease pathophysiology, enhanced diagnostic tests and much-needed treatments.

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Creutzfeldt–Jakob disease (CJD) is a devastating and uniformly fatal human prion disease. The disease typically causes a combination of cognitive and motor dysfunction and is associated with rapid progression, with the majority of affected individuals dying within several months of symptom onset[1–5]. Sporadic CJD (sCJD) is the archetypal human prion disease, belonging to a family of transmissible and universally lethal mammalian diseases[6]. The discovery that prion diseases are associated with the conversion of normal host-encoded cellular prion protein (PrP^C) to a misfolded form (PrP^Sc) by post-translational modification, independently of nucleic acid, became known as the protein-only hypothesis. It was Stanley Prusiner who discovered and characterized prions, for which he received a Nobel Prize in 1997 (REF.[7]). Prion diseases are transmissible and multiple epidemics affecting humans and animals have emerged globally over the last 50 years[5,8–14]. A hallmark of prion disease transmission is the potential for incubation phases lasting several years, sometimes decades[5,9,15,16].

A polymorphism at codon 129 (c129) in the prion protein gene (*PRNP*) strongly influences the susceptibility towards and the clinical features of human prion diseases[1,9,10,17–20]. Over 90% of East Asian individuals are homozygous for methionine at c129 (MM genotype); however, in populations of European descent, ~40% of individuals have the MM genotype, ~50% of individuals are heterozygous for methionine and valine (MV genotype), and ~10% are homozygous for valine (VV genotype)[21]. The treatment of tissue samples with proteinase K followed by western blot examination enables the detection of protease-resistant fragments of PrP^Sc (PrP^res) in individuals with prion disease, providing a 'molecular signature' of the disease[22]. PrP^res is biochemically classified according to the molecular weight of the unglycosylated fragment, which is 21 kDa in type 1 PrP^res and 19 kDa in type 2 PrP^res (REFS[22,23]). Type 2 is further classified into types 2A and 2B; the latter is characterized by a predominant diglycosylated band and is present in individuals with variant CJD (vCJD)[23]. Prion diseases can be classified according to the system suggested by Parchi et al.[17], which is based on a combination of the c129 genotype and PrP^res isotype, providing biological correlates for clinical manifestations of disease[24].

CJD consists of three subtypes: sporadic, inherited and acquired (comprising iatrogenic CJD (iCJD), vCJD

Key points

- Creutzfeldt–Jakob disease (CJD) is a transmissible and universally fatal human prion disease; surveillance programmes exist globally to monitor trends in CJD epidemiology and mitigate public health risks.

- The variant CJD (vCJD) epidemic was a devastating consequence of the bovine spongiform encephalopathy (BSE) epizootic.

- Studies indicate the widespread prevalence of vCJD-associated prion protein in BSE-exposed populations.

- Although new diagnoses of vCJD have declined in parallel with the suppression of BSE, lessons from other prion diseases indicate the potential for highly extensive incubation phases lasting decades.

- Emerging animal prion diseases might harbour the potential for zoonotic transmission to humans.

- Continued CJD surveillance is a necessity to meet the potential for further cases of vCJD or the emergence of novel prion diseases in humans.

and Kuru). All forms of CJD are transmissible and thus pose serious public health challenges. vCJD was first detected in 1996, initially in the UK[25] and subsequently in France[26], and was causally linked to the epizootic of bovine spongiform encephalopathy (BSE), a prion disease affecting cattle. The incidence of vCJD has dramatically declined since the global vCJD epidemic peaked in 2000; seven new cases of the disease have been identified globally since 2012 (REFS[10,16,20,27,28]) (FIG. 1). As CJD clinical surveillance programmes were developed in response to the emergence of BSE in cattle, the question of whether CJD surveillance is still necessary has now emerged. In this Review, we discuss the evidence indicating that further cases of vCJD could arise as a result of extensive incubation, asymptomatic carriage of vCJD-associated prion protein and secondary transmission. We also discuss the potential for secondary transmission of other forms of CJD, occupational risks, emerging prion diseases with zoonotic potential and the growing evidence that other neurodegenerative diseases could harbour the potential for prion-like transmissibility. We highlight the importance of surveillance programmes for accurate case ascertainment, public health interventions and much-needed research into prion diseases. Last, we provide the outline for a model surveillance programme and suggestions for how international surveillance should progress in the twenty-first century.

Clinical subtypes of prion disease
Sporadic CJD

In the majority (~85%) of individuals who develop CJD, the disease arises sporadically[1,29–31]. The onset of sCJD is most common between the ages of 60 and 70 years[32], although cases have been identified across a range of age groups[1]. sCJD has been detected in Europe[1,17,29,30,33,34], North America[31], Central America[35], South America[36,37], Africa[38–40], Asia[41–45] and Australasia[33,46,47], and has a global incidence of 1–2 per million, although the reported incidence varies between nations and is influenced by the methods and extent of surveillance performed[2]. Multiple low-income and middle-income countries have reported cases of sCJD[37–40,43,48,49]; however, as surveillance programmes are absent across much of the world, accurate epidemiological assessment is extremely challenging[21].

The aetiology of sCJD is unknown; however, the leading hypothesis is of an endogenous origin via a somatic mutation in *PRNP* or, alternatively, the spontaneous misfolding of PrP^C into PrP^{Sc} (REF.[50]). Some case–control studies have suggested the presence of exogenous risk factors. For example, two studies identified an association between sCJD and previous surgery[51,52], including non-neurosurgical (particularly ophthalmologic) operations. Another study found an association between sCJD and previous blood-product transfusion[53]. However, such case–control studies of sCJD have methodological limitations, including the potential for various forms of bias such as recall bias, differences in risk factor reporting (in contrast to healthy controls, most individuals with sCJD are unable to provide a direct history, leading to a reliance on relatives to provide information), and heterogeneity between studies in terms of the time windows of exposure assessed[52,53]. A detailed comparison of 18 studies is provided in a 2012 systematic review by de Pedro Cuesta et al.[54]. Evidence indicates that the c129 genotype has a substantial impact on susceptibility to sCJD: ~70% of individuals with sCJD have the MM genotype[17,55].

sCJD classically presents as a rapidly progressive dementia with motor decline that includes ataxia as well as pyramidal and extrapyramidal features; however, symptoms can include visual disturbance (most notably in the Heidenhain subtype[56]), neuropsychiatric manifestations and stroke-like presentations[24]. Myoclonus is common and patients eventually progress to an akinetic, mute, fully dependent state. Diagnostic classification follows the European Creutzfeldt–Jakob Disease Surveillance Network criteria[57] (BOX 1). Diagnosis is based on the presence of typical clinical features, supported by evidence from additional investigations. This supporting evidence includes the identification of characteristic MRI changes in the basal ganglia and/or cortex[58,59] (FIG. 2), EEG showing characteristic periodic sharp wave complexes[60], elevated levels of 14-3-3 protein in cerebrospinal fluid (CSF)[61–63] and the detection of PrP^{Sc} in CSF using real-time quaking-induced conversion (RT-QuIC) (an aggregation assay with almost 100% specificity for the diagnosis of sCJD)[64–66]. The neuropathology of CJD is characterized by vacuolation and/or spongiform change, neuronal loss, gliosis, and the immunohistochemical detection of PrP^{Sc} (REFS[17,67,68]). The median survival for individuals with sCJD is 5 months from symptom onset[24]. sCJD can be categorized by c129 genotype and PrP^{Sc} isotype into six subgroups (MM1, MM2, MV1, MV2, VV1 and VV2) each with characteristic clinical and neuropathological phenotypes[17,58] (FIGS 3,4).

Inherited prion diseases

In 10–15% of individuals with a prion disease[3,4,69], the disease arises secondary to mutations in *PRNP* and is categorized as inherited prion disease (IPD)[69]. Over 50 prion disease-associated *PRNP* mutations have now been described[24,69]. Most of these mutations show autosomal dominant inheritance and high penetrance, although some individuals with IPD do not have a family history of the disease[3,69]. IPD is associated with a longer
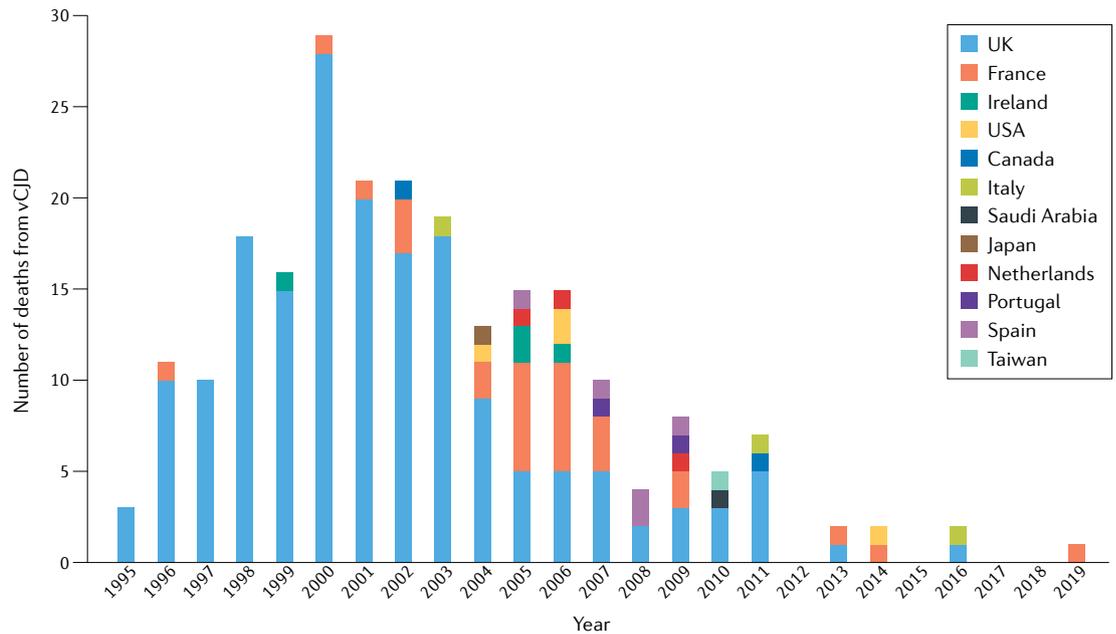
Fig. 1 | **The global burden of vCJD.** Graph shows the annual number of deaths from variant Creutzfeldt–Jakob disease (vCJD) in the 12 countries or territories for which data is available. Data obtained from the European Creutzfeldt–Jakob Disease Surveillance Network (EuroCJD).

survival than sCJD, which means that individuals with IPD comprise a substantial proportion of the prevalent population[70]. This prevalence is accompanied by public health risks relating to transmission. In some individuals, IPD can be difficult to distinguish from sCJD based on clinical characteristics and therefore diagnostic *PRNP* genotyping is often helpful. The extent of the public health risk posed by asymptomatic *PRNP* mutation carriers during interventional procedures and/or blood or tissue donation is not yet clear; risk-reduction measures for these individuals are in place in many countries[71,72].

Considerable heterogeneity in age of onset, duration of disease and clinical features exists between individuals with different *PRNP* mutations as well as between family members with the same mutation[69]. The clinical features of IPD can also mimic other neurodegenerative disorders[69,73]; symptoms can resemble Alzheimer disease[74], Huntington disease[75–77], frontotemporal dementia[78,79] and spinocerebellar ataxia[76]. Individuals with IPD associated with the E200K mutation in *PRNP* often have a clinical presentation that mimics sCJD, with rapid progression from symptom onset to death in <5 months[3]. Individuals with mutations, such as E200K, that are associated with an sCJD phenotype are referred to as having genetic CJD (gCJD). Gerstmann–Sträussler–Scheinker syndrome, which is most commonly caused by the P102L mutation in *PRNP*, causes a progressive ataxia with associated cognitive and sensory abnormalities[76] and has characteristic neuropathological features (FIG. 5). The disease typically progresses more slowly than sCJD, with a mean survival of 49 months from symptom onset[76]. Fatal familial insomnia, a result of the D178N mutation in combination with methionine at c129 on the affected allele (D178N–129M), presents with characteristic sleep disorders, autonomic disease, and gait disturbance and is typically fatal within 2 years of onset[80]. By contrast, individuals with D178N and valine at c129 on the affected allele (D178–129V) develop gCJD[81].

Surveillance systems have greatly enhanced our understanding of the international distribution of IPD-associated mutations[3,41,82,83], yielding valuable insights. E200K is the most common mutation internationally[3,82] but is particularly common in Slovakia, where it is present in >65% of individuals with prion disease[3], and in Jewish individuals with Libyan ancestry, a population prevalent in Israel[84]. Evidence indicates that, in Italy, a nation with a relatively high rate of IPD[3], the V210I mutation is the most frequent and is present in 41.5% of individuals with IPD[85]. Fatal familial insomnia has been observed in Europe, Asia, Australia and the USA[3,21,80,83,86]. T188K is a common cause of IPD in China, where it is present in 23% of affected individuals[83], but is uncommon elsewhere, including other Asian nations such as Japan[41] and Korea[87] where no individuals with the mutation were identified in published IPD case series. Ongoing global surveillance continues to identify novel mutations associated with prion disease, often showing small clusters within regions; for example, the identification of a cohort of individuals with R208H in Sardinia, which suggests a founder population[88]. V180I and M232R are commonly encountered in Japanese individuals with IPD, comprising 41.2% and 15.3% of *PRNP* variants, respectively[41]. However, V180I and M232R might increase the susceptibility to sCJD rather than being disease-causing mutations[69,89]. Some authors[89] have cited factors, including the sCJD-like phenotype and the absence of a relevant family history among affected individuals (present in only 2% of individuals with V180I and in 0% with M232R[41]), as evidence that

Box 1 | **European Creutzfeldt–Jakob Disease Surveillance Network diagnostic criteria for sCJD**

Definite sCJD:
Progressive neurological syndrome and either neuropathological, immunocytochemical or biochemical confirmation.

Probable sCJD:
Rapidly progressive cognitive impairment; two of myoclonus, visual or cerebellar problems, pyramidal or extrapyramidal features, and akinetic mutism; and typical EEG[a].

OR

Rapidly progressive cognitive impairment; two of myoclonus, visual or cerebellar problems, pyramidal or extrapyramidal features, and akinetic mutism; and typical MRI brain scan[b].

OR

Rapidly progressive cognitive impairment; two of myoclonus, visual or cerebellar problems, pyramidal or extrapyramidal features, and akinetic mutism; and positive cerebrospinal fluid 14-3-3 protein test.

OR

Progressive neuropsychiatric syndrome and positive real-time quaking-induced conversion (RT-QuIC) in cerebrospinal fluid or other tissues.

Possible sCJD:
Rapidly progressive cognitive impairment; two of myoclonus, visual or cerebellar problems, pyramidal or extrapyramidal features, and akinetic mutism; and duration <2 years

sCJD, sporadic Creutzfeldt–Jakob disease. [a]Generalized periodic complexes. [b]High signal in caudate and/or putamen on MRI brain scan or at least two cortical regions (temporal, parietal, occipital) either on diffusion-weighted imaging or fluid-attenuated inversion recovery. Adapted from REF.[269], CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

V180I and M232R might be polymorphisms rather than pathogenic mutations. IPD has been reported in South America[90] and India[91]; however, a lack of structured surveillance programmes in these regions means that prevalence remains unclear.

Acquired prion diseases

Kuru. Fewer than 5% of individuals diagnosed with CJD[7] have one of the acquired prion diseases, which consist of iCJD, vCJD and Kuru[2,92]. To date, Kuru has only been detected in the Fore people in Papua New Guinea, in whom an epidemic of the disease was caused by ritualistic mortuary cannibalism[8,9,93,94]. The Kuru epidemic is thought to have started in the 1920s and peaked in the late 1950s[8,9]. The epidemic subsided following the prohibition of cannibalism in the mid-1950s[9,94]; however, in some individuals heterozygous at c129, Kuru did not manifest until several decades after exposure[9]. This observation demonstrates the risk of extensive incubation times in acquired prion diseases.

Iatrogenic CJD. iCJD was first described in 1974 in an individual who had received a transplant of corneal tissue from a deceased donor, in whom sCJD was later identified at autopsy[95]. Subsequent cases of iCJD were traced to a number of causes. The two principal aetiologies are treatment with cadaveric pituitary-derived human growth hormone (c-hGH)[96] and human dura mater (hDM) grafts[5]. Less commonly, iCJD has arisen secondary to treatment with cadaveric gonadotropins[97] and following exposure to contaminated neurosurgical instruments and intracerebral depth electrodes[24].

The iatrogenic transmission of vCJD via blood products (discussed in more detail below) is typically considered separately to iCJD owing to major differences in the pathology and manifestations of the two diseases. Despite effective control measures, including a transition to recombinant hormone synthesis in the mid-1980s[5,15,98], the introduction of enhanced disinfection and processing of hDM grafts in 1987 (REFS[99,100]), shifts in neurosurgical practice away from hDM graft usage[101], and the sterilization and quarantine of infected instruments[71,102], individuals with iCJD are still being reported[1,100]. For some of these individuals, exposure to the prion protein was more than four decades before disease manifestation[103], highlighting the potential for extensive incubation periods[5,15,98].

The hDM-associated iCJD epidemic began in 1985 and peaked globally in 1997 (REF.[5]), although cases continue to be identified[100]. The epidemic arose largely from the use of Lyodura, a hDM product produced in Germany[5,100,104]. The region with the largest number of hDM-associated iCJD cases (154 as of March 2018 (REF.[100])) was Japan, where high numbers of hDM-grafting procedures were performed, although cases were also reported in other Asian nations, Europe, the USA, Australasia and South Africa[5].

c-hGH-associated iCJD was most frequently encountered in France[29], the UK[1] and the USA[105], and less commonly in other European countries, New Zealand, Qatar and Brazil[5]. The epidemic began in 1984 and peaked globally in 1995 (REF.[5]); individuals with extensive incubation continue to be reported[15]. The majority of individuals who developed c-hGH-associated iCJD in France had the MM c129 genotype whereas, in the UK, the VV and MV genotypes were more common[5,106]. c-hGH-associated iCJD is believed to have originated from the preparation of c-hGH from cadaveric sources likely to have had undetected sCJD[15]. Therefore, the presence of different PrP^Sc strains in different cadaveric sources might have contributed to the differing susceptibility to c-hGH-associated iCJD among c129 genotype groups in the UK and France[15].

Important lessons have been learned from the study of iCJD. The incubation period varies, being shortest following exposure to contaminated neurosurgical instruments and longest following exposure to hDM grafts and cadaveric hormones[5]. However, incubation rates also vary between individuals with the same means of exposure[5]. For example, individuals with the MV c129 genotype tend to show longer iCJD incubation periods than individuals with other c129 genotpyes[5]. These insights are relevant to vCJD as legitimate concerns exist that future cases of vCJD could emerge following extensive incubation periods. Long incubation periods are also relevant when considering the potential of secondary transmission of all forms of CJD. The clinical manifestations of iCJD are variable, with peripheral exposures frequently leading to cerebellar-onset presentations and central exposures leading to cognitive-onset manifestations[5]. Last, as a general historical point, medical and agricultural practices that unknowingly posed infection risks at the time have subsequently resulted in the emergence of prion disease, sometimes many years

later. The prompt identification of individuals with iCJD through surveillance was integral to the implementation of the measures that contained the resulting epidemics, illustrating the essential role for surveillance systems in managing novel prion disease epidemics.

Variant CJD. vCJD is the rarest form of human prion disease and was first recognized between 1995 and 1996 following the identification of a series of individuals in the UK with a novel prion disease characterized by atypical demographic, clinical, radiological and pathological features[25,107] (BOX 2). vCJD predominantly presents in the third decade of life and has a median survival period of 14 months, which is longer than that of sCJD[108]. In vCJD, early psychiatric symptoms including withdrawal, anxiety and dysphoria are common before the development of cognitive impairment, ataxia and movement disorders[109,110]. Thalamic pain affects many individuals in the early stages of the disease[109]. The presence of the pulvinar sign on MRI is a highly sensitive marker of vCJD in the appropriate context[111]. The detection of high levels of 14-3-3 protein in the CSF, which is a biomarker with 75–90% sensitivity for sCJD, only shows a 50% sensitivity for vCJD[112]. Furthermore, EEG in individuals with vCJD does not typically show the characteristic periodic sharp wave complexes that are observed in sCJD[24]. vCJD neuropathology is characterized by florid plaques and extensive type 2B PrP^{res} (REF.[68,113]) (FIGS 4,6).

Surveillance programmes accurately mapped case ascertainment and the trajectory of the vCJD epidemic, which was focused primarily in the UK (178 cases) and France (28 cases). At the time of writing (March 2021), a total of 232 cases of vCJD have been identified from 12 countries or territories across Europe, the USA, the Middle East and Asia[10] (FIG. 1). vCJD was causally linked to the epizootic of BSE, a novel prion disease affecting cattle, with the consumption of contaminated beef products being the primary source of vCJD infection[92,114,115].

The BSE epizootic arose as a result of agricultural feeding practices that involved using ruminant-derived rendered meat-and-bone meal (MBM) to feed cattle[11]. However, the origin of BSE itself remains unclear. The most popular hypothesis is that material from a scrapie-infected sheep entered the cattle feed supply, with the scrapie agent becoming altered on passage through cattle, rendering it highly infectious[11,116]. Alternative hypotheses, which have garnered less consensus, include the scrapie agent being altered by the rendering process or the emergence of a novel transmissible spongiform encephalopathy in the UK, possibly in cattle, which then entered the ruminant feed chain[11]. The epizootic peaked in 1992 in the UK, with 37,280 new cases identified in cattle that year[12]. A host of stringent control measures were adopted[117–121]. In the UK, these measures consisted of a ban on feeding ruminant-derived protein to ruminants (1988)[122]; surveillance, reporting and culling of BSE-infected animals (1988)[122]; a ban on feeding specified bovine offal to humans (1989)[122]; and a ban on feeding specified bovine offal to all farmed animals (1990)[122]. The EU also introduced a ban on feeding mammalian protein to ruminants in 1994. These measures resulted in substantial suppression of BSE over the following years[11–13] (FIG. 7).

Following the identification of vCJD in 1996 (REF.[25]), plausibly linked to BSE[123], there was a worldwide ban on British beef exportation[124] along with a ban on feeding mammalian protein to farmed animals (1996 in the UK (REF.[11]), subsequently adopted by the EU in 2001 (REF.[11])) and a ban on human consumption of cattle over 30 months old in the UK[124,125]. The British beef exportation bans were lifted a number of years later (2006 in the EU, 2020 in the USA)[126–129]. In the UK, >184,000 cases of BSE were identified during the epizootic[12] and modelling estimates that the total number of cases was 1–3 million[11], with >4 million cattle slaughtered as part of the containment response[130]. Dietary exposure of the UK population to BSE is likely to have been widespread[131–134] and substantial population exposures occurred in nations importing British beef (both livestock and carcasses), in particular France[135], the largest importer. Smaller domestic BSE epizootics were reported in >20 other countries, posing an additional means of exposure to non-UK citizens[13]. The incidence of BSE is now negligible; occasional cases continue to be reported but control measures are likely to prevent these animals from entering the human food chain[136,137]. The connection between BSE and vCJD was made on the basis of epidemiological evidence that vCJD cases were linked to geographical areas with BSE exposure risk, the observation of parallel epidemic trajectories several years apart (FIG. 7), and a series of transmission experiments and neuropathological studies that provided evidence that BSE and vCJD are caused by the same strain of prion protein[123,138–140].

Existing CJD surveillance programmes[141] were upgraded and new programmes initiated in the early
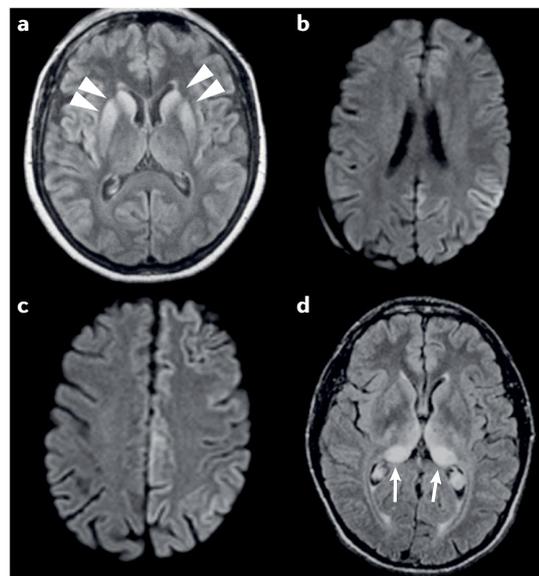

Fig. 2 | **Brain MRI in individuals with CJD.** Bilateral basal ganglia hyperintensities (arrowheads) are seen in sporadic Creutzfeldt–Jakob disease (CJD) (part **a**). Multifocal cortical ribboning can be seen in sporadic CJD, visible in the parietal (part **b**) and interhemispheric (part **c**) cortex in this individual. Bilateral pulvinar hyperintensities (arrows), known as the pulvinar sign, are seen in variant CJD (part **d**).
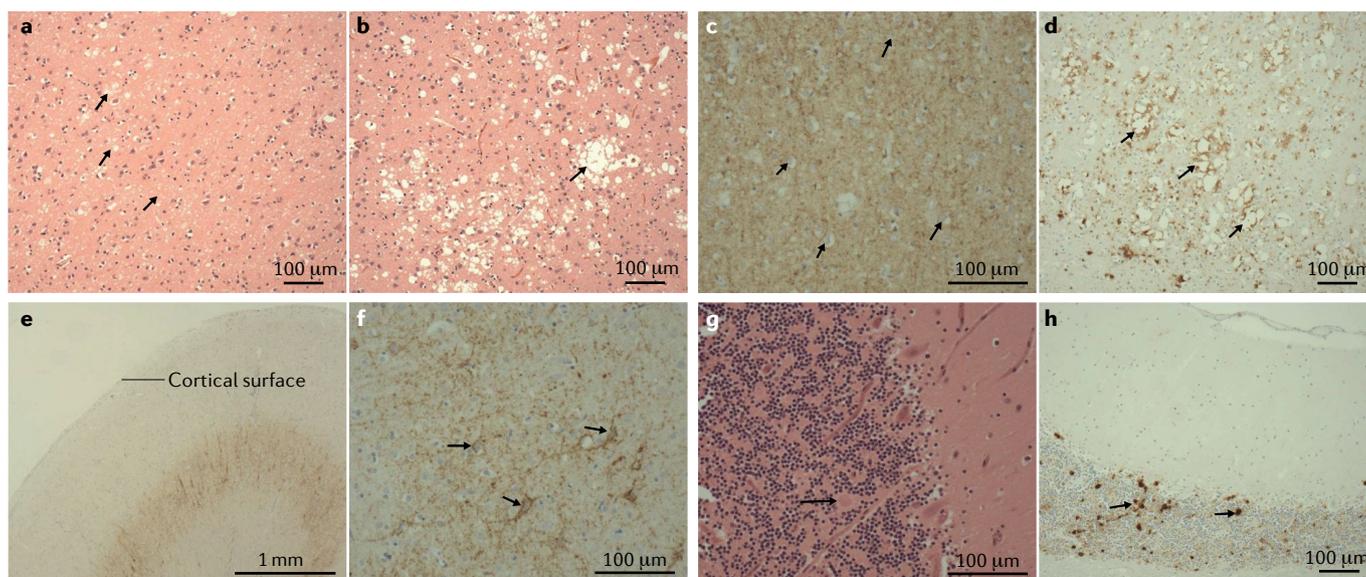
Fig. 3 | **Histological features of sCJD.** Histologically, the characteristic feature of prion diseases is spongiform change. Sporadic, genetic and acquired forms of prion disease show different patterns of spongiform change and, in individuals with sporadic Creutzfeldt–Jakob disease (sCJD), *PRNP* codon 129 genotype and western blot typing of the abnormal prion protein (PrP) also influence the pattern of histological change. In this figure, we provide examples of the histology typically observed in the different forms sCJD. Frontal cortex section from an individual with the MM1 subtype of sCJD showing the fine cortical vacuolation (arrows) that is common in most prion disorders (H&E staining, x100 magnification) (part **a**). Frontal cortex section from an individual with the MM2 subtype of sCJD showing that fine vacuoles can coalesce to form coarse vacuoles (arrow), a feature particularly prominent in this subtype of sCJD (H&E staining, x100 magnification) (part **b**). Frontal cortex section from an individual with the MM1 subtype of sCJD showing a predominantly fine synaptic pattern of PrP antibody staining (brown) counterstained with haematoxylin to visualize cell nuclei (blue; x200 magnification) (part **c**). Frontal cortex section from an individual with the MM2 subtype of sCJD showing coarser PrP antibody staining (brown) that is accentuated around the coalesced vacuoles (arrows; x100 magnification) (part **d**). Frontal cortex section from an individual with the VV2 subtype of sCJD showing a linear pattern of PrP antibody staining in the deeper cortex (x20 magnification) (part **e**). A higher magnification image of the same sample shows that the staining in part **e** is peri-neuronal (frontal cortex section, x200 magnification) (part **f**). Cerebellar cortex section from an individual with the MV2 subtype of sCJD, showing kuru-like plaques (arrow; H&E staining, x400 magnification) (part **g**). These plaques (arrows) are easily visualized with PrP antibody staining (brown; cerebellum, x100 magnification) (part **h**).

1990s following concerns over the potential for BSE transmission to humans[29,30,142,143]. With the identification of the first cases of vCJD in 1996 (REFS[25,26]), many additional nations developed and upgraded CJD surveillance programmes[144,145], leading to international cooperation, for example via the European Creutzfeldt–Jakob Disease Surveillance Network, which is funded by the European Centre for Disease Prevention and Control. International collaboration characterized the global vCJD epidemic[10], which was centred in the UK. France experienced the second highest incidence of vCJD, which was thought to be largely as a result of the consumption of beef imported from the UK[135,146]. Spain had the third highest number of vCJD cases (five), three of which arose in a region with substantial rates of BSE in farmed cattle[147]. vCJD was also detected in nations that did not import British beef or have substantial rates of BSE, including Japan and the USA, and arose in individuals who had either spent time in the UK or in nations that imported British beef (such as Saudi Arabia)[148]. One individual in the USA was found to have vCJD in 2015 and had not spent time in the UK; this individual was thought to have been exposed prior to emigration to the US, presumably while living in Kuwait or Russia, nations known to have imported British beef[27]. This finding demonstrates that vCJD can arise across a broad geographical area.

Ongoing public health concerns

vCJD

Extended incubation. Until 2016, all individuals with vCJD who underwent *PRNP* sequencing were found to have the MM c129 genotype[108]. One individual with vCJD and the MV genotype was identified in 2016 and was described in a paper by Mok et al.[20], published in 2017. This individual presented at 35 years of age with personality change, later developing cognitive impairment, ataxia and myoclonus. MRI showed abnormal diffusion restriction in the basal ganglia, compatible with sCJD; medial thalamic changes were present but pulvinar nuclei were normal. CSF 14-3-3 protein levels were within the normal range and RT-QuIC produced a negative result. The total duration of disease from symptom onset to death was 16 months. Post mortem neuropathological analysis confirmed a diagnosis of vCJD. This was the first individual with the c129 MV genotype to have an autopsy-confirmed diagnosis of vCJD. However, another case of an individual with the MV genotype and suspected vCJD (on the basis of clinical and radiological evidence) was reported in 2009; autopsy of this individual was not performed[149].

The Mok et al. case study[20] added to growing concerns extrapolated from findings in iCJD[5] and Kuru[9] that prion disease transmission might be associated

with extensive incubation (multiple decades) in individuals with non-MM c129 genotypes, adding weight to ongoing concerns of a 'second wave' of individuals developing vCJD. The exact incubation period of primary vCJD is impossible to calculate given the unknown timing of causative dietary exposure in affected individuals. The UK BSE epizootic was first detected in 1986 (REF.[150]), peaked in 1992 and fell to negligible numbers by the mid-2000s[12]; human exposure to BSE is likely to have been minimal after 1996 following the stringent control measures described above[11,124]. All confirmed cases of vCJD prior to 2016 were seen in MM individuals, with global vCJD deaths peaking in 2000 (REF.[10]). The individual described in the study by Mok et al.[20] did not fulfil the diagnostic criteria for vCJD during life but did fulfil those for sCJD. This observation raises the concern that, in non-MM individuals, the disease might present with different demographic, clinical, radiological, biochemical and neuropathological features to the classical vCJD phenotype, analogous to the effect of c129 genotype on sCJD phenotypes[17,151–154]. Such phenotypic variation could make it difficult to detect vCJD and distinguish it from sCJD on the basis of previously validated diagnostic criteria[110] (BOX 2).

The individual in the Mok et al.[20] study was considerably younger than is typical for individuals with sCJD. However, age might lack discriminatory value, as the paradigm that vCJD patients are typically younger than those with sCJD becomes increasingly flawed as time goes on — the BSE epizootic peaked in 1992 and 21 years

have passed since the peak of the first wave of vCJD in 2000. If the final year for potential dietary BSE exposure is 1996, as is generally accepted, then, by definition, the youngest individuals to develop primary vCJD in 2021 would be 25 years old and must have been exposed early in life at the tail-end of the period of BSE exposure. The trends in vCJD incidence by birth cohort suggest that the highest vCJD risk follows exposure to BSE during youth and teenage years, with lower susceptibility in the very young[155]. No individuals born after 1990 have been diagnosed with vCJD in the UK[155]. The highest incidence of vCJD was seen in individuals born before 1980 and this is the population estimated to have received the largest dietary exposure to BSE[134]. Individuals born before 1980 will now be >40 years of age, substantially older than the individuals who comprised the first wave of vCJD infections (median age at onset 26.5 years) and overlapping with the age distribution seen in sCJD (median age at onset 67 years)[1].

Although the scale of a potential second wave of vCJD is uncertain, extensive incubation in Kuru[156] and iCJD[108] is uncommon, which might partly reflect the lower attack rate in individuals with less susceptible c129 genotypes (generally MV[5,9,15]). This factor, in combination with extensive incubation periods, might lead to a more insidious incidence of new cases than was encountered in the most susceptible groups. Furthermore, prion diseases transmit more readily between individuals of the same species than between individuals of different species[157,158]. This characteristic is reflected in the significantly lower attack rate seen in primary vCJD secondary to BSE exposure (232 cases of vCJD worldwide[10] despite widespread exposure in BSE-affected regions[11,135]) than in iCJD[5,104] and Kuru[9,94] (transmitted from human to human) and in the detection of several transfusion-mediated vCJD transmission events[159,160]. However, even with a low attack rate, the potential exists for further cases of vCJD, given the extensive BSE exposure in the UK and in other nations through domestic BSE cases and imports of cattle and beef products.

Peripheral distribution of PrP^{Sc}

***In contrast to sCJD, in vCJD, PrP*^{Sc}** is widely distributed in the lymphoreticular system[161–163]. This peripheral distribution is associated with substantial public health concerns related to iatrogenic transmission through transfusion and surgical procedures. Evidence exists to support the hypothesis that vCJD is acquired through the gut, with gradual spread to the CNS via the lymphoreticular system[164]. A series of immunohistochemical studies have demonstrated prevalent PrP^{Sc} deposition in appendectomy samples from individuals in the UK[165–167] (TABLE 1). Whether or not these individuals represent pre-clinical cases of vCJD and whether they pose a risk to public health through secondary transmission via surgical or medical procedures, blood products and organ donation is not yet clear[165–167]. In the initial study, published in 2004, researchers obtained samples from 14,964 appendectomies and 1,739 tonsillectomies and detected PrP^{Sc} in three appendices, giving an estimated prevalence of 1 in 4,000 (REF.[165]). In a subsequent study,
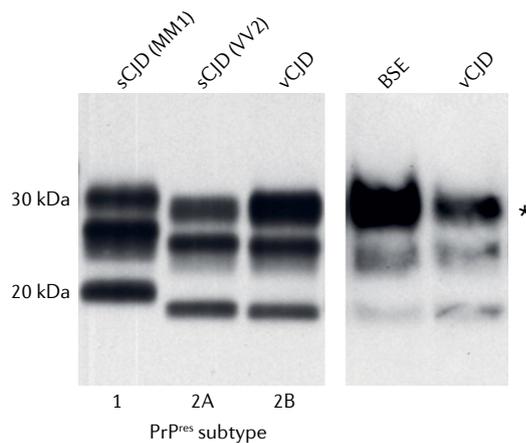
Fig. 4 | **Western blot typing in CJD.** Samples of brain tissue from individuals with Creutzfeldt–Jakob disease (CJD) can be treated with proteinase K before western blotting to detect protease-resistant fragments of misfolded prion protein (PrP^{res}). PrP^{res} is classified according to the molecular weight of the unglycosylated fragment, which is 21 kDa in type 1 PrP^{res} and 19 kDa in type 2 PrP^{res}. Type 2 is further classified into type 2A and 2B (variant CJD (vCJD)). Type 2B, present in both vCJD and bovine spongiform encephalopathy (BSE), is characterized by a predominant diglycosylated band (*). Examples are shown from individuals with sporadic CJD (sCJD) MM1, sCJD VV2, vCJD and from a case with BSE. MM, homozygous for methionine at codon 12 of the gene encoding prion protein; VV, homozygous for valine at codon 129 of the gene encoding prion protein.
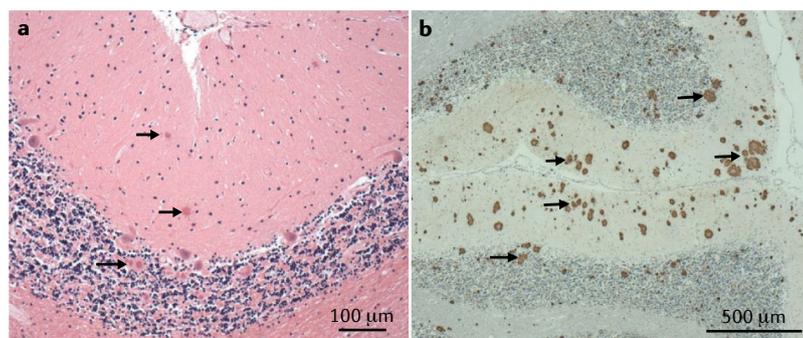
Fig. 5 | **Histological features of genetic forms of prion diseases.** Genetic forms of prion diseases show variable histological features and can resemble sporadic Creutzfeldt–Jakob disease; however, some show unique patterns of pathology. Image of a cerebellar section of an individual with the PRNP P102L-129M variant (the most common haplotype) of Gerstmann–Straussler–Scheinker disease showing multicentric plaques (arrows), which are most numerous in the molecular layer and granule cell layer (H&E staining, x200 magnification) (part **a**). A lower-magnification image from the same individual as in part **a** showing plaques (arrows) stained with prion protein antibody (brown; x40 magnification) (part **b**).

published in 2013, PrP^{Sc} was detected in 16 appendices from a sample of 32,441 specimens, yielding an estimated prevalence of 1 in 2,000 (REF.[166]). The most recent appendectomy study[167], published in 2020, aimed to measure the prevalence of PrP^{Sc} in groups not thought to have been exposed to BSE and thus analysed samples from individuals who either had their appendix removed before 1980 ($n = 14,692$), the estimated beginning of the BSE period, or were born after 1996 ($n = 14,824$), the year from which the exposure risk is presumed to have reduced to a minimum. PrP^{Sc} was detectable in the appendices of participants in both groups and the estimated prevalence (1 in 4,200) was not significantly different from that estimated in the above-mentioned 2013 study of a BSE-exposed population[166,167]. In the most recent study, the samples containing PrP^{Sc} were obtained from patients who underwent appendectomy, or were born, close to the margins of the presumed 'at risk' period, raising concerns that the time-window of exposure to BSE might have commenced in the late 1970s and continued beyond 1996 (REF.[167]), which is a longer period than previously recognized.

Some cautionary notes regarding the appendectomy findings are necessary. First, the confidence intervals on the prevalence estimates are wide, making it difficult to estimate the extent of a possible epidemic relating to ongoing transmission. Second, Clewley et al. analysed 63,007 tonsil specimens from the UK obtained between 2004 and 2008 and did not find PrP^{Sc} in any specimen, including in the 32,661 samples obtained from individuals born prior to 1996 (REF.[168]). Given that the detection of PrP^{Sc} in tonsil is a highly sensitive diagnostic marker of vCJD — Hill et al.[169] found detectable PrP^{Sc} in 100% of tonsil biopsy samples from vCJD-affected individuals and in 0% of individuals in groups with other CJD subtypes or alternative neurological conditions — this result seems surprising . However, the stage at which tonsillar involvement arises in vCJD is unknown[169]. In the study by Hill et al.[169], all patients with vCJD had clinically advanced disease and, to our knowledge, there are

no published reports assessing tonsillectomy specimens obtained at pre-clinical or early clinical stages in individuals who died of vCJD. In addition, most individuals that undergo tonsillectomy are young; in the study by Clewley et al.[168], 50,254 samples (79.7%) were obtained from patients born after 1986. The oldest members of this cohort would have been 22 years of age in 2008, the conclusion of the study period, so samples might have been resected before the disease reached this tissue. Last, the implications of the presence of PrP^{Sc} in the appendix are unclear. One possibility is that PrP^{Sc} in the appendix reflects dietary exposure to BSE-associated PrP^{Sc}, but that only a small proportion of exposed individuals develop vCJD, perhaps influenced by factors such as age, gut maturity, c129 genotype and the total amount of BSE-contaminated material ingested. The factors that influence BSE transmission to humans remain a topic of debate, particularly as individuals living in the same household as an individual with vCJD, sharing a common environment and meals, have not been found to develop the disease. One exception was a mother and son in Spain who both developed vCJD; however, these individuals were from the region with the highest vCJD incidence in the country and are thought to have had dietary exposure to high-risk material[147]. The transmissibility risk in individuals with appendicular PrP^{Sc} is unknown. As the appendectomy studies[165–167] were irreversibly anonymized, no participants were notified of being at-risk of CJD, a status that would carry numerous public health implications.

Blood products and transplantation

Three individuals in the UK were identified as having neuropathologically and biochemically confirmed vCJD related to the transfusion of non-leucodepleted red cells[115,159,160,170,171]. In addition, a case report by Peden et al.[172] described an individual who received a blood transfusion from a donor and subsequently died of a non-neurological illness. This individual was found to have PrP^{Sc} in the spleen but not in the brain, suggesting subclinical infection via the donor, who was known to have developed vCJD[172]. The blood products given to these individuals were obtained from donors before clinical manifestation of vCJD and were transfused before the introduction of leucodepletion for all blood products in 1999 (REFS[159,173]); no transfusion-transmitted cases of vCJD have occurred since this measure was introduced. Splenic PrP^{Sc} was identified at autopsy in an individual with haemophilia who was asymptomatic for neurological disease[174]. In this instance, PrP^{Sc} is thought to have been transmitted through pooled plasma products known to have included a donor with pre-clinical vCJD. Animal studies have demonstrated that vCJD and BSE can be transmitted via the transfusion of blood products[175,176]. In addition, spleen inoculum from the individual described in the report by Peden et al.[172] was shown to transmit vCJD to mice[177]. This observation provides further evidence that individuals with pre-clinical vCJD harbour the potential for transmission.

Epidemiological modelling studies have produced a wide range of estimates of the extent and duration of a potential secondary transmission epidemic of vCJD

in the UK[178–181]. These studies addressed the potential effect of variables, including incubation time, infectivity, c129 genotype and probability of developing subclinical carrier status, and the effectiveness of interventions such as leucodepletion and donation restrictions. One study concluded that a self-sustaining secondary epidemic was possible, although biologically implausible[178]. A detailed review of these studies is beyond the scope of this article but noteworthy are the results of the most recent modelling study, which was published in 2019 and predicted lower numbers of transfusion-associated vCJD cases than previous studies[180]. A particular challenge is estimating the number of individuals with sub-clinical vCJD from transfusion and the resulting risk of ongoing transmission.

International studies matching donor and recipient pairs have not identified the transfusion-mediated transmission of non-variant forms of CJD[160,182,183]. Case–control studies have provided conflicting evidence over whether blood products pose a risk of non-variant forms of CJD[184,185], although the results of an Italian study using a prolonged look-back period suggested an association between blood transfusion and increased risk of these forms of the disease[53]. The prolonged incubation of prion diseases as well as

difficulties in working with records and the potential for various forms of bias, pose challenges for epidemiological studies. Recipients of transfusion might die before manifesting CJD or disease manifestations could be obscured by the comorbid illnesses that necessitated transfusion. In 2017, a case report described two individuals who received UK-derived plasma products and died of autopsy-confirmed MM1-subtype sCJD[186]. This observation raises concerns but does not conclusively demonstrate causality.

Measures to mitigate the risk of blood product-associated CJD[72,187] include leucoreduction, a ban on blood donations by previous transfusion recipients and individuals deemed to be at-risk of CJD, and restrictions on transfusing UK-derived plasma to UK residents born after 1996. The latter restrictions, which mandated the importation of plasma for UK use, were withdrawn in 2019 following a revised risk assessment that demonstrated a low probability of further vCJD deaths arising from plasma exposure[187]. In many nations, individuals who lived in BSE-exposed regions during the epizootic cannot donate blood; however, restrictions in the USA were partially lifted in 2020, partly owing to limitations in the blood supply related to the COVID-19 pandemic[72]. No validated means of testing donors for preclinical vCJD currently exists; such an assay would be invaluable. Protein misfolding cyclic amplification (PMCA) is a highly sensitive and specific diagnostic test for vCJD[188,189] and can identify preclinical vCJD in blood[189], although this finding needs to be replicated in larger cohorts before PMCA can be validated for screening purposes. Furthermore, PMCA has practical limitations as the process amplifies PrP^{Sc}, generating an infectious agent with substantial biohazard potential[190–192]. PMCA results also require time to process, which might be longer than the shelf-life of blood products, limiting utility as a screening test for blood donation. A successful screening test for vCJD would generate additional challenges, including the ethical considerations involved in notifying donors that they have possible preclinical vCJD but that their risk of developing this lethal disease is uncertain.

Potential for laboratory transmission

Strict occupational health measures govern all clinical and research activities concerning prion disease tissue samples[193]. Two laboratory workers who had worked with prion disease samples are known to have died from vCJD[16]. One individual, described in a case report by Brandel et al., had a clear history of a penetrating skin injury from an instrument used to handle BSE material 7.5 years before diagnosis[16]. This individual had a typical prodromal thalamic pain syndrome and neuropsychiatric features as well as a typical MRI with pulvinar and dorsomedial thalamic hyperintensities. RT-QuIC analysis of CSF was negative, PMCA of plasma and CSF was positive, and a definitive diagnosis of vCJD was provided post mortem. The individual had an MM c129 genotype. The interval between injury and clinical onset was consistent with the incubation period observed in individuals with transfusion-transmitted vCJD, suggesting that this injury was the vector for disease transmission as opposed to primary infection through the diet.

Box 2 | Diagnostic criteria for vCJD

Possible features:

1. A. Progressive neuropsychiatric disorder
   B. Duration of illness >6 months
   C. Routine investigations do not suggest an alternative diagnosis
   D. No history of potential iatrogenic exposure
   E. No evidence of a familial form of transmissible spongiform encephalopathy
2. A. Early psychiatric symptoms[a]
   B. Persistent painful sensory symptoms[b]
   C. Ataxia
   D. Myoclonus or chorea or dystonia
   E. Dementia
3. A. EEG does not show the typical appearance of sporadic Creutzfeldt–Jakob disease (CJD)[c] in the early stages of illness
   B. Bilateral pulvinar high signal on MRI scan
4. A. Positive tonsil biopsy[d]

Diagnoses:
Definite vCJD
1A and neuropathological confirmation of vCJD[e]

Probable vCJD
1. 1, four to five of 2, 3A and 3B
2. 1 and 4a[d]

Possible vCJD
1, four to five of 2, and 3A

sCJD, sporadic CJD; vCJD, variant CJD. [a]Depression, anxiety, apathy, withdrawal, delusions. [b]Includes both frank pain and/or dysaesthesia. [c]The typical appearance of the EEG in sCJD consists of generalized triphasic periodic complexes at approximately one per second. These may occasionally be seen in the late stages of vCJD. [d]Tonsil biopsy is not recommended routinely nor in cases with EEG appearances typical of sCJD but might be useful in suspect cases in which the clinical features are compatible with vCJD and MRI does not show bilateral pulvinar high signal. [e]Spongiform change and extensive prion protein deposition with florid plaques throughout the cerebrum and cerebellum. Adapted from REF.[269], CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

An Italian lab worker who had worked with BSE and vCJD brain material died of vCJD in 2016 (REF.[16]) . In contrast to the individual described by Brandel et al.[16], this individual had no history of accidental injury. Evidence exists that scrapie can be transmitted through scarification of the skin, adding to concerns of peripheral transmission of vCJD[16]. The potential for occupational exposure remains an important means of vCJD transmission.

sCJD and iCJD

Peripheral pathogenesis and iatrogenic transmission. Evidence of peripheral pathogenesis in sCJD is increasing[194,195]. Studies have now identified PrP^Sc in retinal and optic nerve tissue[196,197], although at concentrations lower than those found in the brain. PrP^Sc has also been detected in intracranial portions of the vagus nerve, but extracranial portions have not been tested[198]. A recent study[194] demonstrated detectable PrP^Sc in a range of peripheral tissues including skin and femoral nerve. The advent of amplification techniques, including RT-QuIC, has enabled the detection of PrP^Sc in peripheral tissues at concentrations below the threshold for detection by the traditional methods of immunohistochemistry and western blot analysis[199,200]. RT-QuIC is now a validated test for the diagnosis of sCJD from CSF and olfactory mucosal brushings[64]. RT-QuIC has detected PrP^Sc in the skin of individuals with sCJD and gCJD; PrP^Sc levels increased with disease duration[200]. Whether such levels of PrP^Sc are sufficient for transmission via surgical instruments is unclear. However, one study found that bone marrow from individuals with sCJD contains PrP^Sc that can be transmitted to transgenic mice expressing human *PRNP*[201], adding to concerns around potential transfusion-mediated transmission as blood cells arise from haematopoietic progenitor cells in the bone marrow.

Some case–control studies have identified an association between surgery, including abdominal procedures, and sCJD; however, these studies face similar challenges to those used to study blood transfusion, including the need for prolonged look-back periods and the potential for bias[51,52,202]. Evidence indicates that iCJD resulting from the peripheral injection of contaminated c-hGH has a substantially longer incubation period (mean 17 years) than iCJD resulting from neurosurgical instrument-mediated transmission (1.4 years for neurosurgical instruments, 1.3 years for stereotactic EEG needles and 12 years for hDM grafting)[15]. This observation suggests that the hypothetical iatrogenic transmission of CJD via non-CNS and non-ophthalmologic surgical and medical procedures could be associated with decades-long incubation. One study found that intracerebral inoculation with vCJD prion-contaminated steel wires can transmit vCJD to mice even when the wires have been subjected to conventional prion decontamination measures, including the use of sodium hypochlorite, sodium hydroxide and steam sterilization at 134 °C (REF.[203]). This finding raises concerns over the effectiveness of these procedures in sterilizing medical equipment. Unfortunately, tracing patients who have been exposed to shared instruments is more challenging than tracing the origin of blood products.
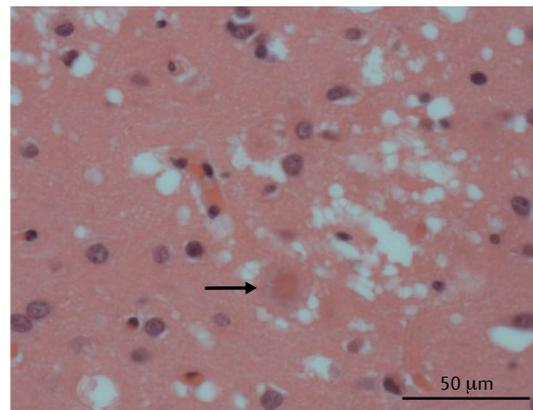

Fig. 6 | **Histological features of vCJD.** Frontal cortex section from an individual with variant Creutzfeldt–Jakob disease (vCJD) showing a pathognomonic florid plaque (arrow), a fibrillar amyloid plaque surrounded by vacuolation (H&E staining, x400 magnification).

The urine of individuals with sCJD was not found to be infective when intracerebrally administered to mice[204]; however, small quantities of PrP^Sc have been detected in the urine of individuals with vCJD using PMCA[205]. The authors of one study raised concern about the safety of urine-derived human gonadotrophins following the detection of prion protein in samples[206], but no evidence exists that recipients of urine-derived hormones are at increased risk of developing CJD. Whether PrP^Sc can be detected in the urine of individuals with preclinical vCJD and whether this PrP^Sc is present in sufficient quantities to enable transmission are not yet known.

Some studies assessing occupational risk have identified a possible increased incidence of sCJD among health-care workers compared with the general population[202,207,208], although other studies have produced conflicting results[202,207,209]. A retrospective cohort study published in 2020 identified an increased incidence of sCJD among medical professionals in Germany compared with the general population[210]; the risk was highest among surgeons. These observations raise concerns over the potential for substantial occupational exposure with decades-long incubation. However, caution is advised in the interpretation of these occupational risk studies as there is potential for methodological biases to influence the results. For example, medical professionals have a heightened understanding and recognition of sCJD and epidemiological survey data on occupation is more complete in this group of individuals than in some other groups. The inherent limitations of case–control studies, such as the potential for recall bias, the effects of confounding variables and the inability to conclusively demonstrate a causal relationship[211], should also be considered.

The rising incidence of sCJD.

sCJD has been identified in many geographical regions[3]. In nations with sophisticated surveillance programmes, including the UK[1], France[2], Germany[30], Australia[47], Canada[212] and the USA[31], the numbers of reported cases of sCJD have

increased over the last 30 years[2,46,108,213,214]. This increase is likely to be the result of a combination of factors, including better case ascertainment with heightened awareness, recognition of atypical phenotypes, the availability of more sensitive tests[215] and revised diagnostic criteria[57], and population growth and ageing owing to advances in medicine and public health. Currently unknown exogenous risk factors could also theoretically account for some of the observed increase in incidence of sCJD. Besides iatrogenic transmission, no evidence exists of person-to-person transmission of sCJD or vCJD[216]. Geographical clustering of individuals with sCJD has been described[217], but the data do not support the existence of local point-source outbreaks or person-to-person transmission of the disease. Heightened local surveillance following reported cases could be one factor underlying spatial clustering[218].

The observed increasing incidence of sCJD underscores the importance of the public health concerns described in this article. A national approach to CJD surveillance facilitates cooperation with national blood services and public health agencies, which is necessary for tracing exposed individuals and mitigating risk. In several nations, large-scale look-back studies are performed in conjunction with surveillance[160,182,183] and are essential in identifying possible cases as well as in managing risk in exposed individuals. In summary, the increasing incidence of sCJD requires careful longitudinal evaluation in a manner that can only be achieved by systematic surveillance programmes.

Prion diseases with zoonotic potential

Chronic wasting disease. Chronic wasting disease (CWD) of cervids was first recorded in a captive deer in Colorado, USA, in 1969 and was classified as a spongiform encephalopathy on histological examination of brain tissue in 1978 (REF.[219]). Eight cervid species are susceptible to CWD; the disease was detected in five of these in natural conditions and the remaining three are

susceptible to experimental transmission[219]. CWD has been detected in 26 states in the USA, in 3 Canadian provinces, and in Norway, Finland, Sweden and South Korea (the cases in South Korea were as a result of the transport of infected live animals)[14,220]. CWD was detected in a wild reindeer in Norway in 2020, highlighting the ongoing risk of CWD transmission[221]. In contrast to BSE, CWD emerges in free-ranging cervids, although the effect of animal husbandry, feeding and agricultural practices contributes to disease propagation[220]. In animals with CWD, PrP^{Sc} is easily shed into the environment through various secretions and excretions, including saliva[222], urine[223] and faeces[224,225], can survive in soil for prolonged periods[226,227], and is resistant to environmental challenges such as freeze–thaw cycles[225,228]. CWD is horizontally transmitted between living animals[222] and through environmental exposure to PrP^{Sc} (REF.[227]). Carcasses are a vector and new animals entering a previously inhabited field can contract the disease, possibly through the consumption of plants growing at the site of carcasses as well as through the soil[226]. PrP^{Sc} is detectable in the flesh of infected animals[229], raising the concern that dietary transmission to humans could be possible.

No proven instances of CWD-associated human prion disease have been reported. Evidence indicates that CWD can be transmitted via intracerebral inoculation to multiple non-cervid species[230–235] as well as via oral or intracerebral exposure to squirrel monkeys[236]. However, evidence indicates that CWD is not transmissible by either route to cynomolgus macaques, which are a primate species genetically closer to humans than to squirrel monkeys[237]. Humanized transgenic mice expressing human *PRNP* are resistant to CWD infection, whereas transgenic mice expressing cervid *PRNP* are not[238]. However, in one study, CWD brain isolates were able to induce the misfolding of human PrP^{C} in vitro[239]. In another study, transgenic mice expressing a form of human prion protein that overlaps with elk prion protein
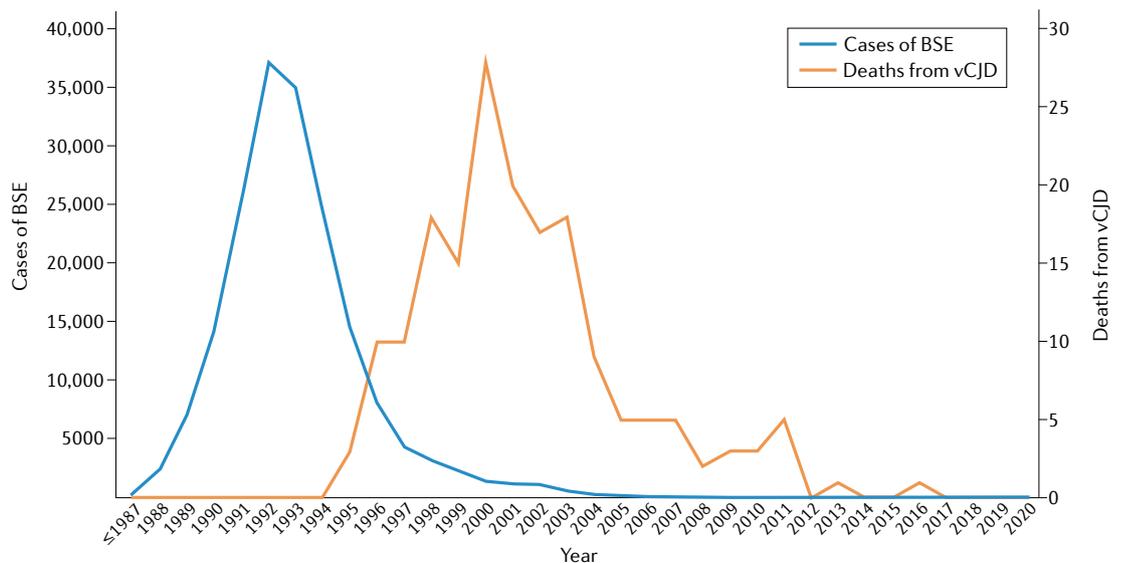

Fig. 7 | **BSE and vCJD in the UK.** Graph shows the trajectory of the bovine spongiform encephalopathy (BSE) epizootic and the subsequent variant Creutzfeldt–Jakob disease (vCJD) epidemic in the UK. Data obtained from REFS[12,288].

Table 1 | **Studies of PrP^Sc carriage in resected lymphoreticular tissues in the UK**

Study	Cohort information	Number of appendices with detectable PrP^Sc	Estimated population prevalence
Hilton et al. (2004)[165]	Born in 1961–1985; operations performed in 1995–1999: 14,964 appendectomies and 1,739 tonsillectomies	3	1 in 4,000
Gill et al. (2013)[166]	Born in 1941–1985; operations performed in 2000–2012: 32,441 appendectomies	16	1 in 2,000
Gill et al. (2020)[167]	Born in 1891–1965; operations performed in 1962–1979: 14,692 appendectomies	2[a]	1 in 4,200[c]
	Born after 1996; operations performed in 2000–2014: 14,824 appendectomies	5[b]	

PrP^Sc, misfolded prion protein. [a]All appendectomies performed in 1977 or later. [b]All from individuals born in 2000 or earlier. [c]Combined prevalence from the two cohorts.

at residues 165–175 were susceptible to CWD inoculation, providing information on the structural elements underlying the species barrier[240].

One study followed up a cohort of individuals who had been exposed to CWD-contaminated products in 2005; no evidence of prion disease or other neurodegenerative diseases emerged between exposure and the end of follow-up in 2011 (REF.[241]). Given that the incubation period for some forms of acquired CJD can be decades long, surveillance must continue to ensure the identification of any individuals who develop CWD-associated human prion disease. How CWD-associated human prion disease might manifest is unknown and it could be challenging to distinguish the new disease from other forms of CJD. vCJD was first identified when the UK surveillance system detected a novel prion disease with previously unseen clinical, radiological, biochemical and neuropathological features[25]. Therefore, large-scale national surveillance programmes are necessary to identify novel diseases that might be linked to CWD as well as to provide registry data for case–control studies on exposure risks, to enable follow-up of exposed individuals through cohort registries and to facilitate international liaison with veterinary surveillance programmes.

Human exposure to CWD is highly likely. A survey of 17,372 US residents found that 67.4% of respondents had consumed venison, much of it obtained from the wild, and 18.5% of respondents reported hunting as a pastime[242]. Without large-scale testing, the proportion of animals infected with CWD is unknown; estimates vary widely[243,244] by region, species and between captive versus wild animals, with one study demonstrating a prevalence of 35.4% among white-tailed deer in Wyoming[245]. At present, validated means of screening slaughtered animals for CWD to ensure safe dietary consumption are not widely employed and current methods are highly time consuming[220]. Furthermore, prions can adhere to steel surfaces[246–248] and instruments used for the slaughter and butchery of cervids are frequently not subjected to validated decontamination measures[220]. Finally, concerns exist over the potential for altered

transmissibility after passage through intermediate host species. This has been demonstrated in CWD, wherein passage through ferrets extends the range of susceptible host species[249], as well as in transgenic mice expressing human or porcine PrP^C, which display an increased susceptibility to sheep-passaged BSE compared with non-sheep-passaged BSE[250,251]. In summary, although the zoonotic potential of CWD is unclear, the risk of human exposure is substantial.

Camel prion disease. A novel prion disease, termed camel prion disease (CPD), was detected in three symptomatic dromedary camels in Algeria in 2018 (REF.[252]). The PrP^res signature of CPD did not match that of scrapie or BSE[252], which raised several concerns. First, the disease was presumed to have arisen naturally; transmission of a prion disease from another species was not suspected, as no BSE had been detected in local cattle and naturally arising scrapie is not known to be present in Algeria[252]. Second, camels were the first non-ruminant species, other than humans, to naturally manifest prion disease, thus extending the spectrum of prion disease-susceptible animals[252]. Third, PrP^Sc was detectable in peripheral lymphoid tissues, raising concern for horizontal transmission[252]. Last is the possibility that the causative agent could undergo alteration on passage through an intermediate host, enhancing transmissibility, as discussed above.

Another camel with CPD was identified in Tunisia in 2019 (REF.[253]). Concerns now exist over the prevalence of this previously unrecognized transmissible spongiform encephalopathy, and recognition of cases will likely increase as a result of heightened awareness[254]. The global dromedary population is in the millions, with large populations in Africa and the Middle East, as well as in Australia[255,256]. The potential for human exposure to CPD is substantial; however, transmission studies will be necessary to determine whether the disease has zoonotic potential. Substantial constraints on resources as well as geopolitical instability in the regions affected by CPD pose major challenges; many affected countries do not have national CJD surveillance programmes.

Other protein-misfolding disorders

Starting in 2010, emerging evidence has indicated that misfolded proteins in non-prion disease disorders, such as Alzheimer disease, cerebral amyloid angiopathy, Parkinson disease and motor neuron disease, could have prion-like characteristics, that is, protein-induced protein misfolding, cell-to-cell transmission and potential inter-subject transmissibility[257–264]. Amyloid-β pathology has been detected in recipients of c-hGH[257,265], hDM grafting[259] and childhood neurosurgery[258], raising questions over the transmissibility of misfolded amyloid-β, which has been demonstrated in transgenic mice[260,261]. Evidence from preclinical studies and studies of recipients of fetal mesencephalic neuronal grafts suggests that α-synuclein can be induced to misfold in the presence of its misfolded form[262]. In mouse models, SOD1-linked motor neuron disease can be transmitted via the injection of spinal homogenates into the sciatic nerves[263]. Studies in transgenic mice have also demonstrated the

transmissibility of tau pathology[264]. Taken together, these findings raise questions over whether other protein-misfolding disorders are transmissible between humans. However, the human studies mentioned above have small sample sizes and the public health implications of the potential transmissibility are still unclear. More evidence is required to establish whether these disorders harbour risks of transmission comparable to prion diseases.

Wider benefits of surveillance
Novel diagnostic strategies
Our ability to diagnose of CJD during life has greatly improved over the last several decades thanks to advances in MRI[58] and CSF biomarkers[64,65,266]. The current diagnostic criteria for sCJD were revised in 2017 (BOX 1) to include multifocal cortical ribboning on MRI and a positive RT-QuIC assay[267–269]. These revised criteria have a sensitivity of 97% and a specificity of 99%
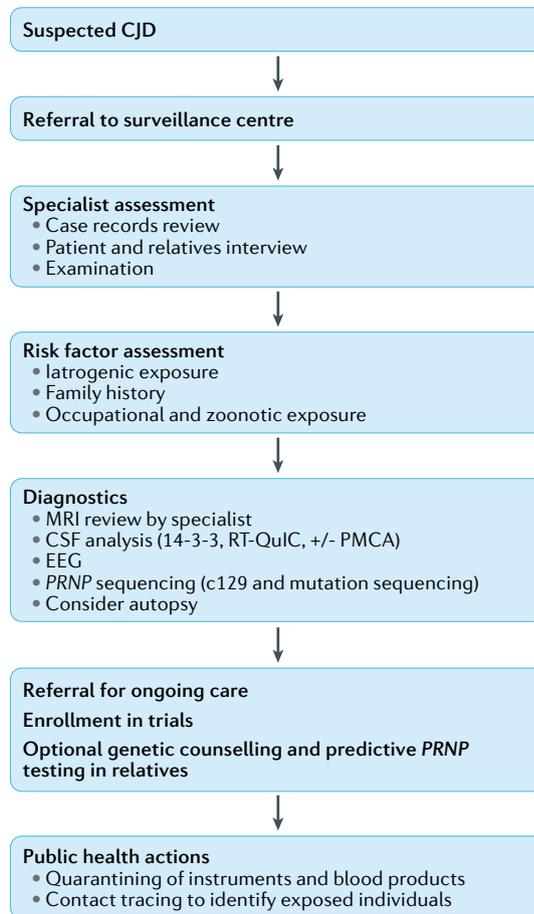

Fig. 8 | **A model CJD surveillance system.** A flowchart depicting a model system for comprehensive national Creutzfeldt–Jakob disease (CJD) surveillance, based on a combination of systems used in the authors' nations, is shown. This system provides a detailed diagnostic assessment including the ascertainment of the CJD subtype, screening for important epidemiological risk factors, and evaluating for and mitigating risks of transmission to others. CSF, cerebrospinal fluid; PMCA, protein misfolding cyclic amplification; RT-QuIC, real-time quaking-induced conversion.

(compared with previously used criteria that had a sensitivity of 74% and a specificity of 99%) and are likely to have contributed to the rising incidence figures[57].

The prompt and accurate diagnosis of CJD during life confers multiple benefits. First, it enables public health measures, such as quarantining of potentially contaminated blood products and medical instruments, to be swiftly enacted. Second, it allows a transition from ineffective and potentially harmful empirical therapies (for example, immunosuppression) and life-prolonging therapies that do not enhance quality of life[270] to palliative care in an appropriate facility. Third, it can rapidly rule out the possibility of CJD in individuals with a mimicking condition, such as autoimmune encephalitis, leading to appropriate, potentially life-saving, treatment[271]. Last, rapid diagnosis is essential for the recruitment of participants for clinical trials.

Clinical trials
CJD is rare and, with the exception of individuals known to be at-risk owing to prior exposures or individuals with inherited mutations, new cases arise in an unpredictable manner with no geographical focus. The latency to diagnosis is often considerable and the duration of survival following diagnosis is typically short. Several of these factors present challenges to clinical trials in CJD: sample sizes are small and the window of time available to enrol patients in studies and to assess the benefit of interventions is short. To date, few randomized controlled trials have been conducted and no interventions have been found to improve outcomes for individuals with CJD[272–278]. However, multinational clinical trials in CJD are feasible[273] and surveillance programmes are instrumental for rapid diagnoses and in coordinating the enrolment of patients in trials, with scope for multinational collaboration to bolster sample sizes. Rapid diagnosis is particularly essential as therapeutic agents shown to work in preclinical studies might not be effective when irreversible neurodegeneration has already occurred.

Recommendations for ongoing surveillance
CJD is likely to be under-recognized in nations that lack sophisticated surveillance systems. Several reports from low-income and middle-income nations have described challenges relating to the diagnosis of CJD, including financial constraints, lack of testing facilities, underdeveloped health-care infrastructure, low numbers of neurologists, and regional disparities between rural and urban centres[36,38,48,49,279]. Geopolitical instability along with the burden of COVID-19 and other communicable diseases will pose further challenges to the ascertainment of CJD in some of these nations. Consequently, substantial public health risks might arise. Nations with established surveillance systems should provide support to those that are developing their programmes. Existing systems range from low-fidelity services, such as the review of death certificates (known to have limitations and to underestimate CJD incidence[31]), through to high-fidelity systems that include mandatory reporting, direct clinical assessment, and integrated specialist neuroradiology, genetic, biochemistry and

neuropathology facilities closely aligned to public health services[1,268]. International collaboration enables the epidemiological comparison between nations as well as the enhanced recognition of atypical forms of prion disease.

A model surveillance system is shown in FIG. 8 and is a hybrid of the high-fidelity systems in place in the authors' nations. The clinical assessment of individuals with suspected CJD can include case record review, liaison between local neurologists and national centres, and the direct assessment of cases by national specialists, in-person or through telehealth[280,281] (of particular utility during the COVID-19 pandemic[282]). Surveillance centres are well placed for integration with biomarker laboratories for rapid diagnostic services as well as for research into newer-generation non-invasive biochemical and imaging biomarkers[200,283] for early diagnosis and screening[284,285], and instrument decontamination testing[286]. Crucially, ongoing surveillance can enable the recruitment of participants for the therapeutic trials that might one day offer hope to people affected by this devastating group of diseases[287].

Conclusions

With the potential for UK population exposure to BSE over a longer period than was previously assumed, evidence of prevalent carriage of vCJD material in the lymphoreticular systems of healthy individuals, and concerns around secondary transmission through blood products and surgery, vCJD remains a priority for surveillance in Europe. Increasing numbers of sporadic and inherited CJD cases are now being recognized globally and evidence of sCJD disease pathogenesis outside of the nervous system suggests the potential for iatrogenic transmission. Individuals who develop iCJD after extensive incubation periods are still being identified globally and the spectrum of inherited prion diseases is ever increasing. Additional concerns arise around potential zoonoses, such as CWD and CPD, and novel findings that suggest the potential transmissibility of other protein-misfolding disorders. Large-scale surveillance with international cooperation remains a priority in order to recognize atypical cases of prion disease in humans as well as to minimize population exposure risks. Finally, national surveillance programmes are uniquely placed to study this devastating family of diseases, improving diagnosis and symptomatic treatment with the aim of finding a cure. We advise that prion disease surveillance remains a public health priority, including when other priorities such as COVID-19 risk take precedent.

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