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Creutzfeldt-Jakob disease: a systematic review of the global incidence, prevalence, infectivity and incubation

Lesley Uttley, Christopher Carroll, Ruth Wong, David A Hilton, Matt Stevenson

School of Health and Related Research, University of Sheffield, Sheffield, S1 4DA, United Kingdom (L Uttley PhD; C Carroll PhD; R Wong PhD; M Stevenson PhD)

Department of Neuropathology, University Hospitals Plymouth NHS Trust, Plymouth, PL6 8DH (D Hilton MD)

Correspondence to:

Dr Lesley Uttley

School of Health and Related Research, University of Sheffield, Sheffield, S1 4DA, United Kingdom

l.uttley@sheffield.ac.uk

ABSTRACT

Creutzfeldt-Jakob disease (CJD) is a fatal disease presenting with a rapidly progressive dementia with most people dying within a year of clinical onset. CJD poses a potential risk of iatrogenic transmission as it can incubate silently in humans for decades before becoming clinically apparent. This systematic review sought evidence on the current incidence and nature of CJD and the prevalence of sub-clinical disease. Electronic databases were searched from 2005-2017 and experts were consulted for relevant data on the incidence, infectivity and incubation periods of CJD. Eligible papers included observational studies, and surveillance data. PROSPERO registration: CRD42017071807.

From 8776 citations, 147 published studies were included. Incidence of sporadic CJD appears to be increasing in some countries. All genotypes are susceptible to CJD with incubation periods up to 40 years reported.

CJD is rare but is still a public health risk due to potential for iatrogenic transmission.

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INTRODUCTION

Creutzfeldt-Jakob disease (CJD) is a progressive, fatal disease affecting the brain and is caused by abnormal transmissible proteins called prions. Once affected, the concentration of CJD prions varies throughout the body, but reaches high levels in the brain and posterior eye (retina and optic nerve),[1, 2] resulting in neurological symptoms including rapidly progressive dementia, cerebellar and extrapyramidal signs, myoclonus and visual symptoms. Most people with clinically diagnosed CJD will die within a year of the symptoms.[1]

There are three major groups of human prion disease: Sporadic, Genetic and Acquired. Sporadic CJD (sCJD) is the most common type of CJD, accounting for around 85% of CJD cases.[3] It generally occurs later in life with a mean age of 67 years and has a short survival post-diagnosis of around 4 months, however, there are at least 6 different clinicopathological subtypes with variable presentations.[4, 5] Whilst there is evidence of a genetic predisposition to sCJD,[6] the precise cause of the disorder is unknown.

Genetic forms of CJD are associated with pathogenic mutations in the prion protein gene (*PRNP*) and include familial CJD, fatal familial insomnia and Gerstmann-Schäussler-Scheinker syndrome. Together, genetic forms of CJD account for between 10-15% of prion diseases.

Acquired forms of CJD include Kuru (related to historic ritualistic cannibalism in New Guinea), iatrogenic CJD and variant CJD. Variant CJD (vCJD) was observed following the exposure of the UK population during the late 1980s and early 1990s to bovine spongiform encephalopathy (BSE) and was presumed to be transmitted to humans by eating food contaminated with BSE infected cattle. The vCJD epidemic peaked in the year 2000 with 28 deaths in the UK and has since declined with only two “definite or probable” vCJD deaths reported in the UK, three cases in France, one case in Italy and one in the USA since 2012. Compared with sCJD, vCJD occurs in a younger age group (mean age at onset 26 years) and has a longer disease duration (median 14 months). [1] All people who contracted symptomatic vCJD have died. A key pathological finding in vCJD is the presence of extensive lymphoreticular deposition of prion protein, which is not seen in other forms of CJD[10] and significantly this is present during the preclinical phase of the disease (Figure 1). The vast majority of iatrogenic CJD (iCJD) cases have been recorded following procedures for dura mater grafts and growth hormone treatment, with a small number of cases resulting from electroencephalography (EEG) needles, neurosurgery, or receipt of corneal grafts, gonadotrophin or packed red blood cells.[11] Iatrogenic transmission could potentially occur from surgery when instruments are used during

high risk neurosurgical procedures in patients who have asymptomatic CJD, but who are infectious because neural tissue has a high infectious load.[12]

<Figure 1. Immunohistochemistry using an antibody to prion protein showing abnormal accumulation (brown staining) in an appendicectomy specimen taken from an individual 8 months prior to the onset of symptoms of vCJD>

It has been over 15 years since the vCJD epidemic, but iCJD still poses a potential risk. The long asymptomatic incubation periods noted in some cases of CJD, the difficulties of eradicating prions from neurosurgical instruments,[15] the high levels of infectivity of CJD in the brain,[16] and a presumed subclinical underlying prevalence in the general population,[17] mean that there is a margin of uncertainty around detecting and quantifying the risk of CJD transmission. This work informed a wider research project[18] which assessed the risk of transmitting CJD via surgery to inform UK National Institute of Health and Care Excellence (NICE) Interventional Procedures (IP) guidance.[19] The aim was to update systematic reviews performed in 2005.[20] Reviews were designed to investigate i.) the incidence of CJD and the prevalence of CJD-related prions in humans; ii.) the risk of secondary transmission of CJD from surgery; iii) the infectivity of CJD; iv.) the incubation periods of CJD. Reviews were informed by best practice guidelines[21] and prospectively registered on the PROSPERO database (CRD42017071807).

METHODS

This study is an assessment of heterogeneous studies with no summary estimate. Summary of the key papers for each review are presented. Fully comprehensive systematic reviews are presented in a monograph of the health technology assessment.[18]

Search strategy and selection criteria

MEDLINE (Ovid); EMBASE: (Ovid); Science Citation Index (SCI-E); Conference Proceedings Citation Index (CPCI); and Web of Science were searched on 14th August 2017 combining CJD with terms for incidence, prevalence, infectivity and incubation. Databases were searched from 2005 to 2017. However, the goal of the review was to include the most recent available data (published and unpublished) therefore surveillance data retrieved after the date of the searches were also included. Searches were not limited by language. The NICE IP committee were also consulted as topic experts for potentially relevant papers. Included papers were subject to bibliography checking and the search strategies were revised in response to relevant studies not captured by the original searches.

Eligible studies were of humans with CJD / CJD-related prions in tissue, including: *in vivo* or *in vitro* studies, observational studies, retrospective reviews, case series/reports, national surveillance reports, unpublished registry data, or pathological surveys. Ineligible studies were of: laboratory parameters only; animal data without implications to humans; discussions or guidance without empirical data; superseded data; treatment or care of patients with CJD; filtering blood for transfusion or other blood products; and prion diseases without specific mention of CJD.

Articles were imported into reference management software, EndNote (version 8, Thompson Reuters), and duplicates removed. Titles and abstracts of retrieved records were examined by one reviewer (LU) and non-relevant citations excluded. A proportion (10%) of randomly selected excluded citations were double-checked by a second reviewer (CC) and any disagreements were resolved by discussion between reviewers. Data from all countries were included.

Data extraction, quality assessment and synthesis

All data were extracted by one reviewer (LU) and independently checked by a second reviewer (CC). Disagreements were resolved by discussion or consultation of a third member of the project team (MS). Reviews did not estimate treatment effects, therefore the typical domains of formal quality assessment such as randomisation, performance bias, detection bias and attrition bias were not relevant. The purpose of the reviews was to describe the relevant literature rather than to aggregate data or rank individual studies. No suitable data were identified for formal aggregation via meta-analysis.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and final responsibility for the decision to submit for publication.

RESULTS

Searches of bibliographic databases yielded a total of 8776 citations. A further 41 papers were identified from other sources; sixteen citations were obtained from clinical experts and twenty-five from checking the bibliographies of relevant studies. A total of 147 studies were selected as relevant to the reviews with some papers relevant for more than one review question (Figure 2).

<Figure 2. PRISMA flow diagram >

Incidence of CJD

Globally CJD incidence figures are gathered by the CJD International Surveillance Network (EuroCJD);[9] however, this online resource was last updated in May 2015 and is therefore not up-to-date. Data obtained through personal communication with EuroCJD yielded figures up to 2018. UK referrals of suspected or definitely/probably CJD-related deaths are recorded by the National CJD Research and Surveillance Unit (NCJDRSU).[22] This source estimates that since 1990 there have been 3873 UK referrals for investigation and 2541 deaths of definite or probable CJD (as of 31st January 2019).

The global incidence of CJD is typically reported to be around 1 to 2 cases per million per year,[9] based on surveillance studies published around the world from 2005 and onwards (Table 1).

<Table 1. Global estimations of CJD incidence >

Higher incidence rates may be more likely to occur in areas with access to established surveillance units for referring suspected cases of prion disease. In the UK since 1990, the NCJDRSU has been mandated to actively monitor and identify all CJD cases. In contrast, a Korean study described that CJD surveillance did not begin in Korea until 2001, and iCJD was not studied in Korea prior to 2011.[27] Geographical variation in how CJD may have been detected and is reported globally is depicted in Figure 3.

<Figure 3. Global reporting of sporadic CJD incidence per million population>

Between 1990 and 2018, the recorded number of deaths in the UK that have been attributed to definite or probable CJD between 1996 and 2018 (data captured 31st January 2019) is shown in Figure 4.[22] A steady increase in sCJD cases is apparent over the 28-year period whilst iatrogenic, genetic and variant forms remain low. Unpublished data from the EuroCJD network obtained through personal communication provides figures for twelve other countries across three continents with data from the same time period of 1996-2018 (Figure 5). A less pronounced, but relatively consistent increase in sporadic CJD cases can also be noted with the apparent drop-off in cases for 2018 being attributed to a delay in obtaining definitive figures for the most recent year.

<Figure 4. Deaths from probable or definite CJD in the UK between 1996 and 2018>

<Figure 5. Deaths from probable or definite sporadic CJD in countries with data between 1996-2018 reported by the EuroCJD network

Possible explanations for the increase in the detection of sCJD cases include: i) improved case-ascertainment due to clinician awareness and/or improvements in diagnostic testing; ii) an age-specific incidence rising in all groups aged over 55 years; iii) an ageing population; iv) population increase; and v) changes to the sporadic case definition to include cerebrospinal fluid and magnetic resonance imaging (MRI) diagnostic tests. The gradual increase in sCJD, but not gCJD adds support to an ageing population being responsible. The increase in only sCJD cases could be taken as evidence that there is a real increase in sCJD.

Case ascertainment is likely to improve in areas where CJD surveillance is strong, where there is greater awareness among health professionals of CJD and where there are more neurologists able to diagnose CJD. This is supported by studies in Australia indicating that the intensity of surveillance can have huge effects on estimated incidence rates in this rare disease.[28, 29] Moreover, in the UK, due to the potential for iatrogenic transmission following vCJD, there has been a focussed collaborative effort to examine evidence of transmission through different exposures by examining links to confirmed cases through retrospective "lookback" studies.[30]

The most detailed analyses in the form of published academic literature appear to come from and around countries which have experienced a CJD epidemic or incidences of iatrogenic CJD (namely the UK, France, USA and Japan). Published reports of increased rates of sCJD were noted from other countries. In Finland, an increased incidence of sCJD was noted between the period 1974-1989 of 0.6 per million to 1.36-1.44 per million in 2007-2013.[31] Additionally one study reported that sCJD incidence rates in Taiwan doubled between 2008 to 2015.[32]

Confirmation of CJD from autopsy or brain biopsy is required for obtaining a definitive sCJD diagnosis. However, autopsy is not routinely performed on sCJD cases. Only around 50% of all cases in the UK referred to the NCJDRSU undergo autopsy[1] and this rate is potentially falling.[4, 22] The most recent case of vCJD appeared, in its clinical presentation and neuroimaging, to be sCJD, but as the age of the patient was atypically young (36 years of age), a pathological examination after death in February 2016 confirmed vCJD despite the absence of clinical epidemiologic diagnostic criteria for probable or possible vCJD.[33] On the basis of this recent vCJD case, pathological examination of every sCJD case would be required to know the true figures of autopsy-proven sCJD and vCJD. Given this, an alternative

possible explanation for the increasing number of sCJD cases over the last 20 years could be the altered incubation and clinical presentation of acquired CJD (vCJD or iCJD) that mimics sCJD or another neurological condition as has been demonstrated in murine models. [34]

Global differences in the culture of pursuing autopsy to confirm any CJD diagnosis and subtype are likely to exist depending on national CJD surveillance protocols and differences in practice and approach. [35-37]

Due to the older median age of onset of sCJD symptoms, it is possible that sCJD cases may be concealed among cases of more commonly encountered, but similarly rapidly deteriorating neurological conditions affecting older people. Numerous reports were noted of sCJD mimicking other conditions including stroke,[38, 39] acute neuropathy,[40] hyperparathyroidism,[41] dementia,[37, 42-45] Lewy body dementia,[37] encephalitis,[37] aphasia,[46] Alzheimer's disease,[37, 44] psychiatric decompensation[36] and movement disorder.[47] The potential for CJD cases to be misdiagnosed was first demonstrated in a study in 1995 which found from an analysis of dementia autopsies that only about 60% of prion disease cases were identified clinically during life.[48] Therefore, the observed rates of any type of CJD could still be an underestimate of the actual rate of CJD deaths, in the absence of definitive pathological examination of all cases. It is also plausible that numerous cases of sCJD which occur later in life, particularly where access to clinicians with experience of diagnosing CJD is limited, are being misclassified as other neurodegenerative disorders.

The annual number of confirmed cases of clinical vCJD has declined since 2005. As of 2016, the NCJDRSU recorded 178 cases of vCJD in the UK.[22] A further 53 cases have been reported from other countries around the world bringing the global total of clinical vCJD cases to 231. Between 2005 and 2014, 68 vCJD cases were reported from 11 countries.[9] Three of the 178 UK cases that occurred up to 2016 are considered to have resulted from blood transfusion.[4] In the fourth case of vCJD transmission through blood transfusion, vCJD was identified in the spleen of an individual (heterozygous at codon 129), who died of a non-CJD-related cause and was considered to have preclinical vCJD.[50]

The most common causes of iCJD are human growth hormones (hGH) and dura mater grafts obtained from human cadavers. A review of worldwide iCJD cases in 2012 identified 469 cases from: dura mater grafts (n=228); hGH (n=226); gonadotropin (n=4) surgical instruments (n=4); EEG needles (n=2); packed red blood cells (n=3); and corneal transplants (n=2).[11] A more recent review of 85 UK iCJD cases between 1970 and December 2016[22] found eight

from dura mater grafts, 76 from hGH and one from human gonadotrophin (hGN). All cases have died with a mean age at death for the hGH/hGN group of 35 years (range of 20-51 years) and 47 years for the dura mater cases (range 27-78 years).

No direct cases of surgically acquired CJD have been noted since 2005.[11] Four historic cases noted between 1952 and 1974 (three in the UK and one in France) occurred prior to the vCJD epidemic, and when methods for cleaning surgical instruments were less rigorous than current decontamination standards. Consequently, the risk of CJD transmission (all types) directly apportioned to surgery appears currently to be low. As sCJD is idiopathic, its etiological basis is presumed to be spontaneous, but this is not known with any certainty.[51] Twelve papers published between 2005 and 2017 implicate a potential relationship between prior surgery and sCJD cases. This includes four case reports,[52-56] a surveillance study,[57] and six case-control studies[58-65] Case-control studies are a frequently encountered design in estimating possible and plausible risk factors for sCJD. Some concerns have been expressed about potential biases affecting CJD case-control studies.[66] This includes highlighting that validity of case-control studies may be undermined by: selection of control cases; exposure assessment in life-time periods of different duration; disregarding 'at- risk' periods for exposure in the controls; or asymmetry in case/control data; and confounding by concomitant blood transfusion or surgery at the time of clinical onset.

Prevalence of subclinical vCJD

In vCJD, prions appear to replicate extensively within lymphoid tissue early in the disease process and, therefore, tonsil and appendix tissues are some of the earliest sites that can be used to assess abnormal prion accumulation. Such abnormal prion accumulation prior to the onset of clinical symptoms is regarded as subclinical vCJD, and is thought to represent a potential background, but low, level of infection in the population.[67] The infectious load of prions is known to be higher in certain tissues, such as Central Nervous System (CNS) tissues in the symptomatic phase of disease,[68] and therefore the risk of infectivity from peripheral tissue has been questioned.[69-72]

The hypothesis of zoonotic transmission through dietary exposure from the BSE outbreak is largely upheld as the most plausible route of vCJD infection in humans and transmission has been replicated in wild-type mice.[73] An analysis of excised peripheral tissues from general population study conducted by Gill *et al* (2013), ('Appendix II' study) found subclinical prion accumulation in cohorts born between 1941-60 and 1961-85.[74] Detection of abnormal prion

accumulation in appendix samples from these two cohorts resulted in a central estimation of 493 per million population (95% confidence interval (CI): 282 to 801 per million) for populations exposed to the BSE epidemic. A further study ('Appendix III') using immunohistochemical (IHC) staining of appendices from two birth cohorts (Table 2)[75, 76] led to a central prevalence of asymptomatic carriers of vCJD in the UK population (previously presumed unexposed to BSE) of approximately 240 per million (95% CI: 16 to 492 per million).[61]

<Table 2. Results of the Appendix III study >

The presence of seven positive abnormally-stained appendices in cohorts of people who were not considered to have had significant exposure to BSE suggests that either there is low background prevalence of abnormal prion protein staining in human lymphoid tissue that may not represent subclinical vCJD, and may be unlikely to progress to vCJD, or that the duration period of human exposure to the BSE epidemic was longer than previously thought. Moreover, planned statistical analysis found no significant difference between the prevalence observed in the cohort considered to be most at risk to the BSE epidemic as described as by Gill *et al* (2013). [74]

Infectivity of CJD

Methionine homozygosity at *PRNP* codon 129 (MM) is considered the most susceptible genotype for CJD with sCJD and vCJD occurring mostly in MM homozygous individuals. In sCJD, both methionine and valine homozygotes (VV) at codon 129 are at increased risk of the disease.[78] In Northern Europe, the MM genotype represents 38% of the general population whilst 11% are VV and 51% are heterozygotes (MV) at codon 129.[79]

The first indication that the valine homozygotes are also susceptible to vCJD infection came from a re-analysis of appendices[80] identified (from the cohort of 12,674 appendix and tonsil samples analysed by Hilton *et al* (2004)[17]) as positive for disease associated prion protein (PrP), which found two of the three were VV genotype. Whilst heterozygosity at *PRNP* codon 129 was previously believed to confer complete resistance to both sporadic and acquired prion diseases[81] the most recent case of clinical vCJD in 2016 was heterozygous.[33] A further possible vCJD case in 2008 was also heterozygous,[82] but diagnosis was not confirmed by autopsy. Case reports have also found subclinical iCJD in the MV genotype[50, 83] highlighting a susceptibility in heterozygous individuals, albeit at a lower level than homozygotes. A study in mice supports the notion that transmission efficiency of vCJD is greatest in MM but indicated

that all genotypes are susceptible, with the MV and VV genotypes benefitting from apparent reduced transmission efficiency and longer asymptomatic incubation periods.[84]

Knowing whether and when asymptomatic carriers of CJD become infectious is important in understanding the potential risks of iatrogenic transmission. Bougard *et al* (2016) describe an assay which detected prions 1.3 and 2.6 years before the clinical onset in plasma samples of two blood donors who later developed vCJD.[85] The authors report that the ability to identify presymptomatic (n=2) and symptomatic (n=18) vCJD positives in a blinded cohort of 256 plasma samples comprising sCJD, Alzheimer's disease, Parkinson's, other neurological diseases and healthy controls, demonstrating the possibility of detecting incubating or silent carriage of vCJD prions in blood and highlighting the potential risk of transmission via blood products.

The ability to detect prion accumulation depends on the sensitivity of the CJD assay employed.[86] For example, the recently identified heterozygous clinical vCJD patient[33] tested negative for 14-3-3 protein, RT-QuIC and the vCJD-focussed direct detection assay, but immunoblotting of brain homogenate at autopsy confirmed the presence of vCJD prions. Moreover, immunostaining performed in this patient for abnormal prion protein-labelled amyloid plaques highlighted a relative lack of peripheral tissue involvement, with only minute amounts detected in the spleen and no detection in the appendix or mesenteric lymph nodes. However, Douet *et al* (2017) used a highly sensitive protein misfolding cyclic amplification assay to assess abnormal prion accumulation in the 82 year old heterozygous subclinical vCJD patient.[87] Previous investigations had not detected abnormal prion protein or infectivity in the brain at the time of death,[50, 70] but using this assay they found vCJD prions in all lymphoid organs and a wide variety of other tissues including salivary gland, lung and liver. The identification of extensive vCJD involvement in the peripheral tissues of a subclinical patient provides further evidence of the potential for iatrogenic disease transmission by surgical procedures.

Incubation periods

Reported incubation periods of iCJD in humans range from 1 to 42 years.[11, 13, 14, 83, 88-101] The shortest durations occurred in surgically transmitted CJD and the longest occurred in Kuru or iCJD via hGH. Diagnosis of definite or probable iCJD depends on correct identification of the probable source of contamination to which patients have been exposed.

As noted above, different incubation times might occur due to the resistance of different genotypes. Evidence from Kuru studies[13, 90] indicates that incubation times are shorter, and

mortality risk is significantly greater, in those with homozygous genotype (MM or VV) compared with the heterozygous genotype (MV): older survivors are more likely to be heterozygous.[89, 91] However, hGH data suggest longer incubation times for MM homozygote patients and shorter times for VV homozygotes. Where proportions of heterozygotes and homozygotes are similar across countries or groups, but incubation times are different, it has been proposed that differences in these incubation times might be due to infection with different strains or subtypes of the CJD agent.[88, 100] For example, most cases of hGH-iCJD in France were of MM genotype, whilst in the UK the VV and MV genotypes predominate. Infections that appear to affect certain genotypes in a location may reflect an absence of genotypic resistance to a particular strain, resulting in shorter incubation times[100]. Hence, it is possible that the MM genotype in the UK hGH-iCJD cohort had the longest incubation times because the infectious strain was of the VV or MV genotype. Other possible factors include higher infectious doses and/or differences in the actual data, for example where the precise date of likely contamination is known, incubation times appear to be shorter.[11]

DISCUSSION

The incidence of all types of CJD is fairly consistent around the World at between 1 and 2 cases per million population, but in some countries, as best highlighted by data from the UK, the incidence of sCJD appears to be increasing. Potential explanations include improved case ascertainment and an ageing population. However, the increase is seen across a wide age-range and there is not a corresponding increase in referrals or increase in other forms of CJD. It should also be noted that the number of observed CJD cases could still be an underestimation because CJD could be mistaken for other neurological conditions, particularly in older people. Additionally, diagnoses of sCJD could potentially be made that are actually iCJD in the absence of reliable neuropathological features to distinguish cases. There have been no reports of any new cases of directly surgically-transmitted CJD in the search period. Whilst many case-control reports implicate a relationship between surgery and CJD their design is known to be at risk of bias and confounding due to reliance on indirect, retrospective evidence. However, as CJD is rare and fatal, few plausible alternative study designs exist.

The prevalence of subclinical vCJD from pathological surveys suggests a constant underlying rate of abnormal prion accumulation in lymphoreticular tissue in the UK population, which may or may not represent disease that will progress to clinical vCJD. Surgical procedures (other than high-risk procedures) that could potentially be regarded as posing a risk of iatrogenic transmission include appendectomy or tonsillectomy. However, no direct evidence currently exits demonstrating a risk from surgical procedures involving tissues that are not high-risk.

When opportunities for CJD transmission occur, a range of factors are likely to influence how the disease will manifest itself in terms of clinical phenotype, neuropathological pattern, incubation period, and disease duration. These factors include an interaction between genotype at *PRNP* codon 129, the infecting prion strain, the route of transmission and the location of prion protein conversion. Moreover, the method of detection and analysis of CJD is crucial to obtaining detailed and accurate neuropathological confirmation of CJD type in order to posit the most plausible explanations for acquisition of iCJD. Global variations in the detection of this rare disease are expected given different surveillance programmes and detection assays employed.

This work provides an updated, comprehensive and interdisciplinary profile on the nature and occurrence of CJD around the world. The methods are inclusive to ensure that any relevant study from to the research questions were included. Whilst narrative reviews focussing on one type or facet of CJD have been published previously, this review provides a complete overview of the trends in all types of CJD from current evidence. The review has been designed and undertaken by experienced systematic reviewers and information specialists at the University of Sheffield, UK, without affiliation to intervention, detection methods or patient advocacy groups for CJD. Input from clinical experts was sought to ensure that the reviews were objective, rigorous and applicable.

A limitation to this study is that, as an update review, published studies previous to 2005 were not included. However, data from retrieved sources that include information prior to 2005 are included and the authors have used the context of what was known from the previous reviews throughout and, as detection and reporting of CJD has improved, the focus on the most recent evidence is appropriate. The reliance on case-control studies and the problems of retrospective, observational designs were discussed. As a result, the analysis is restricted to a narrative: formal statistical aggregation of data was not possible given the scarce presentation of CJD. However, we believe that the comprehensive and flexible design of this review was appropriate to provide a clinical overview on this rare but highly infectious disease.

Clinical trials in this rare disease have been attempted[102] but are not a feasible recommendation for this research question. Prospective national surveillance that follow referrals through to confirmed cases of CJD, and international agreement on standard analytics for CJD detection, may improve reporting where countries allocate resources for surveillance.

Contributors

LU designed the study and wrote the draft manuscript. LU and CC performed the systematic reviews. RW conducted the literature searches. CC, MS and DH provided comments on the manuscript. All authors critically reviewed the methods, results and contributed to writing the report.

Conflicts of interests

We declare that we have no conflicts of interests.

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