

**Systematic review of Creutzfeldt-Jakob disease (CJD) risk via surgical interventional procedures and economic modelling of management policies**

|  |  |
| --- | --- |
| **Produced by** | School of Health and Related Research (ScHARR), The University of Sheffield |
| **Authors** | Matt Stevenson, Professor of Health Technology Assessment, ScHARR, University of Sheffield, Sheffield, UK  Lesley Uttley, Research Fellow in Systematic Review, ScHARR, University of Sheffield, Sheffield, UK  Jeremy Oakley, Professor of Statistics, School of Mathematics and Statistics, University of Sheffield, Sheffield, UK  Christopher Carroll, Reader in Systematic Review and Evidence Synthesis, ScHARR, University of Sheffield, Sheffield, UK  Stephen E Chick, Professor of Technology and Operations Management, INSEAD, Fontainebleau, France  Ruth Wong, Information Specialist, ScHARR, University of Sheffield, Sheffield, UK |
| **Correspondence Author** | Matt Stevenson, Professor of Health Technology Assessment, ScHARR, University of Sheffield, Sheffield, UK |
| **Date completed** | Date completed (16/03/2018) |

**Source of funding**: This report was commissioned by the NIHR HTA Programme as project number 17/48/01.

**Table of Contents**

[List of abbreviations 6](#_Toc525106650)

[Plain English Summary 8](#_Toc525106651)

[Scientific Summary 9](#_Toc525106652)

[Objectives 9](#_Toc525106653)

[Methods 9](#_Toc525106654)

[Results 10](#_Toc525106655)

[Discussion 11](#_Toc525106656)

[Conclusions 12](#_Toc525106657)

[1 INTRODUCTION 14](#_Toc525106658)

[2 CLINICAL EVIDENCE 17](#_Toc525106659)

[2.1 Methods for systematic reviews 17](#_Toc525106660)

[2.2 The incidence of CJD and the prevalence of CJD-related prions in humans in the UK 25](#_Toc525106661)

[2.3 The risk of CJD transmission via surgery 39](#_Toc525106662)

[2.4 Incubation periods of acquired TSEs 46](#_Toc525106663)

[2.5 The infectivity of CJD 53](#_Toc525106664)

[2.6 The evidence on the efficacy of prion decontamination procedures for surgical instruments 59](#_Toc525106665)

[2.7 The evidence that instruments used for high-risk procedures remain in their original sets after decontamination 86](#_Toc525106666)

[2.8 The evidence for complication rates of single-use compared with reusable instruments for high-risk procedures 90](#_Toc525106667)

[2.9 The evidence for the likelihood of future surgery for a patient undergoing high-risk procedures 90](#_Toc525106668)

[3 COST EFFECTIVENESS 93](#_Toc525106669)

[3.1 Background 93](#_Toc525106670)

[3.2 The conceptual model 94](#_Toc525106671)

[3.3 Key model parameters 98](#_Toc525106672)

[3.4 Calibration targets 115](#_Toc525106673)

[3.5 Categorisation of surgical units, establishing PSA configurations that are plausible, and generating likelihood functions for plausible PSA configurations 115](#_Toc525106674)

[3.6 Strategies modelled 120](#_Toc525106675)

[3.7 Epidemiological results 120](#_Toc525106676)

[3.8 Cost-effectiveness results 125](#_Toc525106677)

[4 DISCUSSION AND CONCLUSIONS 131](#_Toc525106678)

[Acknowledgements 134](#_Toc525106679)

[REFERENCES 135](#_Toc525106680)

[Appendix 1: Clinical Effectiveness Search Strategies 149](#_Toc525106681)

[Appendix 2: Cost Effectiveness Search Strategies 160](#_Toc525106682)

[Appendix 3: Excluded studies from the clinical reviews with reasons for exclusion 163](#_Toc525106683)

[Appendix 4: Elicitation exercise relating to epidemiological parameters. Conducted 18th January 2018 165](#_Toc525106684)

[Appendix 5: The operations considered to be at high risk 175](#_Toc525106685)

[Appendix 6: The assumed age profile of patients receiving each operation 182](#_Toc525106686)

[Appendix 7: The calibration methodology 185](#_Toc525106687)

TABLES

[Table 1: Eligibility criteria for each review question 18](#_Toc525106688)

[Table 2: Global estimations of CJD incidence from studies published in 2005 or after 26](#_Toc525106689)

[Table 3: Results of the Appendix III study 36](#_Toc525106690)

[Table 4: Studies estimating the prevalence of CJD from peripheral tissue samples, published after 2005 38](#_Toc525106691)

[Table 5: Studies reporting links between CJD and surgery published between 2005-2017 40](#_Toc525106692)

[Table 6: Characteristics of included studies for incubation periods, ordered alphabetically 47](#_Toc525106693)

[Table 7: Reported number of cases of iCJD (worldwide and UK) and incubation periods 48](#_Toc525106694)

[Table 8: UK only data for iCJD incubation periods 49](#_Toc525106695)

[Table 9: Mean incubation periods by genotype for iCJD due to dura mater grafts 51](#_Toc525106696)

[Table 10: Mean incubation periods reported from included studies by genotype for iCJD due to human growth hormone 52](#_Toc525106697)

[Table 11: Estimated infectious titre of human tissue by surgical procedure in NICE IPG196 54](#_Toc525106698)

[Table 12: Characteristics of studies reporting log reductions in prion contamination on steel surfaces after autoclaving with and without other processes 62](#_Toc525106699)

[Table 13: Results of studies reporting log reductions in prion contamination on steel surfaces after autoclaving with and without other processes 63](#_Toc525106700)

[Table 14: Studies reporting log reductions in prion contamination on steel surfaces after decontamination processes other than autoclaving 66](#_Toc525106701)

[Table 15: Results of studies reporting log reductions in prion contamination on steel surfaces by processes other than autoclaving 68](#_Toc525106702)

[Table 16: Studies reporting infectivity (but not log reductions) from prion contamination on steel surfaces after autoclaving with and without other processes or decontamination processes without autoclaving 72](#_Toc525106703)

[Table 17: Results of studies reporting infectivity (but not log reductions) from prion contamination on steel surfaces after autoclaving with and without other processes or decontamination processes without autoclaving 74](#_Toc525106704)

[Table 18: Study characteristics and results 78](#_Toc525106705)

[Table 19: Study characteristics and results 82](#_Toc525106706)

[Table 20: Characteristics of included studies 87](#_Toc525106707)

[Table 21: Findings of included studies 89](#_Toc525106708)

[Table 22: Characteristics of included studies 91](#_Toc525106709)

[Table 23: Findings of Bird *et al* (2009)208 on subsequent event rates for selected neurosurgical procedures for any patient within the time period 1993-2001 92](#_Toc525106710)

[Table 24: Information relating to mass transferred to a patient, mass washed off in subsequent decontamination cycles and mass harvested from a patient 102](#_Toc525106711)

[Table 25: The number of operations classified as high-risk by the NICE committee (HES data) 114](#_Toc525106712)

[Table 26: Base case results per surgical unit 121](#_Toc525106713)

[Table 27: Results of the scenario analyses per surgical unit using the base case as the foundation 124](#_Toc525106714)

[Table 28: Parameter values used within the cost-effectiveness analyses 126](#_Toc525106715)

[Table 29: Threshold analyses on the cost of single-use sets (including disposal costs) and a completely effective cleaning solution 129](#_Toc525106716)

[Table 30: Threshold analyses on the cost of implementing IPG196 130](#_Toc525106717)

FIGURES

[Figure 1: PRISMA flow diagram of studies included in systematic reviews 24](#_Toc525106718)

[Figure 2: Deaths from probable or definite CJD in the UK using data from the NCJDRSU between 1996-2017 27](#_Toc525106719)

[Figure 3: Age-specific mortality rates from sporadic CJD in the UK 1979-2016 32](#_Toc525106720)

[Figure 4: The conceptual model relating to the infection process 96](#_Toc525106721)

[Figure 5: The conceptual model relating to patient outcome post infection 97](#_Toc525106722)

[Figure 6: The prevalence of CJD prions within central nervous tissue 98](#_Toc525106723)

[Figure 7: The proportion of residual mass transferred to a patient 100](#_Toc525106724)

[Figure 8: The proportion of residual mass removed in a subsequent decontamination cycle 101](#_Toc525106725)

[Figure 9: The reduction in infectivity in the first autoclaving cycle 103](#_Toc525106726)

[Figure 10: The reduction in infectivity in the first detergent cycle 104](#_Toc525106727)

[Figure 11: The proportion of autoclave cycle 1 log reduction achieved by cycles 2 and 3 104](#_Toc525106728)

[Figure 12: The proportion of the incubation period during which the patient is infectious 110](#_Toc525106729)

[Figure 13: The proportion of patients under 60 years with clinical CJD symptoms that are diagnosed with another neurodegenerative disease 112](#_Toc525106730)

[Figure 14: The proportion of patients over 80 years with clinical CJD symptoms that are diagnosed with another neurodegenerative disease 112](#_Toc525106731)

[Figure 15: The simulated proportion of patients aged between 60 and 80 years inclusive with clinical CJD symptoms that are diagnosed with another neurodegenerative disease 113](#_Toc525106732)

[Figure 16: The likelihoods of the PSA configurations being compatible with the observed data (curves are drawn on top of each other) 118](#_Toc525106733)

[Figure 17: The probabilities that S1, S2, S3 and single-use instruments are most cost-effective at a range of cost per QALY thresholds 123](#_Toc525106734)

[Figure 18: The probabilities that S4, S5, S6 and single-use instruments are most cost-effective at a range of cost per QALY thresholds 123](#_Toc525106735)

[Figure 19: Comparing the QALYS lost produced within the base case and when using an alternative assumption related to the distribution of surgical units following IPG196 and in keeping instruments moist 125](#_Toc525106736)

[Figure 20: The assumed age profile of patients undergoing brain surgery who are assumed to have normal life expectancy 182](#_Toc525106737)

[Figure 21: The assumed age profile of patients undergoing brain surgery assumed to die within 12 months 182](#_Toc525106738)

[Figure 22: The assumed age profile of patients undergoing brain surgery who are assumed to have a 50% chance of death within 12 months otherwise who are assumed to have normal life expectancy 183](#_Toc525106739)

[Figure 23: The assumed age profile of patients undergoing neuroendoscopy 183](#_Toc525106740)

[Figure 24: The assumed age profile of patients undergoing posterior eye operations 184](#_Toc525106741)

## List of abbreviations

|  |  |
| --- | --- |
| ACDP | Advisory Committee on Dangerous Pathogens |
| AcOH | acetic acid |
| BH | brain homogenate |
| BSE | bovine spongiform encephalopathy |
| CI | confidence interval |
| CJD | Creutzfeldt-Jakob disease |
| CRD | Centre for Reviews and Dissemination |
| CSEW | Coroners’ Society of England and Wales |
| EEG | electroencephalograph |
| EDIC/EF | episcopic differential interference contrast/Epifluorescence |
| FFPE | formalin-fixed, paraffin-embedded |
| FFI | fatal familial insomnia |
| FML | factor for efficiently maximising the likelihood |
| GSS | Gerstmann-Sträussler-Scheinker |
| HES | Hospital Episode Statistics |
| hGH | human growth hormones |
| hGN | human gonadotrophin |
| H2O2 | hydrogen peroxide |
| ICER | Incremental cost-effectiveness ratio |
| iCJD | iatrogenic Creutzfeldt-Jakob disease |
| IHC | immunohistochemical |
| IP | Interventional Procedures |
| IPAC | Interventional Procedures Advisory Committee |
| IPG | Interventional Procedures Guidance |
| M | Molar concentration |
| MM | methionine homozygous at polymorphic codon 129 |
| MRI | magnetic resonance imaging |
| MV | heterozygous (methionine/valine) at polymorphic codon 129 |
| NaOCl | sodium hypochlorite |
| NaOH | sodium chloride |
| NCJDRSU | National CJD Research and Surveillance Unit |
| NHS | National Health Service |
| NICE | National Institute for Health and Care Excellence |
| NR | not reported |
| OR | odds ratio |
| PK | proteinase K |
| PMCA | protein misfolding cyclic amplification |
| PrP | prion protein |
| PRNP | prion protein gene |
| PrPres | protease-resistant prion protein |
| PrPSc | abnormal PrP scrapie infectious isoform / protease K-resistant prion protein |
| QALY | quality-adjusted life year |
| RMEC | rapid multi enzyme cleaner trial formulation |
| RML | Rocky Mountain Laboratory |
| RT | room temperature |
| RT-QuIC | real-time quaking-induced conversion |
| ScHARR | School of Health and Related Research |
| sCJD | sporadic Creutzfeldt-Jakob disease |
| stCJD | surgically transmitted CJD |
| SDS | sodium dodecyl sulfate |
| SSBA | standard steel binding assay |
| SSDs | sterile service departments |
| TICUw | tissue culture infectious units on wires |
| TSE | transmissible spongiform encephalopathy |
| vCJD | variant Creutzfeldt-Jakob disease |
| VPL | violation of permissible level |
| VV | valine homozygous at polymorphic codon 129 |
| w/v | weight/volume |
| WB | western blot |

# Plain English Summary

The aims of this report were to summarise evidence relating to surgically transmitted Creutzfeldt Jakob Disease (stCJD) cases and to explore the value for money of strategies to reduce the future risks of stCJD cases. Current recommendations include keeping surgical instrument sets for high-risk operations together and using separate instruments for those born after 1996. The project involved reviewing published papers, speaking with experts, and building a computer model.

Literature reviews were performed to find information relevant to the possibility of patients being infected with CJD after having surgery to the brain, back of the eye or neuroendoscopy (high-risk operations). The reviews found that CJD occurs in around one to two per one million people and that no definite cases of stCJD have been observed since the 1970’s. The data found in the reviews were not fully able to inform the model therefore experts were asked the most likely values and ranges to use. Care was taken so that the model output matched the possible number of oberved stCJD cases. Issues that are likely to affect the risk of stCJD include: how effective cleaning practices are, how infectious typical patients undergoing high-risk operations are, and the chance that patients having high-risk operations are infectious with CJD but do not yet show clinical symptoms.

Estimates of the value for money of potential strategies that could be made to reduce the risks of stCJD were then made. For surgical units that do not keep instruments moist prior to cleaning, doing this was likely to save money and reduce future stCJD cases. For units keeping surgical instruments moist, the cost-effectiveness of introducing additional measures including using single-use instruments, ensuring that instruments were kept together, or using separate instruments for those born after 1996 appeared to be poor value for money.

# Scientific Summary

Creutzfeldt-Jakob disease (CJD) is a progressive, fatal disease affecting the brain. CJD is caused by an abnormal infectious protein called a prion. Prions on surgical instruments are unlikely to be completely deactivated by conventional hospital cleansing and sterilisation techniques and therefore patients may be infected iatrogenically with CJD by surgical instruments, resulting in a surgically transmitted CJD (stCJD) case. Previous work involving some of the authors of this report had assessed the cost-effectiveness of single use instruments and other strategies to reduce future stCJD cases, evidence from which was considered by the National Institute of Health and Care Excellence in establishing interventional Procedures Guideline 196 (IPG196).

## Objectives

To evaluate the expected risk of stCJD cases under present surgical conditions and to estimate the cost-effectiveness of strategies that may alter the anticipated risks of stCJD.

## Methods

*Review methods*

Eight systematic reviews were conducted. Four questions were fundamental to understanding CJD and four were undertaken to understand the risks of transmission via surgery. Broadly, the reviews investigated CJD with regards to: (1) prevalence and incidence, (2) risk of transmission via surgery, (3) incubation periods and (4) infectivity, (5) efficacy of current decontamination procedures, (6) adherence to NICE guidance by keeping surgical instrument sets together, (7) evidence of complications from single-use instruments and (8) likelihood of patients who have undergone high-risk surgery returning for further surgery. Literature searches were conducted in major electronic bibliographic databases (MEDLINE, EMBASE, Science Citation Index, Conference Proceedings Citation Index and Web of Science) from 2005 to 2017. Titles and abstracts were examined by one reviewer and a proportion (10%) of randomly selected excluded citations were double-checked by a second reviewer. At full paper stage, all citations excluded from a particular review question were double-checked by the second reviewer.

A systematic review of cost-effectiveness was undertaken. Titles and abstracts were examined by one reviewer, and a proportion (10%) were checked by another reviewer. Where appropriate, full papers were reviewed for pertinent information.

*Evaluation of cost-effectiveness*

The mathematical model used previously to assess the cost-effectiveness of strategies to reduce stCJD was updated in this report. All assumptions were agreed with the NICE committee. Key changes between the earlier modelling work and this work include: re-eliciting key parameters; assuming that all genotypes were susceptible to stCJD infection; taking into account the possibility that patients with stCJD could be misdiagnosed with an alternative neurodegenerative disease; and calibration of predicted model inputs with the number of possible stCJD cases observed between 2005 and 2018. In order to reduce the impact of sampling error, 27 random number streams were used for each Probabilistic Sensitivity Analysis (PSA) configuration. The calibration work was complex and required the use of heuristics to initially rule out parameter configurations that were not compatible with observed data, and then estimating likelihood for remaining PSA parameters, which was used in the calculating the cost-effectiveness of each strategy between 2019 and 2023. Surgical units were categorised into six categories, S1-S3 where it was assumed that patients born after 1996 could be infectious without previous surgery and S4-S6 where it was assumed that these patients were not infectious from birth. S1 and S4 units were assumed to follow IPG196, with the exception of single-use neuroendoscopy instruments, henceforth called following IPG196, and to keep instruments moist; S2 and S5 units were not assumed to follow IPG196 but to keep instruments moist; S3 and S6 units were assumed to neither follow IPG196 nor keep instruments moist. Threshold analyses were undertaken to see at what price per operation single-use instruments, or a completely effective cleaning solution, would need to be to reach chosen cost per QALY values. Further threshold analyses were undertaken to look at the maximum costs associated with following IPG196 to be at, or below, chosen cost per QALY thresholds. Additional analyses explored the impact of removing current regulations that patients born after 1996 should be operated on with separate instruments to the rest of the population.

## Results

Literature searches for the clinical reviews yielded 8549 citations from which 169 papers were identified relevant to the eight review questions. The incidence of any type of CJD cases is reported to be between 1 to 2 per million worldwide but the general rate of sporadic CJD cases is noted to be increasing in some countries. The prevalence of non-clinical CJD prions in tissues in the general population is estimated to be 240 per million based on analyses of appendix specimens. Published evidence indicates that the risk of transmitting iatrogenic CJD via surgery are presently low with no cases reported between 2005 and 2017. The incubation periods of CJD range between 1 and 42 years. The infectivity of CJD is likely to be moderated by a number of factors including the recipient’s genotype, the infecting prion strain, and the route of transmission. Published evidence indicates that the combination of reduction of residual mass to <5µg residual protein per instrument and keeping instruments in moist or wet conditions prior to autoclaving and sterilisation enhances the efficacy of decontamination strategies as opposed to autoclaving and sterilisation alone. A paucity of direct evidence exists to inform the research questions on whether surgical instruments for high-risk procedures stay in their original sets and the risks and benefits of re-usable versus single-use instruments. Evidence to inform about the risk of future surgery for patients undergoing high-risk procedures indicated that between 10% -57% (depending on the type of procedure) of patients have additional procedures within 5-10 years of an index high-risk procedure.

Whilst no data from the literature were directly used in the model, apart from a paper co-written by authors of this report which detailed and updated the evidence considered for IPG196, selected papers were used in discussion with clinical experts to inform the model parameters.

Key results from the cost-effectiveness analyses were that: keeping instruments moist was expected to save money and to provide more health. From a position of keeping instruments moist the cost per quality-adjusted life year (QALY) of single-use instruments was in excess of £2.0 million in all scenarios. From a position of implementing IPG196 and keeping instruments moist the cost per QALY of single-use instruments was in excess of £4.5 million in all scenarios. From a position of keeping instruments moist the cost per QALY of implementing IPG196 was estimated to be in excess of £1.6 million.

The threshold analyses indicated that assuming a cost-effectiveness threshold of £300,000 per QALY a single-use set (or completely effective detergent) would need to be in the region of £50 assuming that instruments were kept moist. At a cost-effectiveness threshold of £30,000 per QALY this value reduced to £15. Threshold analyses exploring the maximum cost associated with IPG196 indicated that this value was approximately £140,000 (assuming a cost-effectiveness threshold of £300,000) and £15,000 (assuming a cost-effectiveness threshold of £30,000) per surgical unit over a five-year period. Analyses undertaken exploring the impact of removing the guidance that patients born after 1996 should have different instrument sets indicated that there would not be a large increase in the numbers of QALYs lost due to stCJD.

## Discussion

Direct evidence to inform the literature review questions was limited due to the rare nature of CJD, the reliance on historical cases of surgically transmitted CJD, observational data, case-control study designs or animal data. Due to the variety and speciality of the papers included, formal critical appraisal of study quality was not deemed to be useful. The apparent increase in sporadic CJD (sCJD) cases noted in several papers is most probably due to improved case ascertainment, population increases and an ageing population. The recent Appendix III study detected abnormal prion protein, using variant CJD (vCJD) specific immunostaining of stored anonymised appendix tissue in cohorts of people considered not to have had significant exposure the bovine spongiform encephalitis (BSE) epidemic. This suggests that either there is low background prevalence of abnormal prion protein staining in human lymphoid tissue that may not be related to the BSE epidemic, or that the duration period of human exposure to the BSE epidemic was longer than previously thought. Whichever interpretation is adopted, the contrast between the prevalence of abnormal prion protein and the number of clinical vCJD cases seen to date suggests that only a few of those with this ‘background’ protein abnormality will develop prion disease. Whilst many studies aim to retrospectively investigate the relationship between prior surgery and risk of developing CJD, these case-control designs are prone to bias and confounding. Data on the likely incubation periods of CJD are limited to retrospective data from iatrogenic CJD, vCJD or Kuru cases. As CJD detection methods advance, more accurate confirmation of CJD pathology will be possible from autopsy and excised tissue samples. Evidence on decontamination of surgical instruments is fragmented with no single study assessing the efficacy of all strategies including: reducing residual mass, keeping instruments moist, autoclaving and sterilisation. Comparison of included studies is also problematic due to being conducted under different conditions and in laboratory settings which limit their external validity to the clinical setting. As published data on instrument set-keeping and single-use instruments were not retrieved, no evidence to substantiate or refute anecdotal claims about the drawbacks and merits of reusable versus single-use instruments is available. Data on the risk of future surgery in those undergoing high-risk procedures is limited in its potential to inform the model as it did not focus solely on high-risk procedures and does not compare the risk of additional procedures with control data for those who had not undergone an index high-risk procedure.

As with any mathematical model attempting to replicate a complex decision problem, simplifications were made. The model structure and the parameterisation of the variables were discussed with the NICE appraisal committee and amended accordingly: it is thus believed that key facets of the decision problem have been incorporated. Whilst running a greater number of probabilistic sensitivity analysis configurations would increase the accuracy in the ICER related to uncertainty in parameter estimates. and running more random number streams would increase the accuracy for a given PSA configuration, the results appear sufficiently robust for decision making. Keeping instruments moist is predicted to save both money and the risk of future stCJD cases. All other strategies evaluated have ICERs in excess of £1,000,000 per QALY. The removal of the need for patients born after 1996 to be operated on using separate instruments did not show a marked increase in the number of predicted stCJD cases. Throughout the modelling there was a conscious decision to be pessimistic if a choice needed to be made, and thus the cost per QALY estimates are likely to be under-estimates rather than over-estimates.

## Conclusions

The systematic reviews were comprehensive and inclusive and retrieved studies providing indirect, observational and speculative data to inform about the likelihood of a rare disease being transmitted via surgery. The limited evidence retrieved indicates that there have been no observed cases of stCJD since 2005. Evidence implicating surgery as a risk factor for CJD is restricted to case-control designs. Due to the rarity of the disease and the difficulties in conducting externally valid studies to provide robust evidence for the clinical setting, direct evidence to inform the review questions is limited.

The modelling undertaken indicates that keeping surgical instruments moist is a dominant strategy, in that it saves money and also increases societal health. Additional strategies aimed at reducing the future risk of stCJD cases do not appear to be cost-effective as they have cost per QALY gained estimates in excess of £1,000,000. It is estimated that removing the requirement to operate on people born after 1996 with different instruments would not markedly increase the risk of stCJD cases.

This study is registered as PROSPERO CRD42017071807.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

# 1 INTRODUCTION

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

Four classifications of CJD exist: sporadic CJD, variant CJD, genetic CJD and iatrogenic CJD. Referrals of suspected CJD, and values for definitely-related CJD death (with neuropathological confirmation) or probably-related deaths (without neuropathological confirmation) are recorded by the National CJD Research and Surveillance Unit in Edinburgh (NCJDRSU).1 This source estimates that since 1990, there have been 3746 referrals for investigation and 2370 deaths of definite or probable CJD (as of 8th January 2018).

Sporadic CJD (sCJD) has historically been the most common type of CJD, accounting for around 85% of CJD cases. The cause of sCJD occurs due to apparently spontaneous generation of an abnormal isoform of prion protein (PrPSc). sCJD generally occurs later in life with a mean age of 67 years and has a short survival post-diagnosis of around 4 months.2 Whilst there is evidence of a genetic predisposition to sCJD, the precise cause of the disorder is unknown.

Genetic CJD (gCJD), also known as familial or inherited CJD is associated with pathogenic mutation in the prion protein gene (PRNP) and includes conditions known as fatal familial insomnia and Gerstmann-Schäussler-Scheinker (GSS) syndrome. Together gCJD accounts for between 5-15% of CJD cases or approximately 10 CJD deaths in the UK per year.

Variant CJD (vCJD) was observed following the exposure of the UK population during the late 1980s and early 1990s to bovine spongiform encephalopathy (BSE) that was presumed to be transmitted to humans by eating food contaminated with the brain, spinal cord, or digestive tract of infected carcasses. The vCJD epidemic peaked in 2000 with 28 deaths and has declined since with only two “definite or probable” vCJD deaths reported since 2012. The majority of cases have occurred in a younger population than observed in sporadic CJD with a mean age of 26 years. The median disease duration post-diagnosis is longer in vCJD (14 months) than observed in sCJD. All people who have contracted clinically observed vCJD have died.

Incidences of iatrogenic CJD (iCJD), which is the transmission of prion disease through medical procedures or equipment, have been recorded for procedures including dura mater grafts, electroencephalograph (EEG) needles, neurosurgery, or receipt of corneal grafts, growth hormones, gonadotrophin or packed red blood cells.3

The current decision problem focuses on the risk of transmission of CJD (of all forms) via surgical instruments. Prions are unlikely to be completely deactivated on surgical instruments by conventional hospital cleansing and sterilisation techniques4 and therefore patients may be infected iatrogenically with CJD by surgical instruments, resulting in a stCJD case. Iatrogenic transmission can occur when surgical instruments, endoscopes or laryngoscopes are used during high risk neurosurgical procedures in patients who have asymptomatic CJD but who are infectious because neural tissue in particular has a high infectious load.5 Four cases of iCJD via neurosurgery were observed between 1952 and 1974 from three sporadic index cases of CJD.6 Stringent Public Health requirements are in place to limit the risk of iatrogenic disease being spread from people with an increased risk of developing CJD, or with CJD, or for whom a diagnosis of CJD is being considered or cannot be excluded.

Immediately following the recognition of vCJD, as a consequence of the BSE outbreak, the potential scale of the number of infections was uncertain and estimations incorporated potential subclinical vCJD infections identified from a histopathological survey of lymphoreticular tissue to be 237 per million (95% confidence interval (CI) 49–692 per million).7-9 Surgical transmission of CJD in this scenario was considered to pose a potential risk to public health by virtue of a self-sustaining iatrogenic epidemic. Therefore, in 2005 the National Institute for Health and Care Excellence (NICE) commissioned the School of Health and Related Research (ScHARR) at the University of Sheffield to conduct a systematic review and perform cost-effectiveness modelling of evidence on patient safety and reduction of risks of transmission of CJD.10 This evidence, together with data collected from experts, was used to populate a mathematical model assessing the cost-effectiveness of single-use surgical instruments11, 12 The outputs from the model and a separate risk assessment conducted by the Department of Health Economics, Statistics and Operational Research (ESOR) Division13 were used to inform the NICE Interventional Procedures Guidance 196 (IPG196) “*Patient safety and reduction of risks of transmission of Creutzfeldt-Jakob Disease (CJD) and vCJD*”.14 The existing guidance includes recommendations on decontamination methods and guidance for set-keeping to ensure that instruments in contact with potentially high-risk tissues do not move from one set to another. Furthermore, supplementary instruments used during high-risk procedures were recommended to either be single use or to remain with the set with which they were introduced. An age split was also recommended with separate instruments used for people born before 1997 (and at risk of dietary exposure to BSE) and those born after 1996 (who were believed at the time of writing IPG196 to be not infected with vCJD). High-risk tissues are regarded as intradural neurosurgical operations on the brain (excluding operations on the spine and peripheral nerves), neuroendoscopy, and posterior eye procedures that involve the retina or optic nerve.14 While the cost-effectiveness analysis indicated that the introduction of single-use instruments for all high-risk procedures was not cost-effective, there was great uncertainty in these results and a recommendation was made by the study authors that policy might need to be revised if new relevant data become available.

An epidemic of CJD has not occurred since the publication of IPG196 and no conclusive evidence of transmission by surgery has transpired to date. However, a number of developments have occurred since 2006 which include:

* a finding of abnormal prion accumulation in the appendices of low-risk cohorts [i.e. those born after 1996],15, 16
* continued evolution of high quality and less expensive single-use instruments,
* anecdotal reports of difficulties implementing the recommendation from IPG196 related to keeping instruments in their original sets across a number of units,
* anecdotal reports of problems in maintaining quarantined instruments for patients born after 1996.

A recent study has also implicated neurosurgery as a possible iatrogenic source for amyloid beta accumulation in the brain, a peptide which is associated with Alzheimer’s disease.17 This finding underlines the potential risk associated with high-risk procedures and the importance of assessing evidence relevant to decontamination or disposal of neurosurgical equipment.

*Purpose of the research*

The objective of the current research is to update selected evidence from the research project conducted in 2005 (project no. IP1553) that informed NICE guidance IPG19611 for the NICE Interventional Procedures (IP) committee to review the decision problem in 2018. The aim is to review the evidence base for the current risk of transmission of CJD (any form) related to surgery in order to provide up-to-date relevant evidence to NICE, and to inform the cost-effectiveness of potential management strategies.

*Research objectives*

1. To perform updates of the systematic reviews completed in 2005 on the clinical evidence on patient safety and risks of transmission of CJD via surgery
2. To update the economic model and where necessary seek new input from expert elicitation to make the model relevant for the decision problem today
3. Undertake modelling to estimate the cost-effectiveness of strategies to reduce the risk of transmission of CJD via surgical procedures.

# 2 CLINICAL EVIDENCE

## 2.1 Methods for systematic reviews

The protocol for this project was developed in consultation with the NICE Interventional Procedures Advisory Committee (IPAC) and was registered on the Centre for Reviews and Dissemination (CRD) systematic review database (PROSPERO registration no. CRD42017071807). The project aimed firstly to update the evidence for the following eight research questions:

1. What is the incidence of CJD and what is the prevalence of CJD-related prions in humans in the UK?
2. What is the risk of secondary transmission of CJD by surgical procedure?
3. What are the incubation periods of acquired Transmissible Spongiform Encephalopathies (TSEs)?
4. What is the infectivity of CJD?
5. What is the evidence on the efficacy of decontamination of instruments with prions?
6. What is the evidence that instruments used for high-risk procedures remain in their original sets?
7. What is the evidence for complication rates of single-use compared with reusable instruments for high-risk procedures?
8. What is the evidence for likelihood of future surgery for a patient undergoing high-risk procedures?

Eight systematic reviews have been completed to best address these research questions in adherence to best practice systematic review methodology according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 200918 standards.

### *2.1.1 Eligibility criteria*

The inclusion and exclusion criteria differ for each review question. These are broadly summarised in Table1.

**Table 1: Eligibility criteria for each review question**

|  |  |
| --- | --- |
| Review Question | Eligibility criteria for inclusion into the review |
| What is the incidence of CJD and what is the prevalence of CJD-related prions in humans in the UK? | Population: Humans with CJD or CJD-related prions in tissue  Outcome: Incidence or prevalence data  Study designs: National surveillance reports, registry data, epidemiological studies or pathological surveys that provide empirical estimates of prevalence. |
| What is the risk of secondary transmission of CJD by surgical procedure? | Population: Humans who have acquired CJD via iatrogenic transmission via surgery  Outcome: Incidence data  Study design: Observational studies such as case series and case reports |
| What are the incubation periods of acquired TSEs? | Population: Humans with CJD or related prion disease (e.g. kuru) as a result of primary or secondary transmission  Outcome: Incubation data  Study designs: Empirical or epidemiological studies; reviews/guidance documents for reference checking |
| What is the infectivity of CJD? | Phenomenon of interest: The infectiousness of CJD in terms of CJD type, subtype or strain, genotype of the recipient, infectivity of infectious tissue, infectious mass required to transmit CJD  Outcome: Trends or themes in CJD infectivity  Study designs: Empirical *in vivo* or *in vitro* studies |
| What is the evidence on the efficacy of decontamination of instruments with CJD/TSE/prions? | Phenomenon of interest: The binding of prions to steel surfaces. The restriction to steel (e.g. steel wires), despite limitations, is because prions adhering to steel better simulate the real-world scenario of surgical instruments than inactivation of prions in brain homogenate or tissue.  Intervention: Autoclaving with/without an additional decontamination process; decontamination processes other than autoclaving  Outcome: Log reductions in the infectious titre, i.e. reduction in the load of infectivity on steel (wires) after decontamination processes.  Study designs: Empirical *in vivo* or *in vitro* studies; reviews/guidance documents for reference checking. |
| What is the evidence that instruments used for high-risk procedures remain in their original sets? | Intervention: Instruments used for specified high-risk surgeries  Outcomes: Set integrity; migration of instruments between sets  Study designs: Empirical or epidemiological studies; reviews/guidance documents for reference checking |
| What is the evidence for complication rates of single-use compared with reusable instruments for high-risk procedures? | Intervention: Single-use instruments for specified high-risk surgeries  Comparator: Reusable instruments for specified high-risk surgeries  Outcomes: Complications  Study designs: Comparative studies; reviews/guidance documents for reference checking |
| What is the evidence for risk of future surgery for a patient undergoing high-risk procedures? | Population: Patients undergoing neurosurgery or specified high-risk surgeries.  Outcomes: Risk of future neurosurgery or additional high-risk surgeries after undergoing a high-risk procedure.  Study designs: Empirical or epidemiological studies; reviews/guidance documents for reference checking |
| The following citations were excluded from all review questions:   * Studies concerning detection of CJD concerning laboratory parameters only * Animal studies without relevant discussion of implications to humans * Discussion papers or papers providing guidance which do not provide relevant empirical data * Papers that are superseded by later or more complete published data * Papers relating only to treatment or care of patients with CJD * Papers relating to filtering blood for transfusion or other blood products from CJD-related prions * Papers relating only to prion diseases without specific mention of CJD or decontamination of prions | |

### *2.1.2 Search strategy*

Literature searches were conducted to retrieve relevant evidence. Electronic databases were searched on 14th August 2017.

* MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations: Ovid, 1946 to 2017
* EMBASE: Ovid, 1974 to 2017
* Science Citation Index (SCI-E) and Conference Proceedings Citation Index (CPCI): Web of Science, 1990 to 2017

A date restriction from 2005 to 2017 was applied for the first seven review questions. For the final review question regarding the risk of future surgery in patients who have had high-risk procedures, as no relevant evidence was found in the previous review, the search strategy was revised and searches were performed from database inception to 2017. No language or study design limits were applied to the searches. The search strategies are presented in Appendix 1.

Members of the NICE IP committee were consulted as content experts, for potentially relevant papers for all review questions. Papers recommended by experts were subject to bibliography checking.

The searches combined terms that would be relevant for more than one review question. Therefore, five targeted literature searches, instead of eight, for all review questions were conducted which combine terms for:

1. Incidence, prevalence and incubation
2. Risk via surgery, infectivity and decontamination
3. Set-keeping of instruments
4. Complication rates of single-use instruments
5. The risk of future surgery in patients who have had high-risk procedures
6. *Searches for the UK incidence and prevalence of CJD and the incubation period of acquired human TSEs*

Electronic literature searches were performed to identify relevant articles. Terms for ‘incidence and prevalence’ or ‘incubation’ (10-15) are combined with ‘CJD’ population terms (1-9). The terms applied were identical to those used in Appendix 1 and 3 in the original systematic review.10

1. *Searches for the secondary transmission of CJD by invasive diagnostic or surgical procedures; Infectious mass required to transmit CJD; and the decontamination of surgical, anaesthetic and diagnostic instruments, scopes and implantable devices*

Electronic literature searches were performed to identify relevant articles. Terms for ‘transmission’ and ‘transfer’ (27) and ‘instrument decontamination’ (28-33) are combined with ‘CJD’ population terms in humans or non-human mammals (18-25).

1. *Searches for the extent to which surgical instruments remain in their original sets following use and decontamination*

Electronic literature searches were performed to identify articles which report on the extent to which surgical instruments remain in their original sets following use and decontamination Terms for ‘instrument decontamination’ (36-41) are combined with ‘high-risk surgical procedures’ (42-56). A list of high-risk surgical procedures were taken from Appendix C of NICE IPG196.14

1. *Searches for the complication rates associated with the use of single-use vs reusable anaesthetic, diagnostic or surgical instruments*

Electronic literature searches were performed to identify articles which report on the complication rates associated with the use of single-use vs reusable anaesthetic, diagnostic or surgical instruments. Terms for ‘disposable or single-use’ instruments (60-63) including specifically named instruments recommended from the NICE committee meeting in June 2017 (63) combined with ‘high-risk surgical procedures’ (65-79) or ‘complications’ (81-84).

1. *Searches for the risk of future surgery following surgery*

Electronic literature searches were performed to identify articles which report on the risk of future surgery following surgery. Terms for ‘reoperation’ or ‘repeat surgery’ combined (88-90) with ‘high-risk surgical procedures’ (92-106). No date restrictions were applied.

*Cost-effectiveness searches*

A literature search was undertaken to identify evidence relevant to the cost-effectiveness model such as relevant economic evaluations in Creutzfeldt-Jakob disease.

Four electronic databases were searched on 7th June 2017 from 2004 until present:

* MEDLINE, MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations: Ovid, 1946 to 2017
* EMBASE: Ovid, 1974 to 2017
* Cochrane Library (Wiley Online) (Cochrane Database of Systematic Reviews, 1996 to 2017; Health Technology Assessment Database, 1995 to 2016; NHS Economic Evaluation Database, 1995 to 2015
* Science Citation Index (SCI-E) and Conference Proceedings Citation Index (CPCI): Web of Science, 1990 to 2017

The search strategy comprised Medical Subject Headings (MeSH) or Emtree Thesauri terms and free-text synonyms for ‘CJD’. Searches were translated across databases and were not limited by language. The search strategies are presented in Appendix 2. Search filters designed to identify economic evaluations were used on MEDLINE and EMBASE.

*Study selection*

Results from the electronic bibliographic searches were imported into reference management software, EndNote (version 8, Thompson Reuters), and duplicates were removed. Titles and abstracts of retrieved records were examined by one reviewer (LU) and irrelevant citations were 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. Consultation with the third designated team member (MS) was not required for any citation. At the full paper stage, all citations excluded from a particular review question by the reviewer for that question were double-checked by the second reviewer. Lists of these citations, with the principal reason for exclusion, are reported for each review in Appendix 3. Data identified from countries outside of the UK were incorporated if deemed relevant.

Literature identified within the cost-effectiveness review was processed in a similar manner. Titles and abstracts of retrieved records were examined by one reviewer (MS) and irrelevant citations were excluded. A proportion (10%) of randomly selected excluded citations was double-checked by a second reviewer (LU). All full text articles were independently assessed for inclusion by two reviewers (MS, LU). No disagreements were required to be resolved through discussion or with involvement of the third designated team member (CC).

*Data extraction*

Bespoke data extraction forms were developed for each review question in Microsoft Excel® to record relevant outcome data for the review question in hand. All data were extracted by one systematic reviewer (LU for reviews 1, 2 and 4; CC for reviews 3, 5, 6, 7 and 8) and independently checked by a second reviewer (LU for reviews 3, 5, 6, 7 and 8; CC for reviews 1, 2 and 4). Any disagreements were resolved by discussion and consensus or by consulting with a third member of the project team (MS).

*Quality assessment*

The role of performing formal quality assessment using standard checklists such as Cochrane Risk of Bias tool was considered in this systematic review. The value of conducting quality assessment is to assess how a study has been conducted in order to balance the numerical findings (or the statistical strength of effects) against the methodological quality. In many cases, the included “studies” in this review were not amenable to quality assessment because: a) they are surveillance reports thereby not constituting the traditional definition of a study or; b) they are laboratory studies using highly specific scientific methods that are not amenable to the quality assessment for clinical trials. None of the review questions sought data that were estimating treatment effects, therefore the typical domains of quality assessment such as randomisation, performance bias, detection bias and attrition bias are less relevant. Assessment of study heterogeneity is less important when not performing formal synthesis to estimate treatment effects. Indeed, limitations to inclusion criteria based on study design, scientific discipline, setting or context would potentially have restricted the external validity of the review. Therefore, no formal quality assessment has been undertaken and the protocol for the systematic review, registered on the PROSPERO database (no. CRD42017071807), was updated accordingly. The purpose of the reviews is primarily to describe the relevant literature rather than to aggregate data or rank individual studies.

*Data analysis / synthesis*

Data were tabulated, synthesised and discussed narratively for each review question. Meta-analyses were planned to be conducted by an experienced statistician using appropriate software and heterogeneity was explored using meta-regression where comparable data were available. No suitable data were identified for formal aggregation using meta-analysis.

*Meta-biases and assessment of external validity*

Due to the complex nature of the clinical topic, the number of review questions, and the diverse information required to inform the economic model, the systematic reviews are methodologically challenging. In order is to obtain high quality, trustworthy data and to maintain the external validity of the reviews, the inclusion criteria were kept broad until full text retrieval. After discussion within the project team and with NICE committee experts, a decision was made to take a broad approach during the assessment of study relevance, rather than applying stringent inclusion criteria.

The risk of this approach is that the evidence generated from the reviews is less amenable to replication. However, the purpose the clinical reviews is to inform commissioners about potential risks of CJD transmission via surgery rather than estimating treatment effect. Therefore, a more inclusive methodological approach by the evidence review group in this complex clinical topic was deemed justifiable.

### *2.1.3 Literature search results*

The literature searches of bibliographic databases were performed on 14th August 2017 and yielded 8466 citations. During the screening process, a citation of potential relevance to review question 2 was identified which had not been picked up by the literature searches. Therefore, the information specialist in consultation with the project team revised the search terms for review 2 to perform an additional search on 2nd October 2017, resulting in a further 310 citations. Forty-one further citations were obtained and assessed for eligibility either from recommendations from NICE committee members (n=16) or through checking the reference lists of relevant citations (n=25). After duplicates were removed, the 8549 titles and abstracts were reviewed by one reviewer (LU). Ten percent of excluded citations were independently assessed by a second reviewer (CC) with very good agreement (Kappa: 0.98). Any disagreements were carried forward for further discussion but none were ultimately deemed as eligible for full-text inspection by either reviewer. A PRISMA flow diagram illustrating the process of identifying citations through to final study selection for each review question is shown in Figure 1.

Figure 1: PRISMA flow diagram of studies included in systematic reviews

Studies included in systematic reviews  
(n = 169 )

*(Some studies used in more than one review)*

Titles/abstracts excluded  
(n = 8350 )

Records screened  
(n = 8549 )

Records after duplicates (n = 268) removed   
(n = 8549 )

Full-text articles assessed for eligibility  
(n = 199 )

**Identification**

**Eligibility**

**Included**

**Screening**

Records identified through other sources  
(n = 41 )

Contact with experts n = 16

Bibliography checking n = 25

Incidence/prevalence ( n = 69 )

Risk via surgery ( n = 35 )

Incubation ( n = 19 )

Infectivity ( n = 38 )

Decontamination ( n = 23 )

Instrument set-keeping ( n = 2 )

Single-use complications ( n = 0 )

Future surgery after high-risk ( n = 1 )

Full-text articles excluded, with reasons  
(n = 30 )

Pre-2005 data (n=2)

No usable data for any review question (n=10)

Not CJD related (n=1)

Not high-risk surgery (n=1)

Review, no original data (n=5)

Superseded data (n=8)

Wrong outcome (n=3)

Records identified through database searching  
(n = 8776 )

## 2.2 The incidence of CJD and the prevalence of CJD-related prions in humans in the UK

The purpose of this review was to identify published and unpublished evidence for:

1. the incidence of CJD (sporadic, genetic, variant and iatrogenic) and
2. the prevalence of CJD-related prions in humans in the UK

The NCJDRSU provides the most comprehensive and regularly updated figures for the UK. Globally figures are gathered by the CJD International Surveillance Network (EuroCJD);19 however, this source was last updated in May 2015 and is therefore less up-to-date than NCJDRSU. The literature searches were also used to retrieve the most recent or complete figures, incidence trends or studies regarding subclinical prevalence of CJD prions in tissue. Sixty-nine published citations were identified as being relevant to the incidence of clinical CJD or the prevalence of subclinical CJD around the world.

### *2.2.1 The incidence of CJD*

The global incidence of CJD is typically reported to be around 1 to 2 cases per million per year,19 based on surveillance studies published around the world from 2005 and onwards (Table 2). 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 paper by Jeon *et al* (2016)20 described that CJD surveillance did not begin in Korea until 2001, and iCJD was not studied in Korea prior to 2011. This indicates geographical variation in how CJD may have been detected and reported in time globally.

Table 2: Global estimations of CJD incidence from studies published in 2005 or after (ordered by date, then alphabetically)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Country** | **Time period of estimation** | **CJD incidence or mortality rate per million** | **CJD types included** | **Study author/ Source** |
| Austria | 1993-2017 | 1.49 | Sporadic | EuroCJD19 |
| Australia | 1993-2016 | 1.20 | Sporadic | EuroCJD19 |
| Belgium | 1997-2017 | 1.19 | Sporadic | EuroCJD19 |
| Canada | 1994-2017 | 1.03 | Sporadic | EuroCJD19 |
| Czech Republic | 2000-2017 | 1.16 | Sporadic | EuroCJD19 |
| Denmark | 1993-2017 | 1.45 | Sporadic | EuroCJD19 |
| Estonia | 2004-2017 | 0.32 | Sporadic | EuroCJD19 |
| France | 1993-2017 | 1.53 | Sporadic | EuroCJD19 |
| Germany | 1993-2017 | 1.36 | Sporadic | EuroCJD19 |
| Hungary | 1997-2017 | 1.07 | Sporadic | EuroCJD19 |
| Italy | 1993-2017 | 1.44 | Sporadic | EuroCJD19 |
| Netherlands | 1993-2017 | 1.21 | Sporadic | EuroCJD19 |
| Norway | 1995-2017 | 0.96 | Sporadic | EuroCJD19 |
| Slovakia | 1993-2017 | 0.85 | Sporadic | EuroCJD19 |
| Slovenia | 1993-2017 | 1.38 | Sporadic | EuroCJD19 |
| Spain | 1993-2017 | 1.30 | Sporadic | EuroCJD19 |
| UK | 1993-2017 | 1.19 | Sporadic | NCJDRSU 20161 |
| USA | 2016 | 1.22 | Excludes vCJD | US Government21 |
| Japan | 1999-2015 | 1.3 | All types | Yamada *et al* 201622 |
| Australia | 1993-2014 | 1.2 | All types | Klug *et al* 201623 |
| Finland | 1997-2013 | 1.45 | Sporadic | EuroCJD19 |
| Cyprus | 1995-2013 | 0.70 | Sporadic | EuroCJD19 |
| Germany | 1993-2013 | 1.33 | Excludes vCJD | EuroCJD19 |
| Holland | 1993-2013 | 1.21 | Excludes vCJD | EuroCJD19 |
| Hungary | 1997-2013 | 1.65 | Excludes vCJD | EuroCJD19 |
| Sweden | 1997-2013 | 1.44 | Excludes vCJD | EuroCJD19 |
| Switzerland | 1993-2013 | 1.72 | Sporadic | EuroCJD19 |
| Argentina | 2008 | 0.85 | All types | Begue *et al* 201124 |
| Greece | 1997-2008 | 0.62 | Sporadic | EuroCJD19 |
| Taiwan | 1998-2007 | 0.55 | Sporadic | Lu *et al* 201025 |

A study by Gao *et al* (2011) does not report an incidence rate per million for CJD in China, but does report that during the period of 2006 to 2010, 261 patients were diagnosed with sCJD and 23 patients were diagnosed with genetic human prion diseases from 624 suspected patients who were referred to China CJD surveillance.26

#### Increase in UK sCJD incidence over time

Between 1990 and 2017, the NCJDRSU recorded figures of iatrogenic CJD (from receipt of human gonadotrophin, human-derived growth hormone or dura mater) and vCJD which are relatively low compared to sporadic CJD. Figure 2 plots the number of deaths in the UK that have been attributed to definite or probable CJD between 1996 and 2017 (2nd May 2018) as reported by the NCJDRSU. An increase in sporadic CJD cases is noted over the 27-year period whilst iatrogenic, genetic and variant forms remain low.

Figure 2: Deaths from probable or definite CJD in the UK using data from the NCJDRSU between 1996-2017

Possible reasons for the increase in the detection of sCJD cases in the UK are speculated to include:

1. improved case-ascertainment due to clinician awareness and/or improvements in diagnostic testing;
2. population increases;
3. an ageing population;
4. changes to the sporadic case definition to include cerebrospinal fluid and magnetic resonance imaging (MRI) diagnostic tests.

An upwards trajectory of CJD cases may be attributable to the way that data are collected for surveillance of CJD. 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. As the national surveillance programme for CJD has been operating since May 1990 and is a prospective surveillance programme, there are likely to be improvements over time with respect to how this rare condition is detected, referred, investigated and reported when compared with retrospective surveillance studies. Moreover, in CJD, due to the potential for iatrogenic transmission, there has been a focussed collaborative effort to examine evidence of transmission through different exposures by examining links to confirmed CJD cases through retrospective “lookback” studies.27

The gradual increase in sCJD, but not gCJD adds support to the ‘ageing population’ theory over merely population increase and improved case ascertainment.

#### Increase in sCJD incidence globally

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 in an abstract by Isotalo *et al* (2015).28 An abstract by Chen *et al* (2016) reports that sCJD incidence rates in Taiwan doubled between 2008 to 2015.29 They also report that age at onset became earlier. Chen *et al* speculate that reasons for the increase in CJD cases include: physician´s sensitivity in recognising CJD; improved reporting systems; concerns around vCJD, and high media coverage. A published study from Belgium noted a relevant trend of significantly increased age-specific incidence of sCJD patients between 70 and 90 years old in the period 2002-2004 compared with 1998-2001 using retrospectively obtained data (1990-1997, p < 0.01).30 The authors conducted a clinical and biochemical analysis to investigate this increase, but could not identify any reason other than an increased vigilance for the diagnosis. Similarly, in Japan, Ae *et al* (2016) report in a study abstract that the annual incidence of human prion diseases has tended to increase since 1999, but particularly in older patients (aged 70 or more), with cases of rapidly developing dementia increasingly being identified by domestic physicians.31

One study from Slovenia reported an apparent fluctuation of sCJD cases in 2015, with 7 definite and 2 probable sCJD cases resulting in an incidence of 4.36 per million for the country that year.32

#### Autopsy and biopsy in CJD

In the UK, confirmation of CJD from neuropathological (via autopsy or brain biopsy), immunocytochemical or biochemical examination is required for obtaining a definitive sCJD diagnosis. For vCJD, confirmation must be through neuropathology.1 Despite the observed increase in sCJD cases over the last twenty years, autopsy is not performed routinely on sporadic CJD cases. In the UK, almost 50% of all cases referred to the NCJDRSU undergo autopsy.2 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 sporadic CJD cases over the last 20 years could be attributable to an altered incubation and clinical presentation of acquired CJD (variant or iatrogenic CJD) that mimics sCJD or another neurological condition. Indeed, surgery has been posited as a risk factor for sCJD from a number of epidemiological studies and a retrospective study by Urwin *et al* (2016) is described as ongoing to investigate this risk factor further in a review of UK sCJD cases.34

Cursory analysis of published literature from studies on CJD around the world generates potential reasons for why autopsy is not always routinely completed in sCJD patients. Brain biopsy and autopsy of suspected CJD cases carry the risk of iatrogenic transmission to medical or pathology staff, meaning that there is an extra burden of duty to ensure stringent infection control protocols are followed. Protocols for instrument decontamination are required for brain biopsy. For example, Shi *et al* (201635) state that whilst an intracranial biopsy procedure is invasive and carries risk of cerebral infection or hematoma, it is generally a safe and well-tolerated procedure; however, special precautions to prevent the spread of prions must be taken. Medical instruments and equipment supplies must be either destroyed by incineration or autoclaved and sterilised. Similarly, Baig *et al* 201336 state that getting a biopsy in a timely manner is commonly not possible given the costly and aggressive nature of the diagnostic test and that the rigorous decontamination and sterilization techniques for handling tissue at biopsy may make it impractical in a community setting.

#### Racial and geographical differences

Variations in CJD incidence according to race were noted in the literature with the age-adjusted CJD incidence for white people in the US reported as being 2.7 times higher than that for black people (1.04 and 0.40, respectively) by Maddox *et al* (2010)37 and Holman *et al* (2010).38 Similarly, the estimated incidence of CJD (0.7 per million) among Asians and Pacific Islanders in the United States between 2003-2009, was reported as being significantly lower than that for white people (p < 0.001) by Maddox *et al* (2013).39

Nakatani *et al* (2015) noted that sCJD appeared to have regional variations in occurrence in Japan, suggesting that the existence of genetic or region-specific factors may affect the incidence of the disease, such as hereditary background or other local factors.40 In this study, geographical clusters of sCJD were scattered in the western half of Japan. However, no direct evidence to support theories about the causative factors underlying this trend in occurrence of sCJD are presented and therefore this particular phenomenon remains to be explored. Klug *et al* (2009) conducted a spatial and epidemiological analysis of sCJD case-clusters in Australia.41 The authors concluded that the observed increase of sCJD cases in a geographic area is likely to be related to better awareness of the disease by local neurologists rather than to an increase in risk factors.

Genetic forms of CJD are most often associated with a mutation at codon 200.42 Mitrova *et al* (2014) report that whilst gCJD represents about 10-15 % of all CJD patients in the majority of countries, in Slovakia, the rate of gCJD has been above 65% since 1975 due to an accumulation of gCJD incidence in two clusters in central Slovakia.43 The authors state that all but one of the 202 patients who had gCJD in Slovakia carried the mutation form E200K and highlight that asymptomatic carriers of this gene could contribute to iatrogenic transmission of CJD. A voluntary genetic testing study conducted by the authors showed positivity for the E200K mutation in 9 out of 2662 subjects who were unrelated to the gCJD cases both inside and outside of the focal cluster. This finding indicates an unusual phenomenon of increased prevalence of the E200K mutation linked to gCJD linked in the Slovak region. A study by Ladogana *et al* (2005) reported similar prevalence of sCJD across the UK, France, Germany, Italy, the Netherlands, and Slovakia, but also reported an excess of genetic cases in Italy and Slovakia.44

#### Diagnosis of CJD

Global differences in the culture of pursuing autopsy to confirm CJD diagnosis and subtype are likely to exist depending on national CJD surveillance protocols. For example, Tuskan-Mohar *et al* (2012) report that post-mortem examination was not performed in any of the five cases of CJD occurring in Croatia between 2001 and 2011 due to patient families’ refusal of the procedure.45 More generally, Kosier *et al* (2017) state anecdotally in a US case report that diagnosis of CJD is often delayed due to clinician bias toward more obvious possible medical or psychiatric causes.46 Litzroth *et al* (2015) highlight that in Belgium, between 1998 to 2012, on average 60% of hospitalised patients who died with suspected CJD were captured by the surveillance system.47 The authors also report that 11% of surveyed neurologists would not refer suspect vCJD cases for autopsy, nor contact a reference centre for diagnostic support and that 61% of surveyed neurologists were not familiar with the surveillance system.

Two studies from Ireland describe a relatively sensitive surveillance system for CJD detection but less accuracy in obtaining a final confirmatory CJD diagnosis. One study found from a review of 21 referrals to the National CJD Centre in Ireland, that only five were positive for CJD, with 12 being referred as part of their differential diagnosis. The authors, Brett *et al* (2017),48 caution that more often than not, the clinical suspicion of CJD was not borne out by the final neuropathological diagnosis and that failure by clinicians to adhere to the recommended CJD investigation algorithm impacts adversely on the neuropathology workload and causes unnecessary concern among operating theatre, laboratory and nursing personnel. Loftus *et al* (2017) also raise the issue that the terms “probable CJD” and “definite CJD” might be used indiscriminately. They highlight from an analysis of 100 cases of CJD in Ireland, that approximately half of cases (n=50/96 referrals) were confirmed as definite CJD via tissue samples through biopsy or autopsy.49 The authors propose an algorithm for CJD referrals to reduce infection control and diagnostic difficulties encountered in CJD surveillance.

Despite the fact that sCJD is a condition known to affect older people, detection is likely to have improved in the last six years. Figure 3 is taken from the 25th Annual Report of the NCJDRSU (2016) and shows a steep increase in the detection of CJD mortality in the UK2, particularly in the age category of 65-69 years. However, incidence using age-adjusted data of CJD-related deaths per million will be influenced by the assumed population in each band. The mortality rates for 1995-2004 use the same census data as 2005-2009. However, if there are proportionately more older people in the more recent age band then the incidence will be inflated.

Figure 3: Age-specific mortality rates from sporadic CJD in the UK 1979-2016: replicated from NCJDRSU Annual Report 2016



Due to the median age of onset of sCJD symptoms, it is possible that CJD and prion disease cases may be concealed among cases of more commonly encountered but similarly rapidly deteriorating neurological conditions affecting older people, such as Alzheimer’s disease. In the published literature, there are numerous reports of CJD mimicking other conditions including stroke,50, 51 acute neuropathy,52 hyperparathyroidism,53 dementia,47,54-57 Lewy body dementia,47 encephalitis,47 aphasia,58 Alzheimer’s disease,47, 56 psychiatric decompensation46 and movement disorder.59 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 with pathologically typical spongiform encephalopathy were identified clinically during life.60 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 CJD which occur later in life, particularly where access to clinicians with experience of diagnosing CJD is limited, may result in some cases of misclassification of CJD, despite potentially improved detection. However, given the rarity of CJD presentation worldwide and consequent clinical expertise, a degree of caution should be exercised in the interpretation of the limited available data.

#### Disease duration

Disease duration is regarded as the time between the onset of clinical CJD symptoms and death. Sporadic CJD is commonly reported to have a disease duration of around 4 to 7 months;2, 19, 61-63 however, Nagoshi *et al* (2011) report that duration of disease was longer for sporadic CJD in Japan than in Western countries. They state that sCJD, which represented 77.0% of cases of prion disease in their surveillance network between 1999-2008, had a mean disease duration of 15.7 months. This longer disease duration in Japan is more akin to the median observed in the UK for variant CJD which is 14 months from the onset of symptoms to death (NCJDRSU 2016 Annual Report) or indeed iatrogenic CJD via hGH, the median of which is reported as 16 months (mean 14 months) for 22 iCJD patients.64 Nagoshi *et al* (2011) also report that disease duration was longer in females (19.7 months) than males (14.5 months) for sCJD and that this tendency was also true for dura mater iCJD and types of gCJD including human Gerstmann-Sträussler-Scheinker (GSS) and fatal familial insomnia (FFI). Nagoshi *et al* also report that younger onset of disease was associated with longer disease duration for all types of CJD.

#### Genotype: codon 129

Methionine homozygosity at 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 PRNP codon 129 are at increased risk of the disease.65 In the north of Europe, the MM genotype represents 38% of the general population whilst 11% are VV and 51% are heterozygotes (MV) at codon 129 of PRNP.66 An epidemiological study by Giaccone *et al* (2009) of the PRNP genotype of 402 consecutive sCJD cases in Italy revealed that 70.4% (n=283) were MM, 15.4% (n=62) were MV and 14.2% (n=57) were VV.67 Whilst the numbers of MV and VV sCJD cases appear comparable in this study, the fact that over half of the population in Europe are MV indicates that the relative incidence of sCJD in heterozygotes at codon 129 is low.

In 2006, a re-analysis of the three appendices by Ironside *et al* (2006) identified (from the cohort of 12,674 appendix and tonsil samples analysed by Hilton *et al* (2004)7) as positive for disease associated prion protein (PrP) found two of the three were VV genotype which provided the first indication that the valine homozygotes are also susceptible to vCJD infection.68 The authors suggested that people infected with vCJD who are VV may have a prolonged incubation period with subclinical infection that could cause secondary infection via blood transfusion or surgery. Additionally, detection of subclinical prion accumulation in peripheral tissue by Gill *et al* (2013)69 from 16 positive appendix samples found that eight were MM, four were MV, and four were VV at PRNP codon 129, indicating genetic susceptibility for subclinical CJD was more equally distributed in the population.

Heterozygosity at PRNP codon 129 was generally believed to confer complete resistance to both sporadic and acquired prion diseases.70 However, the most recent case of clinical vCJD in 2016 was heterozygous33 and an additional possible vCJD case reported by Kaski *et al* in 2008 was also heterozygous, 71 but this possible vCJD case was not confirmed by autopsy. Case reports indicate that the MV genotype is susceptible to both subclinical iCJD; a heterozygous 73-year-old male with haemophilia whose spleen at autopsy gave a strong positive result on repeated testing for protease-resistant prion protein (PrPres) by Western blot analysis, as reported by Peden *et al* (2010).72 This patient had received over 9000 units of factor VIII concentrate prepared from plasma pools known to include donations from a vCJD-infected donor. Furthermore, the case report in 2004 of blood-transfusion-transmitted subclinical vCJD who was heterozygous at codon 129 but died of another cause unrelated to CJD73 highlights the possibility of potential transmission to this genotype. A study using mice supports the notion that transmission efficiency of vCJD is greatest in MM but indicates that all genotypes are susceptible, with the MV and VV genotypes benefitting from apparent reduced transmission efficiency and longer asymptomatic incubation periods.74

#### Disease duration and genotype

PRNP data from 378 of the Japanese patients reported by Nagoshi *et al* (2011) diagnosed with sporadic CJD showed that 364 cases (96.3%) had MM genotype but that disease duration was longest for the 11 patients (2.9%) who had MV genotype (mean, 32.2 months vs 16.6 months for MM and 13.2 months for VV).75 Begue *et al* (2011) report data for disease duration for sCJD from 59 definite cases in Argentina. Genotype analysis indicated that MV was associated with the longest disease duration (10.9 months), followed by VV (5.6 months) and MM (3.6 months).24 Data from Rudge *et al* (2015)64 relating to CJD transmission via hGH in the UK also found that MM patients had the shortest disease duration. MM patients had a mean duration of 7.8 months, the VV patient 17 months and MV had a mean of 18.6 months (range: 10–32 months). In addition, the duration of disease from first symptom was significantly longer in MV patients (P = 0.02, two-tailed t-test). Whilst there were only four patients who were MM, three of these had the most rapid progression (P = 0.04, Mann Whitney U-test).Yamada *et al* (2016) state that the majority of the general Japanese population (93%) carry the MM genotype.22 Considering that a large share of patients in the Argentinian sample also contained MM genotype (n=37, 66%), genotype data at codon 129 alone cannot account for the substantial difference in disease duration for sCJD reported between Japan and other countries.

Data from Japan,75 Argentina,24 and the UK64 therefore indicate that MV genotype is associated with the longest disease duration compared with homozygotes. In gCJD, disease duration was also reported to be significantly longer in codon 129 heterozygotes by Pennington *et al* (2010).76

#### Variant CJD

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.1 The most recent vCJD case occurred in an individual who was heterozygous at codon 129.33 A further 52 cases have been reported from other countries around the world bringing the global total of clinical vCJD cases to 231.77 Between 2005 and 2014, 68 vCJD cases were reported from 11 countries including the UK (n=29), France (n=19), Spain (n=5), Ireland (n=3), USA (n=3), Holland (n=3), Portugal (n=2), Italy (n=1), Canada (n=1), Saudi Arabia (n=1), and Taiwan (n=1).19 Three of the 178 UK cases that occurred up to 2016 are considered to have occurred through blood transfusion.2 A further fourth case of vCJD transmission through blood transfusion was identified in the spleen of an individual (heterozygous at codon 129) who died of a non-CJD-related cause. This is considered to be preclinical vCJD.73 Three further potential, but unconfirmed, cases of CJD transmission through blood transfusion are described by Chohan *et al* (2010)78 and Davidson *et al* (2014).79 A retrospective study by Molesworth *et al* (2014) that was performed to identify situations where the transplantation of organs or tissues might have occurred that involved 177 of the UK vCJD cases, found no evidence of transplant-associated vCJD in the UK.80 The remaining 175 clinical vCJD cases are presumed to be related to dietary exposure to BSE.81

#### Iatrogenic CJD

The most common causes of iCJD were human growth hormones (hGH) and dura mater grafts obtained from human cadavers. A review of worldwide iCJD cases published by Brown *et al* (2012) identified 469 cases from: dura mater grafts (n=228); surgical instruments (n=4); EEG needles (n=2); corneal transplants (n=2); hGH (n=226); gonadotropin (n=4) and packed red blood cells (n=3).3

In the UK, 85 cases of iCJD were identified between 1970 to December 2016 and are described by the NCJDRSU.1 Eight were 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 (with a range of 20-51 years) and 46.5 years for the dura mater cases (range 27-78 years).

Subsequent to the three cases of blood transfusion transmitted vCJD described above, no new cases of transfusion-associated infection have been identified since 2007 based on an epidemiological analysis of CJD cases and blood transfusion recipients by Urwin *et al* (2016).82 The Urwin *et al* study referenced the Davidson *et al* (2014) paper,79 but not the Chohan *et al* (2010) paper.78 These two papers discuss three potential, but unconfirmed, cases of CJD transmission via blood transfusion. Ward *et al* (2009) studied the risks in treatment for haemophilia and concluded that it is unlikely that any of the UK vCJD clinical cases to date were infected through exposure to fractionated plasma products.83 Evidence regarding incidence of iCJD from surgery is discussed in the review on the risk of CJD transmission via surgery.

### *2.2.2 The estimated prevalence of subclinical vCJD in the UK*

In vCJD, prions appear to replicate extensively within lymphoid tissue, 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 CJD for the purposes of risk assessment, and thought to represent a potentially background, but low, level of infection in the population.84 Immunohistochemistry staining is regarded as highly indicative of the abnormal prion protein pattern that has been observed in cases of vCJD, but not observed in other types of CJD and is used to estimate the approximate number of individuals who may go on to develop vCJD or be asymptomatic carriers of the disease.85

A key study conducted by Gill *et al* (2013), and referred to as the ‘Appendix II’ study, examined subclinical prion accumulation in excised peripheral tissues from general population cohorts born between 1941-60 and 1961-85.69 Detection of abnormal prion accumulation in appendix samples from these two cohorts resulted in a central estimation of 1 in 2000 for populations exposed to the BSE epidemic. The Advisory Committee on Dangerous Pathogens (ACDP) TSE subgroup produced a summary of findings following completion of the most recent study of stored appendices (‘Appendix III’) and calculated a rough central prevalence estimate of asymptomatic carriers of vCJD in the UK population, previously presumed unexposed to BSE, of approximately 1 in 4,200 or 240 per million.15, 16 This estimate is based on results of immunohistochemical (IHC) staining of appendices from two birth cohorts which are described in Table 3.

Table 3: Results of the Appendix III study

|  |  |  |
| --- | --- | --- |
| Appendix III cohort | IHC stain results | Central estimate |
| 1. Appendices removed between 1970-1979 and before the BSE epidemic | 2 positive samples from 14,692 appendices | 1 in 7,000 |
| 1. Appendices removed from patients born after 1st January 1996 and after measures to remove BSE were in place | 5 positive samples from 14,824 appendices | 1 in 3,000 |

#### vCJD and BSE

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.86 Moreover, a recent study by Diack *et al* (2016) examined two Spanish cases of vCJD; a mother and son who resided in a BSE endemic area, and who are thought to have ingested bovine brain.87 The resulting strain characteristics are similar to those of UK cases implying that both individuals were infected by BSE and supporting the hypothesis of risk via ingestion of high titre bovine material.

The Appendix III study84 highlights that abnormally- stained appendices associated with variant CJD (vCJD) prion accumulation have been confirmed in cohorts of people who were not considered to have had significant exposure to BSE because they were from: a) appendices removed before the BSE epidemic in the UK (prior to 1980) or b) appendices from patients born after food safety measures to limit BSE were implemented (after 1996). The presence of these 7 positive samples in these cohorts 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 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).88

One possible interpretation is that the prevalence of abnormal prion protein does not vary between cohorts because the staining observed represents a low background prevalence of subclinical vCJD in human lymphoid tissues that is largely unrelated to the BSE outbreak.

Another possible interpretation is that the duration of the BSE epidemic and subsequent ingestion by humans through the food chain was longer than the presumed duration (between the years 1980-1996). These two possibilities are considered by the ACDP TSE subgroup as not necessarily being mutually exclusive nor fully satisfactory.

#### Previous estimates of prevalence of abnormal prion in humans

Primary studies (published after 2005) that provide estimates for subclinical CJD in the general population based on analysis of peripheral tissue are displayed in Table 4. Central estimates range between 0 per million population and 493 per million population. Studies providing evidence of the prevalence of vCJD prions in lymphoid tissues published prior to 2005 are described in a review published by Olsen *et al* (2005).89 This review includes the cross-sectional study by Hilton *et al* (2004) which estimated the prevalence in the sample population to be 120 per million from 11,228 appendices.

Table 4: Studies estimating the prevalence of CJD from peripheral tissue samples, published after 2005

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Study | Design | No. samples | Predicted/estimated prevalence | Description of estimation |
| Gill *et al* 201388 | UK histological analysis of appendix samples from the 1941-60 and 1961-85 birth cohorts | 32,441 | 1 in 2000 or 493 per million 9 (95% CI 282 to 801 per million)  1941-60 = 733 per million (95% CI 269-1596 per million)  1961-85 = 412 per million (95% CI 198 – 758 per million) | Found 16 to be positive for subclinical abnormal prion protein PrP  50% of the 16 positive samples were MM, 25% MV, and 25% VV |
| De Marco *et al* 201090 | Two estimations based on UK tonsil tissue samples from the 1961-1985 birth cohort | 10,075 | High: 109 per million (95% CI 3-608 per million)  Low: 0 per million (95% CI 0-403 per million for the 1961-1985 cohort) | One specimen showed both positive and negative on further tests so the 2 estimates reflect both positive and negative scenarios |
| Clewley *et al* 200991 | UK estimation combining tonsil tissue samples | 63,007  (32,661 from the 1961-95 cohorts) | 0 per million (95% CI 0-289 per million [1961-85 cohort]; 0-113 per million [1961-1995 cohort]; 0-185 per million [1986-95 cohort]; 0-122 per million [1996-2007 cohort]) | Zero positive results from 63007 tonsil specimens from the birth cohort in Britain in which most cases of vCJD have occurred |

#### Obtaining definitive prevalence estimations

Subclinical vCJD can be detected via typical PrP staining in lymphoid tissue or observation of the presence of florid plaques in the brain at autopsy; however, systematic lymphoid or neuropathological examination is not performed routinely in post-mortems. In order to collect a truly accurate picture of the prevalence of CJD in abnormal prion protein in humans, the UK Health Protection Agency proposed the creation of a post-mortem tissue archive.92 The study required tissue from a large number of post-mortems, necessitating the participation of coroners in England and Wales. However, the Coroners’ Society of England and Wales (CSEW) declined to participate in the study, citing various issues including its putative legality, cost and feasibility.93 The CSEW concluded that to participate in the study would, “*adversely affect the independence of the coronial service and would further erode public confidence*”. McGowan *et al* (2011) describe that since death investigation systems with substantial independence are not directly answerable to central government, they cannot be instructed to participate in any disease surveillance programme regardless of how crucial it is to the protection of human health and safety.

### *2.2.3 Discussion/ summary of incidence and prevalence of CJD*

Incidence of CJD is relatively stable around the world (between 1 and 2 cases per million population) but age-adjusted detection of sCJD is increasing in the UK as well as certain other countries. Reasons posited for this increase include improved case ascertainment and an ageing population. The estimated prevalence of subclinical vCJD from lymphoid tissues of people in the UK who were exposed to the BSE epidemic was 1 in 2,000 and the estimate of prevalence of CJD-related prions in lymphoid tissues in the UK population who are not thought to be exposed to the BSE epidemic is 1 in 4,200. This suggests a potentially 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 CJD. Estimations of prevalence are currently limited to retrospective cohort studies of anonymised tonsil or appendix samples.

## 2.3 The risk of CJD transmission via surgery

The literature searches retrieved no further published papers from the period of 2005 to 2017 of confirmed cases of surgically transmitted CJD, further to the four neurosurgical cases which are noted to have occurred between the years 1952 and 1974.3 These four historic cases (three in the UK and one in France) are distinct from the known dura mater and hGH iCJD cohorts, and occurred prior to the vCJD epidemic which began in the late 1980s. The four historic surgical cases therefore represent a small proportion of the known iCJD cases (469 iCJD cases according to Brown *et al* (2012))3 and occurred when methods for cleaning surgical instruments were not adequate assuming current decontamination standards. Consequently, the risk of CJD transmission via surgery according to recent direct evidence appears to be low. However, the long asymptomatic incubation periods noted in some cases of CJD, the difficulties of eradicating prions from neurosurgical instruments (especially once fixed to dry instruments), the high levels of infectivity of CJD in the brain and a presumed subclinical underlying prevalence (albeit low) in the general population mean that there is a margin of uncertainty around detecting and quantifying the risk of CJD transmission via surgery.

### *2.3.1 Observational studies implicating surgery in CJD*

Despite the absence of studies providing direct evidence of further cases of surgically transmitted CJD, a number of papers were identified which allude to a potential relationship between CJD cases and prior surgery. Papers which investigate but do not provide evidence of a direct link to surgery are listed in Table 5.

Table 5: Studies reporting links between CJD and surgery published between 2005-2017

|  |  |  |
| --- | --- | --- |
| **Study** | **Design** | **Source** |
| Kobayashi *et al* (2016)94-96 | Two historic sCJD cases with neuropathological and biochemical features of plaque-type dura mater-acquired-CJD. The authors posit that these cases (a neurosurgeon and a patient with a medical history of neurosurgery without dura mater grafting) represent iCJD through cross-contamination from neurosurgical instruments or through occupational exposure as a neurosurgeon. | Two published papers and conference abstract |
| Gnanajothy *et al* (2013)97 | Case report of 64-year-old man diagnosed with CJD (type of CJD not reported) three months after cataract surgery. The authors discuss the possibility that ophthalmologic surgery events might occur due to visual symptoms at the onset of the disease rather than the procedure itself transmitting the disease. | Published paper |
| Tuck *et al* (2013)98 | Case report of sCJD which was posited to be iCJD via surgery due to the patient’s young age. At 33 years of age, the patient experienced progressive deficits over 3 months.  Review of medical history revealed that a ventriculo-peritoneal shunt was placed at age 11 for hydrocephalus. Autopsy results were consistent with sCJD. | Conference abstract |
| Moreno *et al* (2013)99 | Surveillance study in Meixoeiro Hospital (Spain) reported 12 cases of CJD (ten sCJD and two gCJD) over the period 1997-2010, which represented a high average yearly rate of 4.6 per million (3.8 for sCJD and 0.8 for gCJD). According to the Poisson distribution for the 12 cases (with an expected annual incidence of 1.5 cases per million) only 3.9 cases would have been expected over such a 14-year period. Eight out of the 12 CJD cases had undergone at least one surgical or invasive medical procedure. | Published paper |
| Puopolo *et al* (2011)100 | A case-control study found that ‘history of surgery’ was more frequent in sCJD cases (n=13 (2%) neurosurgery= 12; cornea transplantation= 1), versus no-CJD cases (n=5, neurosurgery=5 (1%)) and none in genetic TSE patients. A crude OR of 1.57 (95% CI 1.14-2.16) was reported. Results did not reach statistical significance when adjusted for a 10-year-time lag. | Published paper (included in de Pedro *et al* (2012)) |
| De Pedro Cuesta *et al* (2011)101  Mahillo-Fernandez *et al* (2008)102 | A case-control study of sCJD to look for risk factors from 167 sCJD cases in Denmark and Sweden. Surgery for ‘lower risk procedures’ (i.e. surgery to veins, peritoneal cavity and lymph nodes) compared to high risk procedures (i.e., surgery to brain, spinal cord, retina and optic nerve) carried out more than 20 years before disease onset was associated with an increased risk of sCJD (OR 2.81 (95% CI 1.62 to 4.88). When tissues or structures were reclassified by hypothetical transmission risk at a latency of ≥ one year, surgery to the retina and optic nerve were the most strongly associated risk factors (OR 5.53 (95% CI 1.08 to 28.0)). | Two published papers (included in de Pedro *et al* (2012)) |
| Hamaguchi *et al* (2009)103, 104 | A case-control study with 753 sCJD patients and 210 controls in Japan. Surgery was not a risk factor for sCJD prior to disease onset. However, 4.5% of sCJD patients underwent surgery after onset of sCJD, including neurosurgery in 0.8% and ophthalmic surgery in 1.9%. Among the neurosurgery cases, the symptoms of sCJD were misdiagnosed as those of other neurological diseases, and the surgeries were performed near disease onset. Authors conclude that despite absence of empirical evidence of transmission via surgery, the risk of contracting CJD via surgery is still present because patients are operated on after disease onset. | Two published papers (included in de Pedro *et al* (2012)) |
| Ruegger *et al* (2009)105 | A case-control study in Switzerland found 69 sCJD patients, compared with 224 controls, were more likely (p<0.05) to have travelled abroad, worked at an animal laboratory, undergone invasive dental treatment, orthopaedic surgery, ophthalmologic surgery after 1980, regular GP visits, taken medication regularly, and consumed kidney. No differences between patients and controls were found for residency, family history, and exposure to environmental and other dietary factors. Other types of surgery were not found to be a possible factor. Previous under-reporting / misdiagnosis was proposed as the most likely explanation for the increased annual mortality. | Published paper (included in de Pedro *et al* (2012)) |
| Ward *et al* (2006)106 | Case-control study of 136 vCJD patients and 922 controls. Investigation of risk factors in the UK identified dietary exposure to contaminated beef products as the main route of infection of vCJD with no convincing evidence of increased risk through medical, surgical, or occupational exposure or exposure to animals. | Published paper (included in de Pedro *et al* (2012)) |
| Ward *et al* (2008)107 | A case-control study in the UK of 431 sCJD patients, compared with 454 controls, found increased risk was not associated with surgical categories chosen *a priori* but appeared most marked for ‘other surgery’, especially the three subcategories: skin stitches, nose/throat operations, and removal of growths/cysts/moles. No convincing evidence was found of links between cases undergoing neurosurgery or gynaecological surgery. | Published paper (included in de Pedro *et al* (2012)) |

#### Issues of reliability and validity in case control studies

As sCJD is idiopathic, its etiological basis is presumed to be spontaneous but this is not known with any certainty.85 Therefore, case-control studies are a frequently encountered design in estimating possible and plausible risk factors for sCJD. De Pedro Cuesta *et al* (2012)108 caution about the potential biases in these study designs in an assessment of 18 case-control studies in CJD. From a combined analysis of studies, the authors found that history of surgery or blood transfusion was associated with sCJD risk in some, but not all, recent studies using a 10-year or longer lag time, when controls were longitudinally sampled. Further, they found that neither surgical history nor blood transfusion, dental treatments or endoscopic examinations were linked to vCJD. However, the authors highlight that the validity of the findings in these 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 at the time of surgery. They also postulate that surgery at early clinical onset might be overrepresented among cases.

As a retrospective study design, case-control studies are inevitably prone to bias. The source of cases and the selection of control (matched or unmatched) cannot be performed blindly or impartially therefore there is a high risk of selection bias on the researcher’s part. Due to long incubation periods and the reliance on family members’ reports of medical histories, there is also substantial likelihood of recall bias. Case-control designs are also less useful when the study exposures are rare, as in the case of surgery or blood transfusion. Therefore, the utility of these studies in attempting to fairly estimate risk factors is limited. However, as CJD is rare, fatal and has a potentially long latency period, there are few plausible alternative study designs to establish potential lifetime risk factors in humans.

#### Risk of CJD through occupational exposure for health professionals

In 2009, the Spanish CJD registry was notified of a case of sporadic CJD in an experienced general pathologist/neuropathologist which prompted investigation into possible risks to health professionals in contact with CJD patients.109 As a result, Alcade-Cabero *et al* (2012)109 reported the data requested from the Euro CJD surveillance network which documented 65 physicians or dentists, (including two pathologists) and 137 healthcare workers from 8,321 registered sCJD cases from 21 countries. Control data using ‘non-cases’ from five countries recorded 15 physicians and 68 other health professionals among 2,968 controls or non-cases and suggested no relative excess of sCJD among healthcare professionals. The study authors also performed a literature review examining reports (n=12) pertaining to 66 health professionals with sCJD, and analytical studies on health-related occupations and sCJD (n=5). A statistically significant finding was observed only for persons working at physicians’ offices (odds ratio: 4.6 (95% CI: 1.2–17.6)). The authors conclude that a wide spectrum of medical specialities and health professions are represented in sCJD cases and that the data analysed do not support any overall increased occupational risk for health professionals. The authors do add caution that there may be a specific risk in some professions associated with direct contact with high human-infectivity tissue. The NCJDRSU continue to monitor occupational exposure to CJD in health professionals.

#### Risk of CJD in surgery and age

De Pedro Cuesta *et al* (2014) performed a retrospective analysis of 167 cases of sCJD between 1987 to 2003.110 They suggest that a younger age at first surgery may increase the risks of acquiring sCJD with odds ratios of 12.80 (95% CI 2.56-64.0) in patients <30 years, 3.04 (95% 1.26-7.33) in 30-39 years, and 1.75 (95% CI 0.89-3.45) in ≥40 years, for anatomically classified surgical procedures. As highlighted by the same authors in a different study, caution should be urged when interpreting conclusions from analyses on indirect evidence in retrospective samples.108 Also, the ≥40 age group contains those who are elderly and may die before clinical symptoms appear or may remain undiagnosed.

Risk of iCJD transmission through surgery can potentially occur when patients are unwittingly treated in hospital at the time of symptom onset. Cruz *et al* (2013) used a cross-sectional design to study surgical procedures in sCJD patients and controls to estimate subclinical and clinical risks to future surgery.111 The authors posit that patients with sCJD in the clinical stage undergo a considerably higher frequency of surgical procedures than non-CJD patients, including neurosurgery. The authors argue that identification of such potentially higher-risk events, where surgery is undertaken in infectious patients around the onset of clinical symptoms, but prior to CJD diagnosis, might well constitute a priority in clinical settings. A conference abstract by Kobayashi (2016) reinforces this concern by providing data from the Japanese CJD Surveillance registry. From an analysis of 760 CJD patients, Kobayashi *et al* identify that 6 patients had undergone neurosurgery, after the onset, but before the diagnosis of CJD during the period 1999 to 2008.112

#### Cases of suspected but unconfirmed transmission via neurosurgery

Patients may be identified as being “at increased risk” of CJD if they have had surgery using instruments that had been used on someone who went on to develop CJD, or someone who was “at increased risk” of CJD.113 A study by Hall *et al* (2014) reports that 154 patients in the UK are considered “at increased risk” of various forms of CJD following neurosurgery.114 This paper reports that of these 154 patients, only 129 have been informed that they are increased risk either because of deaths before notification or because a local decision was taken not to inform the individual. Whilst no incidence of CJD has been reported within the 154 patients, the authors highlight that “at increased risk” patients often have a relatively short life expectancy given their medical conditions. Diagnosing asymptomatic infection requires the testing of specific tissues that are most readily available at post-mortem and few post-mortems have been conducted when “at increased risk” individuals die; therefore, some asymptomatic infections may have been missed.

Two published papers from the United States report instances where potential iCJD exposure via neurosurgery was investigated in hospitals; however, no confirmed cases of transmission were subsequently identified.115, 116

#### Risks in surgery other than neurosurgery

#### Prospective risks to surgery

A study by Baig *et al* (2013)36 described a case report of a male patient (aged 66) who had surgical fixation of hip fracture, most probably near the onset of CJD-symptoms and therefore the standard sterilisation method was appropriately used. The authors highlight that this decontamination method is typically not adequate for eradication of the CJD prion protein virus, presenting a theoretical risk of prion protein transmission through surgical equipment. The focus of this paper is not on the implication that the patient contracted iCJD via surgical transmission but is in fact highlighting a circumstance where subsequent iatrogenic transmission could may have occurred due to a lack of high-risk decontamination procedures. However, surgery of low infective tissues in individuals diagnosed with CJD is noted to be common,106,107 and therefore this surgery which did not involve high (or medium) infectivity tissues would not be regarded as a risk of iatrogenic transmission.

A recent study by Orr *et al* (2016) found infectivity in the skin of sCJD patients, albeit at prion levels 1,000-100,000 times lower than in the brain and only detectable by an extremely sensitive assay.117, 118 However, a study using humanized transgenic mouse models demonstrated that the skin prions were infectious. The study authors argue that extra precautions should be taken during non-neurosurgeries of sCJD patients particularly when instruments will be re-used, as previously infectivity through skin was unknown.

A study by Notari *et al* (2010) found from a neuropathological examination of a vCJD case in the US that as well as detection of PrPres in the brain, lymphoreticular system, pituitary and adrenal glands, and gastrointestinal tract, PrPres was also detected in the dura mater, liver, pancreas, kidney, ovary, uterus, and skin.119 The authors conclude that the number of organs affected in vCJD is greater than previously realised and this further underscores the risk of iatrogenic transmission in vCJD.

#### Risks in eye surgery

Davanipour *et al* (2014) postulate that ocular tonometry is a risk factor for contracting sCJD from a case-control study conducted across 11 states in the US. Contact tonometry is used by ophthalmologists to diagnose glaucoma. The authors conclude that disposable covers or non-contact tonometry should be used in the absence of adequate decontamination processes.120

Tullo *et al* (2006) document three recipients of either cornea or sclera from a woman who died of biopsy-proven carcinoma of the bronchus in 1997 but was later neuropathologically identified as having sCJD.121 At the time of publication, two recipients remained symptom-free of CJD whilst one patient had died, aged 92 (seven years after surgery), showing some signs of dementia that were not considered indicative of iCJD.

Jirsova *et al* (2010)122 conducted an analysis of brain tissue samples from the frontal lobe of 1142 eye donors obtained from 3 tissue banks in the Czech Republic. As no pathogenic prions were found, the authors presume a very low risk of transmission of CJD through corneal graft transplantation. However, the authors’ conclusion can be regarded as a logical fallacy, denying the antecedent, because in the absence of sCJD cases in the analysis, it is not possible to conclude on the risk of CJD transmission via surgery in corneal graft transplantation. Additionally, Maddox *et al* (2008) used data from corneal transplantation and CJD deaths from 1990 to 2006 in a statistical analysis to suggest that a case of coincidental sporadic CJD will occur among the population of corneal transplant recipients approximately every 1.5 years.123

#### Risks in dentistry

Bourvis *et al* (2007) conducted a risk assessment of the transmission of sCJD in endodontic treatment in the absence of adequate prion inactivation.124 The authors developed a mathematical model incorporating experimental and observational data and expert consultation and estimated that without effective prion-deactivation procedures, the risk of being infected during endodontic treatment ranged between 3.4 and 13 per million procedures. The authors consider that strict respect of the official recommendations on decontamination procedures are essential in dentistry, and even suggest that the cost-benefit of single-use endodontic instruments should be re-evaluated. Everington *et al* (2007) found no evidence of increased risk of vCJD associated with reported dental treatments using a case-control study of UK vCJD patients.125 However, the authors do not rule out the possibility that some cases may have resulted from secondary transmission via dental procedures. Azarpazhooh *et al* (2008) highlight that whilst no definite cases of prion disease transmission have been reported, the theoretical risk from dental instruments is low but real and, as a general rule, appropriate family and medical history (including the risk for prion diseases) should be obtained from all patients before all dental procedures.126

### *2.3.2 Discussion/ summary of risk of CJD transmission via surgery*

Whilst no studies have identified a new case of surgically-transmitted case of CJD in the search period covered, many speculative case-control reports of the relationship have been conducted. These analyses provide indirect retrospective evidence implicating neurosurgery or surgery as a risk factor for CJD, but their design is known to be at risk of bias and confounding. However, as CJD is rare, fatal and has a potentially extended incubation period, there are few plausible alternative study designs to establish potential lifetime risk factors for CJD in humans.

Indirect evidence points to other factors as relevant to CJD and surgery including younger age at first exposure, increased risk of surgery around the time of symptom onset, risk to health professionals, and risk from procedures where “high-risk” decontamination measures are not in place. Although less relevant to the decision problem, clinical studies have recently demonstrated low levels of CJD infectivity in skin. Considering 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 exits to highlight a serious risk from surgical procedures involving tissues that are not high-risk.

## 2.4 Incubation periods of acquired TSEs

The purpose of this review was to identify published and unpublished evidence for the incubation periods of acquired TSEs, especially CJD, in human populations. Evidence on incubation periods has implications for determining the risk of transmission from surgical procedures. Eighteen full text papers were identified as relevant to incubation periods of acquired TSEs, which are described in Table 6.

### *2.4.1 Studies of incubation periods*

Studies relating to incubation periods of acquired TSEs are described in Table 6.

Table 6: Characteristics of included studies for incubation periods, ordered alphabetically

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Study** | **Design** | **Population** | **Source of infection** | **Location** | **n=** |
| Ae at al (2016)31 | Epidemiological surveillance | iCJD | Dura mater graft | Japan | 149 |
| Brown (2012)3 | Epidemiological surveillance | iCJD | All | International | 469 |
| Brown (2015)6 | Review | iCJD | Neurosurgery | International | 6 |
| Chohan *et al* (2010)78 | Case study | iCJD | Blood products | UK | 1 |
| Collinge *et al* (2008a)127 | Epidemiological surveillance, cohort | Kuru | Ingestion | Papua New Guinea | 11 |
| Collinge *et al* (2008b)128 | Review | Kuru | Ingestion | Papua New Guinea | NA |
| Collinge *et al* (2006a)129 | Epidemiological surveillance, cohort | Kuru | Ingestion | Papua New Guinea | 11 |
| Collinge *et al* (2006b)130 | Letter: reply re: 2006b | Kuru | Ingestion | Papua New Guinea | NA |
| Davidson *et al* (2014)79 | Retrospective cohort | iCJD | Blood products | UK | 9 |
| Haïk *et al* (2014)131 | Review | CJD | All | International | N/A |
| Hamaguchi *et al* (2013)132 | Epidemiological surveillance | iCJD | Dura mater graft | Japan and international | 195 |
| Heath *et al* (2006)133 | Epidemiological surveillance | iCJD | Dura mater graft | UK | 8 |
| Hirst *et al* (2005)134 | Epidemiological surveillance | iCJD | Human Growth Hormone | UK | 1 |
| Peden *et al* (2010)72 | Case study | iCJD | Blood products | UK | 3 |
| Meissner *et al* (2009)135 | Retrospective cohort | iCJD | Dura mater graft | Germany | 10 |
| Ritchie *et al* (2017)136 | Epidemiological surveillance, retrospective cohort | iCJD | Human Growth Hormone, Dura mater graft | UK | 37 |
| Rudge *et al* (2015)64 | Epidemiological surveillance, cohort | iCJD | Human Growth Hormone | UK | 22 |
| Wroe *et al* (2006)137 | Case study | iCJD | Blood products | UK | 1 |

The diagnosis of definite or probable iCJD depends on identification of the probable source of contamination to which patients have been exposed, as well as fulfilling the basic requirements for the definite or probable diagnosis of CJD. Wherever possible, only the most recent and/or up-to-date data are presented, unless there is potential value in comparisons with data from earlier samples or earlier publications which provide relevant details that are not reproduced in the more recent papers.

Table 7: Reported number of cases of iCJD (worldwide and UK) and incubation periods (mean and range)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Source of infection | No. cases | | Incubation periods for overall data | | Studies / reports |
|  | Overall | UK only | mean, years | (range, years) |  |
| Primary transmission |  | | | | |
| vCJD from ingestion / BSE | 229 | 175a | 12 | (-) | Haik (2014)131, NCJDRSU (2017)113 |
| Kuru | - | 0 | 12\* | (4 to >40) | Haik 2014131, Collinge (2006)129, Ritchie (2017)136 |
| Secondary transmission |  | | | | |
| Dura mater graft | 228 | 8 | 12 | (1.3 to 30) | Brown (2012)3, Haik (2014)131 |
| Neurosurgical instruments | 4† | 3 | 1.4 | (1 to 2.3) | Brown (2015)6, Brown (2012)3, Haik (2014)131 |
| EEG needles | 2 | 0 | - | (1.3, 1.7) | Brown (2015)6, Brown (2012)3, Haik (2014)131 |
| Corneal transplant | 2 | 0 | - | (1.5, 27) | Brown (2012)3, Haik (2014)131 |
| Growth hormone | 226 | 78  21 | 17  20 | (5 to 42)§  (8-31) | Ritchie (2017)136  Ritchie (2017) Online Table 1 |
| Gonadotropin | 4 | 0 | 13.5 | (12 to 16) | Brown (2012)3 |
| Packed red blood cells | 3  2 | 3  2 | - | (6.5 to 8.3) ‡ | Brown (2012)3, Haik (2014)131  Wroe (2006)137, Peden (2004)73, Ironside (2010)138; Chohan (2010)78 |
| Total (secondary) | 471 | 81 |  |  |  |

a UK only: Advisory Committee on Dangerous Pathogens 2016; National CJD Research and Surveillance Unit (<https://www.cjd.ed.ac.uk/> ) n= 178 (but this includes the three cases of blood transfusion). However, no incubation data were provided.

\*Collinge *et al* (2008a) reported 11 new cases from 1996-2004 with a much longer mean incubation period of 48.7 years (range 39 to 56 years) and with a much higher proportion of heterozygotes: 80% compared with <50% in earlier samples (Cervenova *et al* 1998, Klitzman *et al* 1984).

†Possible additional probable cases of iCJD as a result of neurosurgery have also recently been identified (Brown 2015; Kobayashi 2015, Xiao 2014), but no incubation data are available.

‡Incubation data are only available for the three clinical cases; two cases were non-clinical, i.e. there was transmission by transfusion but the patients died asymptomatic.

§Based on assumed midpoint date of multiyear periods of treatment, and the onset of symptoms (Brown 2012)

#### UK data on incubation

A summary of data on incubation from iatrogenic CJD in the UK is presented in Table 8.

Table 8: UK only data for iCJD incubation periods (reported or calculated by the reviewer in years)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Source of infection | No. cases | Mean incubation period, years | (range, years) | Studies / reports |
| Dura mater graft  1990-2012§ | 8\*  3 | 7.8†  11\*\* | (3.8–14.8) †  (8-15) | Heath (2006)133, Ritchie (2017)136\*\* |
| Neurosurgical instruments | 3 | 1.4 | (1.3, 1.5, 1.6) | Brown (2015)6 |
| EEG needles | 0 | NA | NA | - |
| Corneal transplant | 0 | NA | NA | - |
| Growth hormone  1990-2012§ | 78  65  21 | NR  20  19 | NR  (7-39)  (11-31) | Ritchie (2017)136  Brown (2012)3  Ritchie 136 2017\*\* |
| Gonadotropin | 0 | NA | NA | - |
| Packed red blood cells | 3 | - | (6.5-8.3) | Brown (2012)3,  Haik (2014)131 |

\*1, of which was a porcine not human source of graft, †Data reported as months, calculated by the reviewer as years \*\*Supplementary online Table 1 §Sample with frozen tissues from patients who died 1990-2012

#### Dura mater grafts and genotypes

Frequency data and mean incubation periods by genotype are presented in Table 9 for the UK subset of the known cases only. As reported in Table 9, the worldwide number of iCJD cases due to dura mater surgery worldwide exceeds 200, and it is known that the majority have occurred in Japan (n=149, Ae 201631). Frequency data and mean incubation periods by genotype, extracted from Brown (2012)3, are presented in Table 9 for a subset of the worldwide affected population. Hamaguchi *et al* (2013)139 reported a mean incubation period of 12.1 years (range 1-30) for 142 patients in Japan and 11.3 years (range 1-23) for a subset of 53 patients with published data from the other countries, although this sub-set did not include a Dutch case of DM-related iCJD that had an incubation period of 28 years, which is the longest reported incubation period outside of Japan.140

Meissner (2009)135 reported on a sample of 10 cases (9 from Germany, 1 from Croatia) of iCJD related to dura mater identified in the years 1993-2006. The median incubation was 18 years (range, 9-23 years), with 90% being homozygotes, principally of the MM genotype (80%). This study also reviewed published evidence from the literature on 27 international patients with iCJD due to dura mater grafts and having MRI data. Data on incubation periods were available for 22 of these patients: the mean incubation period was 11.5 years (range 1.6 – 23 years), with 95% being homozygotes, principally of the MM genotype (81%).

#### Human growth hormone and genotypes

Table 10 presents frequency data and mean incubation periods by genotype for a subset of the known cases due to hGH. It is reported that one particular preparation of hGH was most probably responsible for cases of iCJD due to hGH in the UK to date (Rudge (2015)64, Brown (2012)3). As reported in Table 7, 78 cases had been reported in the literature for the UK as of 2017 (Ritchie 2017), an increase from the 65 cases reported by Rudge *et al* (2015)64 previously. Ritchie *et al* (2017)136 present data on subsets of 21 and 37 patients with available tissue samples; analysis was conducted on frozen tissue samples for the former group. Both samples demonstrated the same pattern: patients with the MM genotype were fewer and had consistently longer incubation periods; the VV genotype had the shortest mean incubation period. The heterozygous genotype MV was the most frequently identified in both subsets. There is potential for some crossover of data, and therefore inconsistency, between included studies which cannot be accounted for in this review.

These findings were broadly similar to those reported for another subset analysis of iCJD patients using imaging, molecular and autopsy data by Rudge (2015).64 Rudge (2015)64 present data on a subset of 22 patients from 56 patients with genotypic data available. They studied a cohort of 22 patients diagnosed from 2000 to 2014 and combined relevant data from these patients with data for 34 published cases up to 2000. In the cohort of 22 patients, Rudge (2015)64 presented a range of possible incubation times calculated from: 1) the last injection of any type of growth hormone to onset of symptoms; 2) the midpoint of that series of injections to onset of symptoms; and 3) the first injection to onset of symptoms. The mean and ranges were as follows: 1) mean 25.9 years (range 18.3–33.6); 2) mean 29.3 years (range 20.6–37.6); 3) mean 32.8 years (range 23.2–43.3) (Rudge 2015).64 Rudge (2015)64 also compared incubation times between the cohort of 22 patients and a large subset of the UK group as whole. The mean incubation times were longer in the later cohort, but there was a noteworthy change in the proportion of MM and VV homozygote genotypes between the two periods: there was only a single case of the VV genotype in the period 2000-2014, with 14 occurring before 1998 Rudge (2015),64 while seven of the eight MM homozygotes occurred after 2004 Rudge (2015).64 These findings are quite distinct from those for dura mater grafts in terms of the distribution of genotypes and their incubation periods: incubation periods for iCJD due to dura mater grafts appear shorter and are dominated by the MM genotype (Table 9). The group with iCJD affected by hGH are also equally distinct, in terms of genotype, from individuals with sCJD (Ritchie (2017)136).

Table 9: Mean incubation periods by genotype for iCJD due to dura mater grafts

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Location | No. cases | MM | | MV | | VV | |
| Frequency | Incubation period | Frequency | Incubation period | Frequency | Incubation period |
| Not Japan 3, 132 | 54† | 65% | 12 years | 20% | 16 years | 15% | 12 years |
| Japan\* 3, 132 | 54§ | 96% | 16 years | 4% | 13 years | 0% | - |
|  | | | | | | | |
|  |  | Homozygous | | Homozygotes | | Heterozygotes | |
|  |  | Frequency | | Incubation period | | Incubation period | |
| Not Japan |  | 80%† | | 12 years | | 16 years | |
| Japan\* |  | 96% | | 16 years | | 13 years | |

\*142/228 known worldwide cases are from Japan (Brown 2012, Hamaguchi 2013): Note: According to an abstract by Ae 2016, 149 cases now reported in Japan, with a mean incubation period of 13 years and a maximum period of 30 years. † Hamaguchi 2013 reports data for a subset of 29 patients with both MM and MV mean incubation periods being 13 years, with 74.3% of a subset of 35 patients being homozygotes. §Hamaguchi (2013) reports the same figures for 58 patients.

Table 10: Mean incubation periods reported from included studies by genotype for iCJD due to human growth hormone

| Location | Cases with genotype data / Total known cases | MM | | MV | | VV | | Homozygotes | | Heterozygotes | Studies |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Frequency | Incubation period | Frequency | Incubation period | Frequency | Incubation period | Frequency | Incubation period | Incubation period |
| UK | 21/78 (1990-2012§) | 10%  (n=2) | 30 years | 57%  (n=12) | 18.5 years | 33%  (n=7) | 15.7 years | 43% | 19 years | 19 years | Ritchie 2017\*\*136 |
|  | 37 | 10% |  | 68% |  | 22% |  | 32% |  |  | Ritchie (2017)136 |
|  | 56/65 | 14%  (n=8) | 30.8 years | 59%  (n=33) | 23.4 years | 27%  (n=15) | 14.3 years | 41% |  | 23 years | Rudge (2015)64 |
| 22 (2000-2014) | 18%  (n=4) | 31.8 years | 77% (n=17) | 28.6 years | 5%  (n=1) | 20.6 years | 23% |  | 29 years | Rudge (2015)64 |
| 28 | 4%  (n=1) | 21 years | 50% (n=13) | 23 years | 46% (n=14) | 18 years | 54% | 20 years | 23 years | Brown (2012)3 |
| France | 111/119 | 54% | 12 years |  |  | 15% | 9 years | 69% | 11 years | 17 years | Brown (2012)3, }, Haik (2014)131 |
| USA | 11/29 | 55% | 21 years |  |  | 18% | 18 years | 73% | 20 years | 23 years | Brown (2012)3 |

\*\*Online Tables 1 and 3 §Sample with frozen tissues from patients who died 1990-2012 Hirst (2005) reports a case of hGH with an incubation period of 24 years.

### *2.4.2 Discussion/ summary of incubation data*

The incubation periods in CJD reported in the published literature range from 1 to 42 years with the shortest durations occurring in surgically transmitted iCJD and the longest occurring in Kuru or iCJD via hGH. Different incubation times might occur due to the resistance of different genotypes. Evidence from kuru studies (Collinge (2006a)129, Collinge (2008b)128) 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), which has longer incubation times: older survivors are more likely to be MV (heterozygous) (Collinge (2008a)127, Collinge (2006b)130). However, the hGH data suggest that this might not always be the case, given the 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 (Haik *et al* 2014,131 Ritchie *et al* 2017).136 For example, most cases of hGH-iCJD in France were of MM genotype, whilst in the UK the VV and MV genotypes predominate. Infections in that appear to affect certain genotypes per location may reflect an absence of genotypic resistance to a particular strain, and thus shorter incubation times. Hence, it is believed that 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 (Brown *et al* 2012).3

Diagnoses of sCJD could potentially be made that are actually iatrogenic in origin. Correct identification can be difficult if cases of iCJD may initially be presenting as sCJD. Ritchie (2017)136and Kobayashi (2015)141 report that some of the MM1 genotype present as sCJD, but others might be able to be distinguished as iCJD based on the presence of kuru plaques: this has been demonstrated for hGH in the UK by Ritchie (2017).136 Consequently, there might be more evidence forthcoming on incubation of iCJD as more cases are identified that previously were considered to be sCJD, but revised to iCJD following neuropathological examination.

## 2.5 The infectivity of CJD

The purpose of this review was to identify relevant published and unpublished evidence on the infectiousness of CJD in terms of CJD type, subtype or prion strain, genotype of the recipient, infectivity of infectious tissue, and the infectious mass required to transmit CJD.

Few relevant papers addressing the research question in humans were identified; however, 38 papers from a range of scientific approaches were found to highlight themes that potentially relate to CJD infectivity. Therefore, papers were organised thematically for CJD infectivity and are presented as a narrative secondary discourse.

### *2.5.1 Studies discussing the infectivity of CJD*

#### Infectious mass required to transmit CJD

The risk of any individual becoming infected by CJD is considered to be related to the dose of infectious material received. A quantitative estimation of infectivity in CJD is traditionally ascertained using end-point dilution titration and is expressed as median infective dose in terms of ID50s. One ID50 is considered to be the dose needed to infect 50% of individuals receiving it.

No new evidence regarding the quantity of infective material required to transmit CJD in humans was identified in the period covered by the searches. The estimations used in the original mathematical model to estimate risk of vCJD transmission via surgery (Stevenson *et al* (2009)12 and Bennett *et al* (2005)13) and implemented in IPG196 reported in Table 11).

Table 11: Estimated infectious titre of human tissue by surgical procedure in NICE IPG196

|  |  |  |
| --- | --- | --- |
| Risk of CJD transmission | Surgical procedure | Infectivity |
| High | Brain and pituitary gland  Posterior eye, retina and optic nerve  Intradural spine operations  Neuroendoscopy | 108 ID50s / g |
| Medium | Spinal cord  Tonsils  Spleen  Lymphoid tissue  anterior eye  peripheral nerves | 106 ID50s / g  105.5 ID50s / g  105.5 ID50s / g  104.5 ID50s / g  103.5 ID50s / g |

Higher infectious titres than those estimated in Table 11 have been detected in animal studies using novel methods for end-point titration. For example, Makarava *et al* (2012) used protein misfolding cyclic amplification with beads (PMCAb) to propagate PrPSc in Syrian hamsters.142 Using this method they were able to detect infectious titres ranging from 108.6 to 10.12.8 A study by Halliez *et al* (2014) also found that it was possible to detect higher levels of vCJD infectious titre in a human spleen using a novel spleen-based, compared with gold-standard immunoblot bioassay.143 As methods for end-point titration improve, it is therefore likely that some variation to the estimated titres used in IPG196 and noted in Table 11 will be observed in the future.

#### Codon 129 genotype and susceptibility

All individuals, irrespective of genotype at codon 129 (MM, MV or VV), are now known to be susceptible to sCJD and secondary transmission of vCJD through routes such as blood transfusion, but the phenotype (or observable physical properties) for MV and VV cases has been noted to be less predictable due to reduced transmission efficiency and increased incubation periods.74, 85 The vCJD prion or agent appears to replicate in lymphoid tissues during the asymptomatic phase of the incubation period.144 Study of abnormal prion protein accumulation in peripheral tissues from MV individuals has been undertaken to understand infectivity and the risk of horizontal transmission. Bishop *et al* (2013) inoculated mice with brain and spleen samples from the subclinical vCJD recipient as well as the clinical vCJD donor.145 They found transmission of vCJD to mice from the spleen, but not from the brain of the subclinical vCJD recipient, whereas there was transmission from both the spleen and the brain tissues from the clinical vCJD donor. The authors conclude that spleen tissue from MV genotype can propagate the vCJD agent and that the infectious agent can be present in the spleen without CNS involvement and that 'silent' spread within the human population is therefore a possibility from heterozygous carriers. This finding was also echoed by Halliez *et al* (2014) in their evaluation of novel methods for end-point titration for vCJD in the human spleen. The authors posit the notion that lymphoid tissue exhibits a higher capacity than the brain to replicate prions even after low-dose infection and highlight as a key issue potential silent carriers of vCJD in lymphoid tissue.143

#### Subtype or phenotype of CJD

In sCJD, an interaction between host genotype at codon 129 and the causative agent identified as either PrPSc type 1 or type 2 produces different clinical and histopathological phenotypic expressions which may also be potentially influenced by other factors such as route of infection or locations of the initial PrPSc conversion.146 In sCJD, six major subtypes carrying diverse clinical and pathological features have been identified: (i) MM1/MV1; (ii) VV2; (iii) MV 2K; (iv) MM 2-cortical (MM2C); (v) MM2-thalamic (MM2T) or sporadic FI; and (vi) VV1.147 All subtypes have been found to be transmissible to at least one genotype in mice studies (Bishop *et al* 2010).148 Four major prion strains have been proposed to underlie sCJD, iCJD, Kuru and some gCJD cases termed M1, V2, M2 and V1.85 Variant CJD, however, can be distinguished from other categories of CJD due to the unique PrPres biochemicalglycotype referred to as type 2B or type 4, also found in cases of natural BSE and other BSE-related conditions.86

Definitive information on the phenotype can be identified only following neuropathological examination which provides the opportunity to establish whether CJD may have been acquired as opposed to sporadic or genetic causes. Kobayashi *et al* (2016),94 for example, propose the distinctive combination of 129M/M genotype, kuru plaques, and intermediate type PrPSc, as a reliable criterion for the identification of iatrogenically acquired CJD cases among presumed sporadic cases. Additionally, some studies highlight that whilst exclusive type 1 (sCJDMM1) or type 2 (sCJDMM2) cases do exist, a frequent co-occurrence has been noted of both PrPSc types 1 and 2 in sCJD in different areas, or the same area, of the brain from a single sCJD patient.149 This finding complicates the diagnosis and the current classification of sCJD146 with Parchi *et al* (2009) highlighting the importance of assessing the cerebral cortex from each of the 4 lobes (striatum, hippocampus, thalamus and cerebellum) to avoid misclassification of disease.147 For example, Jansen *et al* (2012) report from an analysis of CJD cases in the Netherlands that a "pure" phenotype was demonstrated in 60.1% of patients, whereas a mixed phenotype was detected in 39.9% of all sCJD cases.150 Similarly, an abstract by Mackay *et al* (2013) reports that 26 of 108 sCJD patients (24%) had both type 1 and 2 proteins on western blot analysis.151 Mackay *et al* argue that the lack of distinct clinical or pathological findings in the six discrete subtypes suggest that these groups do not represent unique strains of prions, but rather groupings over a spectrum of disease. These findings underline the importance of neuropathological assessment of CJD cases to document phenotypic variability and help to disclose the aetiology of CJD strains and efficiency of transmission, where possible.

#### Route of transmission

Route of transmission may also be relevant to infectivity of iCJD. A study of five dura mater iCJD cases conducted by Iwasaki *et al* (2008) indicated that the initial symptoms at perceived sCJD onset appear to be closely related to the graft site in the brain, indicating a direct transmission of CJD from the graft site to the adjacent brain.152 Sakai *et al* (2013) also support the finding of a relationship between initial clinical manifestation and the site of graft in patients with dura mater graft-associated CJD.153 Beringue *et al* (2008) demonstrated in a study of transgenic mice that prion strain divergence can occur upon transmission of human, primary vCJD, and that peripheral exposure in mice resulted in inefficient neuroinvasion with asymptomatic, life-long infection of the lymphoid compartment.154

Beringue *et al* (2008) raise the possibility that human-to-human transmission of vCJD might produce alternative neuropathological phenotypes and that lymphoid tissue examination of CJD cases classified as sporadic might reveal an infection by vCJD-type prions.155 Cali *et al* (2015) demonstrated that novel phenotypes may arise potentially due to adaptation of heterologous prion strains of sCJD through contaminated growth hormone.156 A conference abstract by Peden *et al* (2016) also describes that human-to-human transmission of prion disease may affect the seeding properties of PrPSc associated with the disease.157 Their analysis compared the seeding properties of iCJD tissue samples (including both hGH and dura mater) with sCJD tissue samples using a real-time quaking-induced conversion (RT-QuIC) assay, which showed lower seeding properties for secondary iCJD cases than for sCJD cases. The authors note that their findings refute the hypothesis that secondary transmission of a human prion disease results in acquired virulence (or harmfulness). This is supported by a study by Galeno *et al* (2017) who found that a novel strain from an atypical CJD in a heterogeneous 69-year old woman who had been treated with phospholipids extracted from bovine brains was not transmissible to transgenic mice but transmitted exclusively to bank voles. The authors note that bank voles are susceptible to a variety of human and animal prions with an efficacy that is often higher than that observed in transgenic mice.63

#### Detection of CJD

Whether and when asymptomatic carriers of CJD become infectious is important in understanding the potential risks of contamination during surgery. 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.158 The authors report that the ability to identify presymptomatic (n=2) and symptomatic (n=18) vCJD positives in blinded cohort of 256 plasma samples comprising sCJD, Alzheimer’s disease, Parkinson’s, other neurological diseases and healthy controls indicates the possibility of detecting incubating or silent carriage of vCJD prions.

Identification of abnormal prion accumulation in peripheral lymphoreticular tissue is commonly considered to be a marker of subclinical vCJD that may subsequently develop into clinical CJD. However, the reliability of this marker for representing subclinical or indeed, clinical, vCJD has been questioned. Mead *et al* (2014) highlight a case of clinical vCJD whose presentation, imaging findings, cerebrospinal fluid investigation results, and clinical progression were typical of other vCJD cases. However, subsequent examination of multiple tissues from biopsy and at autopsy showed minimal deposition of disease-associated prion protein in tonsil tissue.159 This patient also received a negative score from a blood test specifically for vCJD, the direct detection assay. The authors note that this case demonstrates that even patients with end-stage vCJD may have minimal prion colonisation in lymphoreticular tissue.

Absence versus presence of abnormal prion accumulation may occur due to the sensitivity of the CJD assay employed. Examination of 14-3-3 proteins in cerebrospinal fluid and RT-QuIC assay are commonly employed tests considered to be sensitive and specific for sCJD detection, although less so for vCJD.160 For example, the identified heterozygous clinical vCJD patient, aged 36 years in 201633 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 (PMCA) assay to assess abnormal prion accumulation in the identified heterozygous subclinical vCJD patient, aged 82 years in 2017.161 Previous investigations had not detected abnormal prion protein or infectivity in the brain indicating a lack of central nervous system (CNS) involvement at the time of death.73, 145 However, 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 authors caution that the identification of wide vCJD involvement in the peripheral tissues of a preclinical patient further indicates the potential for iatrogenic transmission of this fatal neurologic condition by surgical procedures.

#### Transmission to and from peripheral tissues

The infectious load is known to be higher in certain tissues, such as CNS tissues14, and therefore the risk of infectivity from peripheral tissue has been questioned. Studies report conflicting findings regarding the infectivity of peripheral tissues. For example, Bishop *et al* (2013, 2010) reported that spleen tissue from the MV preclinical vCJD blood recipient was transmissible in a study using transgenic and wild-type mice. The authors highlight that significant levels of infectious agent are present in the spleen before CNS involvement.145, 162 However, Wadsworth *et al* (2011) found from an animal study of transgenic mice that whilst vCJD prion infection was readily reported following inoculation with frozen vCJD brain or appendix, and also formalin-fixed, paraffin-embedded (FFPE) brain, no infectivity was detected from FFPE vCJD spleen or FFPE appendix samples.163 The authors caution that the absence of detectable infectivity in fixed, known positive vCJD lymphoreticular tissue precludes interpreting negative transmissions from vCJD prevalence study using appendix specimens. However, in contrast, Halliez *et al* (2014), more recently found that lymphoid tissue exhibited higher capacity than the brain to replicate prions using novel detection methods.143

#### Infectivity of genetic CJD

The potential for horizontal transmission of gCJD, discussed previously, was raised due to unusually high prevalence of gCJD in Slovakia by Mitrova *et al* (2014).43 Ritchie *et al* (2016) report from an animal study of squirrel monkeys that no clinical or pathologic signs of CJD were observed following blood transfusion, of either sCJD or vCJD, of the intracerebral inoculated monkeys after euthanasia at 7 years.164 However, there was evidence that GSS, a form of gCJD, transmitted autopsy-proven disease to two intracerebral-inoculated monkeys after incubation periods of 34 and 39 months. Brown *et al* (2015) conclude that these results and other studies from rodents and non-human primates suggest that blood donations of GSS (and perhaps other familial forms of TSE) carry more risk than those from vCJD.165 The infectiousness of CJD via blood is not directly relevant to the current decision problem of CJD risk via surgery. However, consideration of potential differences of infectiousness of the CJD types may be relevant when considering the risks of horizontal transmission in the future and in particular localities.

#### MV genotype as protective: PrPSc Allotype

Allotype refers to an inherited set of determinants or sequence of amino acids and other proteins demonstrating heterogeneity, which is specific for an individual but more common in a racial group. The relative contribution of each prion protein allotype to the infectious disease associated with the abnormal isoform of prion protein (PrPSc) is unknown. Moore *et al* (2016)166 found from an analysis of four heterozygous cases of sCJD, that the PrPSc allotype ratio is highly variable, with PrPSc (-M129 and –V129) differing markedly between different regions within the same sCJD brain.166 However, an analysis of six heterozygous cases of iCJD found the composition of PrPSc iCJD was more homogenous and tended to contain a higher proportion of PrPSc-V129 when compared to heterozygous cases of sCJD. The presence of two different PrP allotypes in the same brain can often lead, in a dose-dependent manner, to inefficient PrPSc formation and increased disease incubation. However, the study authors report that in both types of CJD, the PrPSc allotype ratio had no correlation with CJD type, age at clinical onset, or disease duration. This evidence suggests therefore that factors other than PrPSc allotype abundance must influence the clinical progression and phenotype of heterozygous cases of CJD.

### *2.5.2 Discussion/ summary of infectivity of CJD*

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 PRNP 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. Whilst little data regarding infectious dose or infectious titre have been published in humans to supersede the information used to populate the model built by ScHARR in 2005 some animal studies using advanced detection methods indicate that infectious doses greater than 108 ID50s are possible.

## 2.6 The evidence on the efficacy of prion decontamination procedures for surgical instruments

The purpose of this review was to identify published and unpublished evidence for the efficacy of decontamination procedures in terms of reducing the infectivity of prions adhering to steel wires or other steel materials. The review focuses principally on log reductions in the infectious titre, i.e. the reduction in the load of infectivity on steel (wires) before and after the decontamination processes. Log reductions are a common measure of decontamination and the review could inform this parameter in the health economic model. This systematic review includes studies that investigate autoclaving – the principal process currently employed in the NHS – as well as decontamination procedures that might be used in addition to autoclaving.

According to a 2014 report by the House of Commons Science and Technology Committee, a potentially effective decontaminant (Rely+On), to be used prior to autoclaving, experienced barriers to its uptake in the NHS due to: 1) the perceived low risk of iCJD due to surgical transmission; and 2) resistance to the inclusion of an additional step in the decontamination process (House of Commons, 2014).167 It should therefore be noted that, first, based on the number of known cases, the risk of iCJD due to surgical transmission has not increased markedly since 2013-14, which suggests evidence on new decontaminants might not be taken-up in practice. Second, any decontaminants identified by this systematic review as potentially being effective, but also representing an additional step, might experience the same barriers to uptake.

### *2.6.1 Decontamination studies*

#### Studies reporting log reductions of prion infectivity after autoclaving with / without other processes

Five studies reported this outcome after autoclaving with and without other decontamination processes (see Table 12). In terms of prion strain, three studies used 10% brain homogenate of 263K hamster scrapie (Lehmann *et al* (2009),168 Lemmer *et al* (2008),169 Rogez-Kreuz *et al*, 2009170); two used vCJD ((Belondrade *et al* (2016),171 Rogez-Kreuz *et al*, 2009170); and the following prion strains were investigated in only a single study: 127S (Belondrade *et al* (2016)171), M1000 (Lawson *et al* 2007172) and BSE 6PB1 (Rogez-Kreuz *et al*, 2009170). All studies used steel wires contaminated with the prion (one study also used steel sheets: Rogez-Kreuz *et al* 2009170); and all studies investigated autoclaving at 121°C or 134°C for specified amounts of time as a decontamination procedure.

The efficiency of autoclaving was assessed alone and in combination with a range of other decontaminants. These included sodium chloride (NaOH); sodium hypochlorite (NaOCl); sodium dodecyl sulfate (SDS); hydrogen peroxide (H2O2) and various other enzymatic and alkaline detergents. These decontaminants were also investigated alone or in combination with other decontaminants. Selected results from these investigations are reported in Table 13.

The log reductions produced by autoclaving at 134°C for 18 minutes for the 263K prion strain ranged from 4.11 (Lehmann *et al* 2009)168 to >5-6 (Rogez-Kreuz *et al*, 2009),170 with transmission rates of 57% and 50% respectively. The log reduction was only 2.2 (100% transmission) for the M1000 strain. Autoclaving at 134°C for 18 minutes, combined with NaOH or an alkaline detergent, produced log reductions of >5 to 6, as well as lower transmission rates (28% for NaOH and 0% for the alkaline detergent) for the 263K prion strain (Rogez-Kreuz *et al*, 2009).170 Autoclaving at 134°C for 5 minutes, combined with alkaline cleaners or SDS 0.2%/NaOH 0.3%, at different concentrations and/or different durations, also produced log reductions of >5.5 for the 263K prion strain (Lemmer *et al* (2008)169).

The only process reported to have produced a log reduction of >5 and a transmission rate of 0% is: autoclaving at 121°C for 20 minutes plus Rapid Multi Enzyme Cleaner trial formulation (RMEC) B 0.3% at 60°C for 30 minutes (Lawson *et al* 2007172).

Table 12: Characteristics of studies reporting log reductions in prion contamination on steel surfaces after autoclaving with and without other processes

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Prion strain** | **Source material**  **(% w/v)** | **Steel** | **Decontamination methods** | | **Assay used** |
| **Autoclaving** | **Other** |
| Belondrade *et al*, 2016171 | 127S scrapie,  vCJD | BH  (10%) | Wires | 121°C - 20 mins  134°C - 20 mins | NaOH 0.1N (15 mins)  NaOH 1N (60mins)  NaOCl 0.2% (15 mins)  NaOCl 2% (15 mins)  SDS 0.2% / NaOH 0.3% (10mins) | PMCA |
| Lawson *et al*, 2007172 | M1000 | BH  (10%) | Wires | 121°C - 20 mins  134°C - 18 mins | RMEC A (Enzymatic detergent)  RMEC B (Enzymatic detergent)  NaOH 1M - 60mins | Tga20 mice  WB |
| Lehmann *et al*, 2009,168 | 263K scrapie | BH  (10%) | Wires | 134°C - 18 mins | H2O2 (30 mins)  AF (10 mins)  Np-Np- H2O2/Cu (10 mins – 5 mins – 15 mins)  Dp-Dp- H2O2/Cu (10 mins – 5 mins – 15 mins)  Np-Dp- H2O2/Cu (10 mins – 5 mins – 15 mins)  Nmp-Nmp- PAA/Cu (10 mins – 5 mins – 15 mins, 40°C) | Syrian golden hamsters |
| Lemmer *et al*, 2008,169 | 263K scrapie | BH  (10%) | Wires | 134°C - 5 mins | NaOH 1.0 M (60 mins 23°C)  NaOCl 2.5% (60 mins 23°C)  Alkaline cleaner 0.5% and 1% (5/10 mins 55°C)  SDS 0.2% /NaOH 0.3% (5/10 mins 23°C)  Disinfectant with PAA 0.2% / NaOH 0.075-0.225% (120 mins 23°C) | Syrian golden hamsters |
| Rogez-Kreuz *et al*, 2009170 | 263K scrapie, vCJD†,  BSE 6PB1† | BH  (10% or 20%) | Wires, sheets† | 134°C - 18 mins | NaOH 1N (60mins)  H2O2 (10 mins, 20 mins)  Enzymatic detergent 2% (10 mins, 37°C)  Alkaline detergents A 1% (10 mins 70°C)  Alkaline detergents B 1% (10 mins 55°C) | Syrian golden hamsters  WB† |

BH: Brain homogenate; PMCA: protein misfolding cyclic amplification; NaOH: Sodium Hydroxide; NaOCI: Sodium Hypochlorite; SDS: Sodium dodecyl sulfate; RT: Room temperature; SSBA: Standard Steel Binding Assay; RMEC: Rapid Multi Enzyme Cleaner trial formulation; w/v: weight/volume; AF (alkaline detergent, surfactants, chelatant); H2O2: Hydrogen peroxide; mins: minutes

†In vitro only

The aim of some studies is development of a prion detection assay, rather than the development of the decontaminant, e.g., Belondrade *et al* (2016).

Table 13: Results of studies reporting log reductions in prion contamination on steel surfaces after autoclaving with and without other processes

| **Study** | **Prion strain** | **Decontamination methods** | | **Log reduction** | **Transmission rate** | **Incubation period days (SD)** |
| --- | --- | --- | --- | --- | --- | --- |
| **Autoclaving** | **Other** |
| Belondrade *et al*, 2016171 | 127S | 121°C - 20 mins |  | > 5 | 10/12 (83%) | NR |
| 134°C - 20 mins |  | FE | 0/12 (0%) | NR |
| vCJD | 121°C - 20 mins |  | 5 | 1/8 (12.5%) | NR |
| 134°C - 20 mins |  | FE | 0/8 (0%) | NR |
| Lawson *et al*, 2007172 | M1000 | 121°C - 20 mins |  | 1.6 | 100% | 106 (2) |
| 134°C - 3 mins |  | 1.5 | 100% | 104 (3) |
| 134°C - 18 mins |  | 2.2 | 100% | 120 (5) |
| 134°C - 3 mins | RMEC B 0.3%, 60°C - 30 mins | >4.5 | 10% | 166 (NR) |
| 121°C - 20 mins | RMEC B 0.3%, 60°C - 30 mins | >5 | 0% | - |
| Lehmann *et al*, 2009,168 | 263K | 134°C - 18 mins |  | 4.11 | 57% | 140 |
| Lemmer *et al*, 2008,169\* | 263K | 134°C - 5 mins | Alkaline cleaner 0.5% (5 mins 55°C) | >5.5 | NR | NR |
| 134°C - 5 mins | Alkaline cleaner 0.5% (10 mins 55°C) | >5.5 | NR | NR |
| 134°C - 5 mins | Alkaline cleaner 1% (5 mins 55°C) | >5.5 | NR | NR |
| 134°C - 5 mins | Alkaline cleaner 1% (10 mins 55°C) | >5.5 | NR | NR |
| 134°C - 5 mins | SDS 0.2% /NaOH 0.3% (5 mins 23°C) | >5.5 | NR | NR |
| 134°C - 5 mins | SDS 0.2% /NaOH 0.3% (10 mins 23°C) | >5.5 | NR | NR |
| 134°C - 5 mins | Disinfectant with PAA 0.2% / NaOH 0.075-0.225% (120 mins 23°C) | >2 to <3 | NR | NR |
| Rogez-Kreuz *et al*, 2009170 | 263K | 134°C - 18 mins |  | >5 to 6 | 50% | 428 ±103 |
| 134°C - 18 mins | NaOH 1N (60mins) | >5 to 6 | 28% | 554 ±197 |
| 134°C - 18 mins | Enzymatic detergent 2% (10 mins, 37°C) | 4 | 100% | 131 ±17 |
| 134°C - 18 mins | Alkaline detergent A 1% (10 mins 70°C) | >5 to 6 | 0% | 525 ±149 |
| 263K in vitro | 134°C - 18 mins |  | >5.4 | NR | NR |

BH: Brain homogenate; PMCA: protein misfolding cyclic amplification; FE: Fully efficient as no positive wires found; NaOH: Sodium Hydroxide; NaOCI: Sodium Hypochlorite; NR: Not reported; SDS: Sodium dodecyl sulfate; RT: Room temperature; SSBA: Standard Steel Binding Assay; RMEC: Rapid Multi Enzyme Cleaner trial formulation; w/v: weight/volume; AF (alkaline detergent, surfactants, chelatant); H2O2: Hydrogen peroxide; TICUw: tissue culture infectious units on wires

Room temperature (RT) unless otherwise stated. \*Bioassay 2 only (bioassay 1 = 2004 data).

#### Studies reporting log reductions of prion infectivity after processes other than autoclaving

Eleven studies reported log reductions of prion infectivity after various decontamination processes, principally enzymatic detergents that did not use autoclaving (see Table 14). In terms of prion strain, seven studies used 10% or 20% brain homogenate of 263K hamster scrapie (Beekes *et al*, 2010,173 Bellon *et al*, 2014,174 Fichet *et al*, 2007,175 Herve *et al*, 2010a,176 Lehmann *et al*, 2009,168 Lemmer *et al*, 2008,169 Rogez-Kreuz *et al*, 2009170); three used vCJD (Beekes *et al*, 2010,173, Bellon *et al*, 2014,174, Belondrade *et al*, 2016171); two used ME7 (Herve *et al*, 2010b,177 Howlin *et al*, 178); and the following prion strains were investigated in only a single study: RML (Edgeworth *et al*, 2011179); BSE 6PB1 and TGB1 (Fichet *et al*, 2007,175); M1000 (Lawson *et al*, 2007172); and 127S (Belondrade *et al*, 2016171). Nine studies used steel wires contaminated with the prion; one study used steel tokens (Herve *et al*, 2010b,177) and one, steel sheets (Rogez-Kreuz *et al*, 2009170).

The efficiency of a range of decontaminants was assessed. Selected results from these investigations are reported in Table 15. It was reported by Edgeworth *et al* (2011)179 that the following processes inactivated RML prions below the detection limit of the *in vitro* standard steel-binding assay (SSBA), stated to be equivalent to a reduction of 8 logs: Rely+On PI (DuPont), Prionzyme + 2 molar concentration (M) NaOH, and 2 M NaOH. It was noted, however, that the decontaminating effect of Prionzyme (Genencor) was indistinguishable from that of the diluent in which the decontaminant was prepared (2 M NaOH solution, following the manufacturer's instructions), i.e. treatment with 2 M NaOH alone also resulted in no detectable infectivity remaining on the steel surface. The only process reported to have produced a log reduction of >5 and a transmission rate of 0% for the RML prion strain is Rely+On PI.

The only processes, or combination of processes, reported to have produced a log reduction of >5 and a transmission rate of 0% for the 263K prion strain were: SDS 0.2% / NaOH 0.3% in 20% or 30% *n*-propanol (Beekes *et al*, 2010,173); NaOH 0.2 mol/L, at 15°C for 60 mins; NaOH 0.45 mol/L at 15°C for 15 or 30 mins; NaOH 0.45 mol/L at 25 °C for 240 mins; NaOH 0.45 mol/L at 40°C for 5 mins; NaOH 0.1 mol/L at 45°C for 5 or 15 mins (Bellon *et al*, 2014,174); 2mg/L gaseous H2O2 at 30°C for 3 or 6 pulses (Fichet *et al*, 2007,175); H2O2 for 30 minutes; AF (alkaline detergent, surfactants, chelatant) for 10 minutes; and combinations of enzymatic detergents and disinfectants, Np-Dp- H2O2/Cu (for 10 minutes – 5 minutes – 15 minutes) (Lehmann *et al*, 2009,168); the alkaline detergent B 1% for 10 minutes at 55°C; the Sterrad NX1 advanced cycle and Sterrad NX2 continuous advanced cycles (H2O2 and gas plasma); and the alkaline detergents A or B, 1% for 10 minutes at 55°C, in combination with the Sterrad NX1 advanced cycle (Rogez-Kreuz *et al*, (2009)170); and Cold Atmospheric Plasma (Herve *et al*, 2010a,176). According to Rogez-Kreuz *et al*, (2009),170 no insoluble prion (PrPres) signal was detected for BSE 6PB1 or vCJD “after exposure to steam in either of the two Sterrad systems”. The only process reported to have produced a log reduction of >5 and a transmission rate of 0% for the BSE prion strains 6PB1 and TGB1 were 2mg/L gaseous H2O2 at 30°C for 3 pulses (Fichet *et al*, 2007,175). None of the treatments for the ME7, vCJD, 127S or M1000 prion strains reported a log reduction of at least 5 and a transmission rate of 0% (Herve *et al*, 2010a,176 Howlin *et al*,178 Belondrade *et al*, 2016,171 Lawson *et al*, 2007172).

Table 14: Studies reporting log reductions in prion contamination on steel surfaces after decontamination processes other than autoclaving

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Study | Prion strain | Source material  (% w/v) | Steel | Decontamination methods other than autoclaving | Assay used |
| Beekes *et al*, 2010,173 | 263K scrapie,  vCJD(MM1), sCJD | BH  (10%) | Wires | SDS 0.2% / NaOH 0.3% in 20% or 30% *n*-propanol | Hamsters, WB |
| Bellon *et al*, 2014,174 | 263K,  vCJD (mouse adapted) | BH  (20%) | Wires | NaOH 0.1-0.45 mol/L, 4°C-45°C (5-240 mins) | Hamsters  WB |
| Belondrade *et al*, 2016171 | 127S scrapie,  vCJD | BH  (10%) | Wires | NaOH 0.1N (15 mins)  NaOH 1N (60mins)  NaOCl 0.2% (15 mins)  NaOCl 2% (15 mins)  SDS 0.2% / NaOH 0.3% (10mins) | Surf-PCMA |
| Edgeworth *et al*, 2011179 | RML | BH  (10%) | Wires | Rely+On  Prionzyme  HAMO100 PID 0.8% and 1.6%  2 M NaOH  NaOCl 20% | Tga20 mice,  Tg20 mice  SSBA |
| Fichet *et al*, 2007,175 | 263K scrapie,  6PB1 BSE,  TGB1 BSE | BH (10%) | Wires | 6% liquid H2O2, 20°C (60 mins)  2mg/L gaseous H2O2, 30°C (3 pulses)  2mg/L gaseous H2O2, 30°C (6 pulses) | Animal, WB |
| \* Herve *et al*, 2010a,176 | 263K scrapie | NR | Wires | Cold Atmospheric Plasma (CAP) | Animal |
| Herve *et al*, 2010b,177 | ME7 | BH  (NR) | Tokens | Four unspecified enzyme cleaning products, commonly used in UK SSDs (43°C or 50°C for 5 mins) | EDIC/EF and WB |
| Howlin *et al*, 178 | ME7 | BH  (10%) | Wires | Pre-soak, plus unspecified enzyme pre-treatment [containing proteases], plus alkaline detergent [includes potassium hydroxide] (HAMO100) | EDIC/EF and WB |
| Lawson *et al*, 2007172 | M1000 | BH  (10%) | Wires | RMEC A (Enzymatic detergent)  RMEC B (Enzymatic detergent)  NaOH 1M - 60mins | Tga20 mice  WB |
| Lehmann *et al*, 2009,168 | 263K scrapie | BH  (10%) | Wires | H2O2 (30 mins)  AF (10 mins)  Np-Np- H2O2/Cu (10 mins – 5 mins – 15 mins)  Dp-Dp- H2O2/Cu (10 mins – 5 mins – 15 mins)  Np-Dp- H2O2/Cu (10 mins – 5 mins – 15 mins)  Nmp-Nmp- PAA/Cu (10 mins – 5 mins – 15 mins, 40°C) | Hamsters |
| Lemmer *et al*, 2008,169 | 263K scrapie | BH  (10%) | Wires | NaOH 1.0 M (60 mins 23°C)  NaOCl 2.5% (60 mins 23°C)  Alkaline cleaner 0.5% and 1% (5/10 mins 55°C)  SDS 0.2% /NaOH 0.3% (5/10 mins 23°C)  Disinfectant with PAA 0.2% / NaOH 0.075-0.225% (120 mins 23°C) | Hamsters |
| Rogez-Kreuz *et al*, 2009170 | 263K scrapie, vCJD†,  BSE 6PB1† | BH  (10% or 20%) | Wires, sheets† | NaOH 1N (60mins)  H2O2 (10 mins, 20 mins)  Enzymatic detergent 2% (10 mins, 37°C)  Alkaline detergents A 1% (10 mins 70°C)  Alkaline detergents B 1% (10 mins 55°C) | Hamsters  WB |

BH: Brain homogenate; PMCA: protein misfolding cyclic amplification; NaOH: Sodium Hydroxide; NaOCI: Sodium Hypochlorite; SDS: Sodium dodecyl sulfate; RT: Room temperature; SSBA: Standard Steel Binding Assay; RMEC: Rapid Multi Enzyme Cleaner trial formulation; w/v: weight/volume; AF (alkaline detergent, surfactants, chelatant); H2O2: Hydrogen peroxide; EDIC/EF: Episcopic Differential Interference Contrast/Epifluorescence; WB: Western blot; SSDs: Sterile Service Departments; NR: Not reported

†In vitro only

Table 15: Results of studies reporting log reductions in prion contamination on steel surfaces by processes other than autoclaving

| **Study** | **Prion strain** | **Decontamination methods** | **Log reduction** | **Transmission rate** | **Incubation period days (SD)** | **Other (e.g. TICUw)** |
| --- | --- | --- | --- | --- | --- | --- |
| Beekes *et al*, 2010,173 | 263K | SDS 0.2% / NaOH 0.3% in 20% *n*-propanol | >5.5 | 0/10 | 503 |  |
| SDS 0.2% / NaOH 0.3% in 30% *n*-propanol | >5.5 | 0/9 | 503 |  |
| vCJD | SDS 0.2% / NaOH 0.3% in 20% *n*-propanol | 3.3 | NR | NR |  |
| sCJD | SDS 0.2% / NaOH 0.3% in 20% *n*-propanol | 3.3 | NR | NR |  |
| Bellon *et al*, 2014,174 | vCJD | NaOH 0.1-045 mol/L, 25°C-45°C (5-240 mins) | >3.8 | 0/8 | NR |  |
| 263K | NaOH 0.45 mol/L, 4°C (60 mins) | 4.9 | 2/8 | 441 |  |
| NaOH 0.2 mol/L, 15°C (15 mins) | 5 | 1/5 | 237 |  |
| NaOH 0.2 mol/L, 15°C (60 mins) | >5 | 0/8 | NR |  |
| NaOH 0.45 mol/L, 15°C (30 mins) | >5.2 | 0/8 | NR |  |
| NaOH 0.45 mol/L, 15°C (60 mins) | >5.2 | 0/8 | NR |  |
| NaOH 0.15 mol/L, 25 °C (60 mins) | 4.1 | 5/9 | 215 |  |
| NaOH 0.45 mol/L, 25 °C (60 mins) | 4.7 | 3/10 | 382 |  |
| NaOH 0.45 mol/L, 25 °C (240 mins) | >5.4 | 0/8 | NR |  |
| NaOH 0.45 mol/L, 40°C (5 mins) | >5.3 | 0/8 | NR |  |
| NaOH 0.45 mol/L, 40°C (15 mins) | 5.1 | 1/6 | 364 |  |
| NaOH 0.1 mol/L, 45°C (5 mins) | >5.4 | 0/8 | NR |  |
| NaOH 0.1 mol/L, 45°C (15 mins) | >5.4 | 0/8 | NR |  |
| Belondrade *et al*, 2016171 | 127S | NaOH 0.1N - 15 mins | > 3 | 12/12 | NR |  |
| vCJD | NaOH 0.1N - 15 mins | 3 | 6/8 | NR |  |
| Edgeworth *et al*, 2011179 | RML | Rely-On PI‡ | 5.5 | 0/19 | >250 |  |
| Rely-On PI§ | 8 | NR | NR | <0.003TICUw |
| Prionzyme+2 M NaOH§ | 8 | NR | NR | <0.003TICUw |
| 2 M NaOH§ | 8 | NR | NR | <0.003TICUw |
| HAMO 100 0.8%§ | NR | NR | NR | 0.3† |
| HAMO 100 1.6%§ | NR | NR | NR | 0.07† |
| Fichet *et al*, 2007,175 | 263K | 6% liquid H2O2, 20°C (60 mins) | 1 | 11/11 (100%) | 114 (13) |  |
| 2mg/L gaseous H2O2, 30°C (3 pulses) | >5.5 | 0/8 | >540 |  |
| 2mg/L gaseous H2O2, 30°C (6 pulses) | >5.5 | 0/8 | >540 |  |
| 6PB1 BSE | 2mg/L gaseous H2O2, 30°C (3 pulses) | >5.5 | 0/9 | >540 |  |
| TGB1 BSE | 2mg/L gaseous H2O2, 30°C (3 pulses) | >5.3 | 0/9 | >540 |  |
| \* Herve *et al*, 2010a,176 | 263K | Cold Atmospheric Plasma (CAP) | >6 | NR | NR |  |
| Herve *et al*, 2010b,177 | ME7 | Cleaner 4 (most efficient): 50°C for 5 mins | 3 | NR | NR | 99.21% of initial prion amyloid load removed |
| Howlin *et al*, 178 | ME7 | Unspecified enzyme pre-treatment [containing proteases] without pre-soak | Approx. 2 log greater reduction in prion amyloid than pre-soak alone even if allowed to dry; and 3 log reduction if process was started immediately after contamination (wet) | | | |
| Unspecified enzyme pre-treatment [containing proteases] with pre-soak | 1 log reduction in prion amyloid if process was started immediately after contamination (wet) instead of being allowed to dry | | | |
| Unspecified enzyme pre-treatment [containing proteases] plus alkaline detergent w/d | Prion-associated amyloid concentration levels were reduced below the experimental cut-off value of 0.001ng/mm2, wet or dry | | | |
| Lawson *et al*, 2007172 | M1000 | NaOH 1M - 60mins | 2.7 | 100% | 130 (19) |  |
| RMEC A 1%, 50°C - 30 mins | >4.5 | 80% | 204 (18) |  |
| RMEC B 0.3%, 60°C - 30 mins | >3.5 | 60% | 147 (13) |  |
| Lehmann *et al*, 2009,168 | 263K | H2O2 (30 mins) | >5.25 | 0% | >370 |  |
| AF (10 mins) | >5.25 | 0% | >370 |  |
| Np-Np- H2O2/Cu (10 mins – 5 mins – 15 mins) | 4.55 | 43% | 133 |  |
| Dp-Dp- H2O2/Cu (10 mins – 5 mins – 15 mins) | >5.25 | 20% | 159 |  |
| Np-Dp- H2O2/Cu (10 mins – 5 mins – 15 mins) | >5.25 | 0% | >370 |  |
| Nmp-Nmp- PAA/Cu (10 mins – 5 mins – 15 mins, 40°C) | 3.43 | 67% | 102 |  |
| Lemmer *et al*, 2008,169 | 263K | NaOH 1.0 M, 60 mins 23°C | >5.5 | NR | NR |  |
| NaOCl 2.5%, 60 mins 23°C | >5.5 | NR | NR |  |
| Alkaline cleaner 0.5% (5 mins 55°C) | >4 to<5 | NR | NR |  |
| Alkaline cleaner 0.5% (10 mins 55°C) | >5 to<5.5 | NR | NR |  |
| Alkaline 1% (5 mins 55°C) | >5 to<5.5 | NR | NR |  |
| Alkaline cleaner 1% (10 mins 55°C) | >5.5 | NR | NR |  |
| SDS 0.2% /NaOH 0.3% (5 mins 23°C) | >5.5 | NR | NR |  |
| SDS 0.2% /NaOH 0.3% (10 mins 23°C) | >5.5 | NR | NR |  |
| Disinfectant with PAA 0.2% / NaOH 0.075-0.225% (120 mins 23°C) | >5 to<5.5 | NR | NR |  |
| Rogez-Kreuz *et al*, 2009170 | 263K | H2O2 (10 mins) | >5 to 6 | 50% | 443 ±140 |  |
| H2O2 (20 mins) | >5 to 6 | 50% | 428 ±142 |  |
| Enzymatic detergent 2% (10 mins, 37°C) | 1.1 | 100% | 95 ±0 |  |
| Alkaline detergent A 1% (10 mins 55°C) | >5 to 6 | 11% | 446 ±153 |  |
| Alkaline detergent B 1% (10 mins 55°C) | >5 to 6 | 0% | 524 ±42 |  |
| Sterrad NX1 advanced cycle | >5 to 6 | 0% | 570 ±18 |  |
| Sterrad NX2 continuous advanced cycles | >5 to 6 | 0% | 574 ±0 |  |
| Alkaline detergent A 1% (10 mins 55°C), plus Sterrad NX1 advanced cycle | >5 to 6 | 0% | 559 ±22 |  |
| Alkaline detergent B 1% (10 mins 55°C), plus Sterrad NX1 advanced cycle | >5 to 6 | 0% | 562 ±16 |  |
| 263K in vitro | Sterrad NX1 advanced cycle | >5.4 | NR | NR |  |

BH: Brain homogenate; RML: Rocky Mountain Laboratory; PMCA: protein misfolding cyclic amplification; NaOK: Sodium Hydroxide; NaOCl: Sodium Hypocholorite; SDS: Sodium dodecyl sulfate; TICUw: tissue culture infectious units on wires; \*In vivo; †By far the least effective – more ineffective than autoclaving, or Rely-On for prionzyme, or 2 M NaOH. Note: prionzymne’s effectiveness is no different from the solution of 2 M NaOH in which it is prepared), plus neither is suitable for decontamination of certain surgical instruments, and 2 M NaOH is high hazardous (Edgeworth 2011), ‡By bioassay in Tga20 mice alone, §By SSBA

#### Supplementary evidence: Studies reporting outcomes other than log reductions after autoclaving with / without other processes

Six studies reported outcomes other than log reductions (see Table 16). In terms of prion strain, two studies used 10% or 20% brain homogenate of RML (Jackson *et al* (2005)180, Edgeworth *et al* (2011)179), and two studies investigated sc237 and sCJD (Peretz *et al* (2006)181 and Giles *et al* (2007)182), with the following prion strains investigated in only a single study: 263K scrapie (Baxter *et al* (2005)183), and 301V BSE and cattle BSE (Giles *et al* (2007)182). Five studies used steel wires contaminated with the prions, and one study used steel spheres (Baxter *et al* (2005)183); all studies investigated autoclaving, either at 121°C, 134°C or 137°C for specified amounts of time as a decontamination procedure; one study investigated autoclaving at 65°C and 121°C (Giles *et al* (2007)182).

The efficiency of autoclaving was assessed alone and in combination with a range of other decontaminants. These included sodium dodecyl sulfate (SDS); acetic acid (AcOH); sodium hydroxide (NaOH); radio-frequency (RF) gas plasma; trigene disinfectant and various other enzymatic detergents. Selected results from these investigations are reported in Table 17.

Only one study reported the outcome ‘tissue culture infectious units on wires’ (TICUw) (Edgeworth *et al* (2011)179). This study recorded that autoclaving at 134°C for 18 minutes reduced the TICUw measure of the RML prion strain to 0.03, which is reported to be equivalent to a reduction of 5.5 logs (see Table 15, above).

The remaining studies all reported transmission rates. The transmission rates produced by autoclaving at 134°C for 15 minutes and 30 minutes for the 301V BSE prion strain were 96% and 57% respectively, and for cattle BSE, 84% and 100% (Giles *et al* (2008)184). The transmission rates produced by autoclaving at 134°C for 20 minutes for the RML prion strain ranged from 25% (1/4) to 100% (13/13) in Tg20 mice and 0% (0/9) in CD-1 wild mice (Jackson *et al* (2005)180). The unusually high transmission rate in the larger sample of Tg20 mice was explained by the autoclaving process being affected by partial sealing of the glass tubes containing the steel wires, which impaired the penetration of the steam (Jackson *et al* (2005)180). The transmission rates produced by autoclaving at 121°C for 15 minutes and 30 minutes for the Sc237 prion strain were 100% and 20% respectively, and for sCJD, 22% and 0% (Peretz *et al* (2006)181and Giles *et al* (2007)182). Finally, the transmission rates produced by autoclaving at 134°C for 15 minutes and 30 minutes for the Sc237 prion strain were 87% and 55% respectively, and for sCJD, 73% and 63% (Peretz *et al* (2006)181).

Table 16: Studies reporting infectivity (but not log reductions) from prion contamination on steel surfaces after autoclaving with and without other processes or decontamination processes without autoclaving

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Study | Prion strain | Source material  (% w/v) | Steel | Decontamination methods | | Assay used |
|  | Autoclaving | Other |
| Baxter *et al* (2005)183 | 263K | BH (20%) | Spheres | 137°C - 18 mins | Trigene disinfectant  Radio-frequency (RF) gas plasma | Hamsters |
| Edgeworth *et al* (2011)179 | RML | BH  (10%) | Wires | 134°C - 18 mins | Rely+On  Prionzyme  HAMO100 PID 8% and 1.6%  2 M NaOH  NaOCl 20% | SSBA |
| Giles *et al* (2007)182 | Sc237  sCJD | BH  (10%) | Wires | 65°C – 30 mins, 120 mins, 18 hours  121°C – 15, 30, 120 mins | 2% SDS + 1% AcOH | Tg7 and Tg23372 mice |
| Giles *et al* (2008)184 | 301V BSE  Cattle BSE | BH  (10%) | Wires | 65°C - 8 mins  121°C - 120 mins  134°C - 120 mins | 4% SDS + 1% AcOH | Tg2091 mice Tg4092 mice |
| Jackson *et al* (2005)180, McKintosh *et al* (2005)185 | RML | BH  (10% & 20%) | Wires | 121°C - 20 mins  134°C - 20 mins | Enzymes: SDS-PK-Pronase  2 M NaOH  LpH, LpHse  Endozyme Plus | Tg20 mice,  CD-1 mice  WB |
| RML | BH  (10%) | Wires | 134°C - 20 mins | Enzymes | Tg20 mice,  CD-1 mice  WB |
| Peretz *et al* (2006)181 | Sc237  sCJD | BH  (10%) | Wires | 121°C – 15, 30, 120 mins  134°C - 15, 30, 120 mins | 2% SDS + 1% AcOH  4% SDS + 1% AcOH | Tg7 and Tg23372 mice Micro BCA Protein assay (Pierce, Rockford, IL) |

w/v: weight/volume; AcOH: Acetic Acid; PK: Proteinase K

The following combinations of autoclaving and other processes are reported to have produced a transmission rate of 0% or <5%: autoclaving at 134°C for 15, 30 or 120 minutes plus 4% SDS + 1% AcOH for the 301V, cattle BSE (Giles *et al* (2008)184), Sc237 and sCJD prions strains (Peretz *et al* (2006)181); autoclaving at 121°C for 15, 30 or 120 minutes plus 2% SDS + 1% AcOH for the 301V and cattle BSE prion strains (Giles *et al* (2008)184); and autoclaving at 65°C for 18 hours plus 2% SDS + 1% AcOH for the Sc237 and sCJD prions strains (Giles *et al* (2007)182). Autoclaving at 134°C for 20 minutes plus SDS-PK-Pronase at 40°C for 60 mins also produced a 0% transmission rate for RML prion strains (Jackson *et al* (2005)180).

Without autoclaving, trigene disinfectant and RF gas plasma, and SDS-PK-Pronase at 40°C for 60 mins, also produced transmission rates of 0% in the 263K and the RML prion strains, respectively (Baxter *et al* (2005)183, Jackson *et al* (2005)180).

Table 17: Results of studies reporting infectivity (but not log reductions) from prion contamination on steel surfaces after autoclaving with and without other processes or decontamination processes without autoclaving

| **Study** | **Prion strain** | **Decontamination methods** | | **Transmission rate** | **Incubation period days (SD)** |
| --- | --- | --- | --- | --- | --- |
| **Autoclaving** | **Other** |
| Baxter *et al* (2005)183 | 263K | 137°C - 18 mins | Trigene disinfectant | 5/5 | 202 ±28 |
|  | Trigene disinfectant | 0/5 | 466† |
|  | Radio-frequency (RF) gas plasma | 0/5 | 466† |
| Edgeworth *et al* (2011)179 | RML | 134°C - 18 mins | NR | 5% | NR |
| Giles *et al* (2007)182§ | Sc237 in Tg7 mice | 65°C - 30 mins | 2% SDS + 1% AcOH | 100% | 82 ±0.7 |
| 65°C - 120 mins | 2% SDS + 1% AcOH | 68% | 269 ±3.2 |
| 65°C – 18 hours | 2% SDS + 1% AcOH | 0% | >400 |
| 121°C - 15 mins | NR | 100% | 160 ±7.3 |
| 121°C - 30 mins | NR | 20% | >400 |
| 121°C - 120 mins | NR | 0% | >400 |
| 121°C - 15 mins | 2% SDS + 1% AcOH | 0% | >400 |
| 121°C - 30 mins | 2% SDS + 1% AcOH | 0% | >400 |
| 121°C - 120 mins | 2% SDS + 1% AcOH | 0% | >400 |
| sCJD in Tg23372 mice | 65°C - 30 mins | 2% SDS + 1% AcOH | 86% | 354 ±1.6 |
| 65°C - 120 mins | 2% SDS + 1% AcOH | 44% | >500 |
| 65°C – 18 hours | 2% SDS + 1% AcOH | 25% | >500 |
| 121°C - 15 mins | NR | 22% | >500 |
| 121°C - 30 mins | NR | 0% | >500 |
| 121°C - 120 mins | NR | 73% | 414 ±15 |
| 121°C - 15 mins | 2% SDS + 1% AcOH | 0% | >500 |
| 121°C - 30 mins | 2% SDS + 1% AcOH | 0% | >500 |
| 121°C - 120 mins | 2% SDS + 1% AcOH | 0% | >500 |
| Giles *et al* (2008)184 | 301V | 134°C - 15 mins | NR | 96% | 161 |
| 134°C - 30 mins | NR | 57% | 438 |
| 134°C - 120 mins | NR | 14% | >600 |
| NR | 1% AcOH, 65°C - 18 hrs | 100% | 117 |
| NR | 4% SDS, 65°C - 18 hrs | 100% | 127 |
| NR | 4% SDS + 1% AcOH, 65°C – 30 mins | 73% | 267 |
| NR | 4% SDS + 1% AcOH, 65°C – 120 mins | 33% | >600 |
| NR | 4% SDS + 1% AcOH, 65°C – 18hrs | 58% | 410 |
| 134°C - 15 mins | 4% SDS + 1% AcOH | 5% | >600 |
| 134°C - 30 mins | 4% SDS + 1% AcOH | 0% | >600 |
| 134°C - 120 mins | 4% SDS + 1% AcOH | 0% | >600 |
| BSE | 134°C - 15 mins | NR | 84% | 384 |
| 134°C - 30 mins | NR | 100% | 375 |
| 134°C - 120 mins | NR | 89% | 420 |
| NR | 1% AcOH, 65°C - 18 hrs | 91% | 354 |
| NR | 4% SDS, 65°C - 18 hrs | 100% | 368 |
| NR | 4% SDS + 1% AcOH, 65°C – 30 mins | 42% | >500 |
| NR | 4% SDS + 1% AcOH, 65°C – 120 mins | 26% | >500 |
| NR | 4% SDS + 1% AcOH, 65°C – 18hrs | 4% | >500 |
| 134°C - 15 mins | 4% SDS + 1% AcOH | 0% | >500 |
| 134°C - 30 mins | 4% SDS + 1% AcOH | 0% | >500 |
| 134°C - 120 mins | 4% SDS + 1% AcOH | 0% | >500 |
| Jackson *et al* (2005)180, McKintosh *et al* (2005)185 | RML (20% w/v)  Tg20 mice | 121°C - 20 mins | NR | 0/6a | NR |
| 134°C - 20 mins | NR | 0/4b | NR |
| NR | LpH | 5/5 | 91 (SEM 2.6) |
| NR | LpHse | 3/5c | 70 (0) |
| NR | Endozyme Plus | 5/5 | 81 (1) |
| NR | Enzymes: SDS-PK-Pronase, 40°C – 60 mins | 0/3 | NR |
| 121°C - 20 mins | Enzymes: SDS-PK-Pronase, 40°C – 60 mins | 0/5d | NR |
| 134°C - 20 mins | Enzymes: SDS-PK-Pronase, 40°C – 60 mins | 0/4 | NR |
| RML (20%w/v)  CD-1 mice | 134°C - 20 mins | NR | 0/9 | NR |
| 134°C - 20 mins | 2 M NaOH | 0/10 | NR |
| 134°C - 20 mins | Enzymes: SDS-PK-Pronase, 40°C – 60 mins | 0/8 | NR |
| NR | Enzymes: SDS-PK-Pronase, 40°C – 60 mins | 0/10 | NR |
| RML (10% w/v) Tg20 mice | 134°C - 20 mins | NR | 13/13\* | 108 (12.4 SEM) |
| NR | Enzymes: SDS-PK-Pronase, 40°C – 60 mins | 1/18 (101) | NR |
| Peretz *et al* (2006)181 | Sc237  Tg7 mice | 121°C - 15 mins | NR | N=10, 100% | 160 ±7.3 |
| 121°C - 30 mins | NR | 20% | >400 |
| 121°C - 120 mins | NR | 0% | >400 |
| 121°C - 15 mins | 2% SDS + 1% AcOH | 0% | >400 |
| 121°C - 30 mins | 2% SDS + 1% AcOH | 0% | >400 |
| 121°C - 120 mins | 2% SDS + 1% AcOH | 0% | >400 |
| 134°C - 15 mins | NR | 87% | 96 ±0.6 |
| 134°C - 30 mins | NR | 55% | 262 ±10 |
| 134°C - 120 mins | NR | 9% | >400 |
| 134°C - 15 mins | 4% SDS + 1% AcOH | 0% | >400 |
| 134°C - 30 mins | 4% SDS + 1% AcOH | 4% | >400 |
| 134°C - 120 mins | 4% SDS + 1% AcOH | 0% | >400 |
| sCJD  Tg23372 | 121°C - 15 mins | NR | N=10, 22% | >500 |
| 121°C - 30 mins | NR | 0% | >500 |
| 121°C - 120 mins | NR | 73% | 414 ±15 |
| 121°C - 15 mins | 2% SDS + 1% AcOH | 0% | >500 |
| 121°C - 30 mins | 2% SDS + 1% AcOH | 0% | >500 |
| 121°C - 120 mins | 2% SDS + 1% AcOH | 0% | >500 |
| 134°C - 15 mins | NR | 73% | 218 ±4.1 |
| 134°C - 30 mins | NR | 63% | 242 ±2.8 |
| 134°C - 120 mins | NR | 46% | >500 |
| 134°C - 15 mins | 4% SDS + 1% AcOH | 0% | >500 |
| 134°C - 30 mins | 4% SDS + 1% AcOH | 0% | >500 |
| 134°C - 120 mins | 4% SDS + 1% AcOH | 0% | >500 |

BH: Brain homogenate; RML: Rocky Mountain Laboratory; PMCA: protein misfolding cyclic amplification; NaOH: Sodium Hydroxide; NaOCl: Sodium Hypocholorite; SDS: Sodium dodecyl sulfate; TICUw: tissue culture infectious units on wires; \*In vivo; †By far the least effective – more ineffective than autoclaving, or Rely-On for prionzyme, or 2 M NaOH; Total numbers infected (but only apparent post-mortem): a=2/6, b=1/4; c=4/5, d=1/5 † All animals in these groups were clinically sound when euthanized at 466 days \*Wires being placed in partially sealed glass tubes appears to have impaired the autoclaving process §The data for decontamination at 121°C are the same data as reported in Peretz 2006.

#### Supplementary evidence: Studies reporting evidence for levels of protein residue on surgical instruments after cleaning

*Studies reporting evidence for levels of protein residue on surgical instruments after cleaning*

Nine studies reported this outcome after autoclaving with and without other decontamination processes (see Table 18): seven studies for surgical instruments and two studies for endoscopes (Herve 2013177, 2016186). All studies were conducted in the UK: seven studies reported on protein residue on instruments acquired from between one and nine NHS trusts; the number of trusts involved was not reported in two studies (Baxter R, 2006187; Herve 2016186). All studies reported that cleaning essentially involved conventional procedures for the equipment concerned. With the exception of two studies (Baxter R, 2006187; Murdoch, 2006188), the assay appears to have involved detection of proteins *in situ* on the instruments. Where reported, the number of instruments ranged from two to 1000.

There was no consistency in the measures used to quantify and report the residual protein contamination of surgical instruments after conventional cleaning and sterilisation in a sterile service department (SSD). Murdoch (2006188) reported a mean protein per instrument of 71.67µg (range, 8-91 µg); R Baxter (2006187) reported a median range of 163-756µg per instrument; Lipscomb (2006a189 & b190) reported residual contamination using an un-validated ‘Contamination Index’ (CI) and reported that 56% of instruments (out of a total of 23) from a single NHS trust showed severe contamination (CI score, >3 to 4) in at least one of the sample regions, while 66% of instruments (n=260) from nine NHS primary care trusts showed equivalent severe contamination (CI score, >3 to 4). According to this CI, a classification of 3 represents 0.42-4.2 µg of protein/mm2 and 4 is >4.4µg/mm2. The most recent study, Smith *et al* (2018191), reported residue ‘per instrument side’ for evaluated instruments from craniotomy sets (n=187): 87% were found to have <5µg per instrument side and 96% <10µg per instrument side. Two papers did not explicitly quantify the residual protein but only noted its presence (Baxter H 2006192 & 2009193). The studies assessing endoscopes reported either <10ng/mm2 after processing (Herve 2013177) or the ‘*equivalent to 1–4µg of proteins per channel, except in one channel which harbored … equivalent to almost 33 µg of residual proteins for the whole channel*’ (Herve 2016186).

Table 18: Study characteristics and results

| **Study** | **Country** | **Source** | **Surgical instruments**  **(number)** | **Cleaning cycle** | **Assay / in situ** | **Residual protein contamination of surgical instruments after conventional cleaning and sterilization in a sterile service department (SSD)** | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Mean protein**  **per instrument (µg)** | **Median protein**  **per instrument (µg)** | |
| Baxter R, 2006187 | UK | SSDs from a random sample of NHS trusts | Five trays (n=120) | ‘routine hospital cleaning and sterilization’ | Ninhydrin /  Acid stripping of surfaces and hydrolysing of proteins | NR | 163-756 µg (range)§ | |
| Lipscomb 2006a189\* | UK | SSD from one NHS trust | Ranged in shape and size (n=23) | ‘Traditional machine washer-disinfector cleaning procedures’ | SYPRO Ruby and EDIC/EF microscopy  Unclearb | Results indicated that over half (56%) of the instruments inspected showed severe (classes 3–4) contamination in at least one of the sample regions, 35% were moderately contaminated (class 3), and only 9% displayed low-level deposition (class 0–2). The overall mean CI value for all the instruments was 2.8.  *Contamination index (CI): class 3 is 0.42-4.2 µg of protein/mm2 and class 4 is >4.4µg/mm2.* | | |
| Lipscomb 2006b190\* | UK | SSDs from nine anonymous NHS primary care trusts | Nine sets (n=260) | ‘Traditional machine washer-disinfector cleaning procedures’ | SYPRO Ruby and EDIC/EF microscopy  *In situ* | The scores were averaged for each instrument; the results indicated that 66% of all the instruments inspected showed severe (CI score, >3 to 4) contamination in at least one of the sample regions, 27% were moderately contaminated (CI score, >2 to 3), and only 7% displayed low-level soiling (CI score, 0 to 2). The mean CI per instrument set differed among the nine trays (range, 2.4 to 3.6), with the overall mean CI value for all the instruments being 3.2.  *Contamination index (CI): class 3 is 0.42-4.2 µg of protein/mm2 and class 4 is >4.4µg/mm2.*  Statistical analysis indicated that there was significant difference in the levels of contamination between the different types of instrument, with needle holders and tissue forceps (as hinged instruments) showing contamination levels significantly higher than some other instruments. ​ | | |
| Murdoch 2006188 | UK | Five Department of Health hospitals | A range of instruments (n=43) | ‘autoclaved’ | 'protein extraction and quantification methods', i.e. levels of protein removed from instruments and identified in the ‘buffer’ or ‘'wash' | 71.67 µg ‡  8-91 µg (range)† | NR | |
| Baxter H, 2006192 | UK | One NHS trust | A basic neurosurgical tray in regular use (n=6) | ‘conventional hospital SSD procedures’ [washing and autoclaving] n=3; ‘conventional hospital SSD procedures’ + RF gas plasma, n=3 | EDX  Unclearb | Protein contamination on instruments was identified after the conventional SSD procedure, but was 'not directly quantified ... the analyses simply show the elemental composition of these residues'. | | |
| Baxter H, 2009193 | UK | One NHS trust | Forceps (n=2) | ‘conventional hospital SSD procedures’ [washing and autoclaving] | EDX  *in situ* | Measure of residual protein is by units of fluorescence after conventional SSD processes, but before and after RF gas plasma treatment | | |
| Smith, 2018191 | UK | One NHS trust.  Some instruments ‘artificially soiled’ with Edinburgh soil | The five most-commonly used neurosurgery sets (n=1000) | ‘automated washer disinfector’ in SSD (untreated), plus instruments treated with two types of wetting agents (Steris pre-klenz and sterile water) | SDS extraction and OPA, ProReveal  Unclearb | 10 craniotomy sets only: instruments, n=305 (OPA assay, and includes 40 artificially-soiled instruments):  <30 µg, except for one untreated instrument: sharp elevator: 44.02 µg a    Different sets: instruments n=187 (ProReveal assay): 87% (163/187): <5µg per instrument side;  96% (179/187): <10µg per instrument side | | NR |
|  | | | | | | | | |
| Herve 2013177 | UK | Manufacturer, contaminated with ‘Edinburgh soil’ | Endoscopes (n=NR) | An ‘enzymatic cleaner used in a number of endoscopy units’ | SYPRO Ruby and EDIC/EF microscopy  Unclear | Contamination was < 10 ng/mm2 after standard cleaning (see Figure 3 in paper for details) | | |
| Herve 2016186 | UK | Unknown number of ‘hospital-based endoscopy units’ (n=6) | Endoscopes (n=6) | An ‘enzymatic cleaner: Enzol’ | SYPRO Ruby and EDIC/EF microscopy  Unclear | ‘basal level of microdecontamination … absorbed on the luminal surface early in the endoscope’s life’: 0.1–0.9 µg of proteins per metre. Protein residues remained under …values … equivalent to 1–4 µg of proteins per channel, except in one channel which harbored … equivalent to almost 33 µg of residual proteins for the whole channel.’ | | |

Abbreviations: SSD: Sterile Service Department; NR: Not reported; EDIC/EF: Episcopic differential interference contrast/epifluorescence; EDX: Energy dispersive X-ray spectroscopic; OPA: Orthophthaladehyde; SDS: Sodium Dodecyl Sulphate

\*Contamination index (see screen-shot below) §A significant difference was observed in mean levels of protein contamination between trays (p<0.0001) ‡Calculated from Table II: 3082 (total protein µg per instrument / 43 (total number of instruments) †A significant difference was observed in mean levels of protein contamination between hospitals (p<0.0001) aSmith 2018191, Supplemental table XV.

bUnclear: not reported in Methods, but detection methods indicate evaluation of proteins *in situ*.

### *2.6.2 Residual mass/protein studies*

#### Studies reporting the impact on protein absorption and/or the relative efficacy of cleaning when keeping instruments wet or dry before processing

Four studies (five papers) reported a comparison between ‘wet’ and ‘dry’ instruments in terms of pre-cleaning protein absorption or post-soaking or cleaning protein residue. All studies were conducted in the UK, used steel tokens or wires and the same contaminant: 1µL drops of ME7-infected brain homogenate. Detection was made of *in situ* contamination using the same techniques: SYPOR Ruby and EDIC/EF microscopy. Across the studies, drying times before assessment ranged from 15 minutes (Secker 2015194) to 24 hours (Secker 2011195, Secker 2015194).

The process to keep steel tokens or wires ‘wet’ was different in each study: Secker (2015194) used a ‘wet bag’ (Humibag), i.e. a sealed bag containing 35ml distilled water for set time periods; Secker (2011195) used an air-tight container lined with moist tissue for 17 hours; Howlin (2010178) treated steel wires immediately, rather than allowing them to dry; and Lipscomb (2007196) treated steel tokens with one of four pre-soak treatments for 5 minutes, followed by 17 hours’ drying time. The dry conditions for comparison were: air dry or a ‘dry bag’ for comparable times to the ‘wet bag’ (Secker 2015194); air dry for 24 hours (Secker 2011195); air dry for 16 hours (Howlin 2010178) and air dry for 17 hours (Lipscomb 2007196). Different temperatures were evaluated but this text will only focus on the findings for room temperature (or the closest available data) across studies. Three of the four studies used the enzymatic cleaner Klenzyme.

Both Secker studies (2011195, 2015194) reported on protein residue after 24 hours at room temperature before cleaning: 324.7±15.0 ng/mm2 for the air dry conditions compared with 6.0±3.5 ng/mm2 for the wet conditions (98.2% reduction compared to air dry, p<0.001) (Secker 2011195) and 1000±205.0 ng/mm2 for the air dry conditions compared with 31.9±5.3 ng/mm2 for wet conditions (Secker 2015194). After the application of pre-soaks or cleaners, Lipscomb (2007196) reported a reduction in protein between 64% and 96% on the pre-soaked or treated tokens compared to the dry, untreated controls; and Howlin (2010178) reported a reduction of approximately 2 logs in protein residue for tokens treated immediately (not allowed to dry) with the pre-klenz pre-soak compared with wires that were allowed to dry for 16 hours. Secker (2015194) and Lipscomb (2007196) also reported that the longer the drying times, the more difficult it was to remove the contamination.

Table 19: Study characteristics and results

| **Study** | **Country** | **Contam-**  **inant** | **Steel medium** | **Pre-treatment** | **Assay / in situ** | **Dry** | **Wet** | **Differences in residual protein (ng/mm2) contamination of wires or tokens** | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  |  |  |  |  | **Dry** | **Wet** |
| Lipscomb 2007196 | UK | 1µL drops of ME7-infected BH | Surgical 316L grade SS tokens (10mm x 25mm) | Klenzyme;  Endozyme AW;  Enzol;  Liquid 52 | SYPRO Ruby and EDIC/EF microscopy  *In situ* | DT =17h  No pre-soak / pre-treatment | DT=17h  5 minutes for each:  Klenzyme, 8ml/L;  Endozyme AW, 4ml/L;  Enzol, 8ml/L;  Liquid 52, 8ml/L | Final residual protein contamination at 22oC\*:  Control = 100% | Percentage of final residual protein contamination compared with control at 22oC\*:  Klenzyme = 19%  Endozyme AW=36%  Enzol=4%  Liquid 52= 17% |
| Howlin 2010178 | UK | 1µL drops of ME7-infected BH | Surgical 316L grade SS wires (5mm x 0.16mm) | Klenzyme;  Pre-Klenz (pre-soak gel) | Western blot  *In situ*§ | DT=16h followed by pre-treatments | DT = 0h (immediate treatment) | Total protein removal (ng/mm2):  Immediate treatment with Pre-Klenz, produced a 2 log reduction compared with ‘dry’ controls | |
| Secker 2011195\* | UK | 1µL drops of ME7-infected BH | Surgical 316L grade SS tokens (25mm x 75mm) | Klenzyme;  Endozime | SYPOR Ruby and Thioflavin T, EDIC/EF microscopy  *In situ*§ | DT=24h  Air  RT or F (4oC-8oC) | DT=24h  Moist: Air-tight container lined with moist tissue  RT or F (4oC-8oC) | RT=324.7±15.0 ng/mm2  F=243.8±17.9 ng/mm2  Klenzyme applied after 2h: RT=18.0±9.3 ng/mm2 (90.1% reduction compared to untreated air dry control)  Endozime applied after 2h: RT=194.3±7.9 ng/mm2 | RT=6.0±3.5 ng/mm2 (98.2% reduction compared to dry, p<0.001)  F=56.8±12.9 ng/mm2 (76.7% reduction compared to dry, p<0.001) |
| Secker 2015194 | UK | 1µl drops of ME7-infected BH (equivalent to 1µg total protein) | Surgical 316L grade SS tokens (10mm x 30mm) | Prolystica 2x alkaline detergent, working pH 10.1  Or  Progenica detergent, working pH 10.9 | SYPOR Ruby and Thioflavin T,  EDIC/EF microscopy  *In situ*§ | Air for (DT): 15mins, 30mins, 1h, 2h, 24h  (RT and F) | Wet bag: Sealed bag with 35ml distilled water for (DT):  15mins, 30mins, 1h, 2h, 24h  (RT and F) | 24h Humidity:  RT: 55%-70%  F: 46%-69%  Protein absorption pre-cleaning(RT):  15mins: 15.3±4.8 ng/mm2  24h: 1000±205.0 ng/mm2  Prolystica (RT):  1h: 54.8±13.7 ng/mm2  2h: 918.6±54.0 ng/mm2  24h: 1026.1±92.5 ng/mm2  Prolystica (F):  1h: Data NR  2h: Data NR  24h: 605.1±89.5 ng/mm2  Progenica (RT):  1h: Data NR  2h: 112.0±41.4 ng/mm2  24h: 743.2±155.5 ng/mm2  Progenica (F):  1h: Data NR  2h: 1095.6±359.1 ng/mm2  24h: 1247.9±132.1 ng/mm2 | 24h Humidity:  RT: 90%  F: 90%  Protein absorption pre-cleaning(RT):  15mins:18.5±4.2 ng/mm2  24h: 31.9±5.3 ng/mm2  Prolystica (RT):  1h: Data NR  2h: Data NR †  24h: Data NR †  Prolystica (F):  1h: Data NR  2h: Data NR †  24h: Data NR †  Progenica (RT):  1h: Data NR  2h: Data NR  24h: Data NR†  Progenica (F):  1h: Data NR  2h: Data NR  24h: Data NR† |
| Dry bag: Tied clear polythene bag for (DT):  15mins, 30mins, 1h, 2h, 24h (RT and F) | 24 h Humidity:  RT: 55%-80%  F: 47%-90%  Protein absorption pre-cleaning(RT):  15mins: 30.6±27.7 ng/mm2  24h: 785.6±310.8 ng/mm2  Prolystica (RT):  1h: 84.7±30.9 ng/mm2  2h: Data NR†  24h: Data NR†  Prolystica (F):  1h: Data NR  2h: Data NR†  24h: 181.5±39.4 ng/mm2†  Progenica (RT):  1h: Data NR  2h: Data NR  24h: 154.5±7.0 ng/mm2†  Progenica (F):  1h: Data NR  2h: Data NR  24h: Data NR † | *(Repeat from above)*  24h Humidity:  RT: 90%  F: 90%  Protein absorption pre-cleaning(RT):  15mins:18.5±4.2 ng/mm2  24h: 31.9±5.3 ng/mm2  Prolystica (RT):  1h: Data NR  2h: Data NR †  24h: Data NR †  Prolystica (F):  1h: Data NR  2h: Data NR †  24h: Data NR †  Progenica (RT):  1h: Data NR  2h: Data NR  24h: Data NR†  Progenica (F):  1h: Data NR  2h: Data NR  24h: Data NR† |

Abbreviations: SS: Stainless Steel; DT: Drying time; BH: Brain Homegenate: RT: Room Temperature; F: Refrigerated; h: hour(s); NR: Not reported; EDIC/EF: Episcopic differential interference contrast/epifluorescence; EDX: Energy dispersive X-ray spectroscopic;

\*\*Secker 2010197, abstract too \*Data for 30oC too but ‘efficacy changes little between the ambient temperatures’ †Level of difference is p<0.05 compared with the RT Air sample for same time point (data for dry bag and wet bag indicate statistically significantly reduced levels of residual protein). §Unclear: not reported in Methods, but comments in Discussion sections of papers indicate measurement was of in situ proteins, e.g. Howlin (2010178): ‘A concentration of 0.03 ng/mm2 prion-associated amyloid was detected in situ on the wires’; Secker (2015194): ‘ThT/SR dual stain alongside sensitive EDIC/ EF microscopy was the chosen detection method due to its sensitivity down to the picogram range and its ability to detect in situ amyloid contamination as well as total protein’.

### *2.6.3 Discussion/ summary of studies on residual mass and decontamination*

The published evidence suggests that standard cleaning practices within SSDs do not achieve levels of <5µg residual protein per instrument for all instruments, as required by current guidance (Department of Health and Social Care, 2016198). However, these published data are based on different assays and detection methods and the most recent data (Smith *et al* 2018191) suggest that as much as 87% of assessed instruments might have protein residue of <5µg per instrument side, and 96% might have residue of <10µg per instrument side. Recent papers (Secker 2011195, 2015194) also report very large differences in protein absorption on instruments kept in dry or wet conditions, with the latter producing as much as a 98.2% reduction in protein absorption compared to dry conditions (p<0.001) (Secker 2011195). Standard cleaning in SSDs might therefore be expected to produce residual protein levels of <5µg per instrument side for neurosurgical instruments kept in moist or wet conditions before processing. There is also some evidence for reduced contamination of endoscope channels if kept wet, although the evidence is more equivocal (Herve 2013177).

The findings for autoclaving at 134°C for 15-20 minutes in the more recent sample of studies are generally similar to those previously reported for publications up to 2004: log reductions of between 4 and 5, while transmission rates are highly variable (ranging from 0% to 100%) but are generally more than 50%. It is generally accepted that autoclaving alone only partially inactivates TSE prions (Bonda *et al* (2016),199 Belay *et al* (2013),115 Rutala *et al* (2010),200 Dickinson *et al* (2009),201 Fichet *et al* (2004)202). The majority of studies published in 2004 and before focused on the 263K scrapie prion strain, while the more recent data have investigated efficiency of autoclaving on a wider range of prions, e.g. RML and various CJD and BSE strains. Some strains, such as the M1000 strain, appear to be more resistant to autoclaving.

Certain combinations of autoclaving and enzymatic or alkaline detergents have also been reported to achieve log reductions of infectivity in excess of 5 and transmission rates of 0% in animal assays: for the 263K, RML, 301V, cattle BSE, Sc237 and sCJD prions strains, alkaline detergents (Rogez-Kreuz *et al* (2009)),170 SDS 0.2%/NaOH 0.3% (Lemmer *et al* 2008)169, Rapid Multi Enzyme Cleaner trial formulation (RMEC) B (Lawson *et al* 2007)172, 4% SDS + 1% AcOH (Giles *et al* 2008)184, Peretz *et al* 2006)181, H2O2 and gas plasma (Sterrad NX1 and 2 cycles) (Rogez-Kreuz *et al* 2009). 170 It has been reported that, based on the evidence, the following should be sufficient to achieve adequate levels of inactivation and decontamination for prions bound to steel wires: a combination of an alkaline or enzymatic detergent followed by autoclaving, with each process known to produce a log reduction of >5 (Rutala *et al* (2010)200).

Within the specified requirements of dose, time and temperature of exposure, a number of decontaminants, without autoclaving, were also reported to achieve log reductions of at least 5 and/or 0% transmission across a range of prion strains. These included Rely+On PI (DuPont) and prionzyme (Genecor) (Edgeworth *et al* (2011)179); sodium chloride (NaOH) (Edgeworth *et al* (2011),179 Bellon *et al* (2014)174); trigene disinfectant and RF gas plasma (Baxter *et al* (2005)183); SDS-PK-Pronase (Jackson *et al* (2005)180); H2O2 and gas plasma (Rogez-Kreuz *et al* 2009,170 Lehmann *et al* 2009168); and combinations of enzymatic detergents and disinfectants (Lehmann *et al* (2009)168). However, it has also been stated that sodium hydroxide and sodium hypochlorite, while effective, “*are not compatible with various pieces of medical equipment, and … present a serious handling hazard for healthcare employees*” (Lehmann *et al* (2009),168 Rutala *et al* (2010)200), although sodium hydroxide is reported to be less corrosive than sodium hypochlorite (Belay *et al* (2013)115). A combination of immersion in sodium hydroxide or sodium hypochlorite, followed by autoclaving, is recommended by the WHO (Belay *et al* (2013)115; WHO).

It has been acknowledged that these studies do not permit a direct comparison of their respective findings and that the findings are, in some cases, contradictory or discrepant because they have been conducted under different conditions (such as differing prion strains, drying times, whether *in vitro* or *in vivo*, different animal assays, infectious titre of the material used, time and temperature of the exposure to the decontaminant, dose of the decontaminant, observation period, substrate used, infectivity detection method used (Belay *et al* (2013),115 Rutala *et al* (2010),200 Rochefort *et al (*2010),203 Jackson *et al* (2005),180 Rogez-Kreuz *et al* (2009)170 and Bonda *et al* (2016)199). Such differences also make direct comparison between findings difficult for human prions and other TSE prions (Belondrade *et al* (2016)171). It is also noted that all are laboratory studies that do not necessarily reflect procedures used in clinical settings; the papers retrieved for this systematic review included studies of surgical instruments and Sterile Service Departments (SSDs) (Baxter *et al* (2005),183 Murdoch *et al* (2006),188 Herve *et al* (2010)204), but they only report contamination with proteins (not prions) after standard decontamination processes. While steel wires are generally accepted to be the most useful simulator to test prion adherence to steel surgical instruments, it is also recognised that they do not clean in the same manner as larger, more complicated surfaces (Herve *et al* (2010),204 Dickinson *et al* (2009)201).

## 2.7 The evidence that instruments used for high-risk procedures remain in their original sets after decontamination

The purpose of this review was to identify relevant published and unpublished evidence to determine the extent to which instruments used in neurosurgery remain in a specific set after decontamination procedures as per NICE guidance (IPG196).14 Labelling or tracking systems may be in place to maintain the integrity of such sets and to reduce or prevent the migration of instruments between sets. Evidence for the migration of instruments between sets might have implications for the risk of transmission of disease between patients undergoing neurosurgery. A report by the Advisory Committee on Dangerous Pathogens' Transmission Spongiform Encephalopathy (ACDP TSE) Subgroup estimated that the likelihood of at least one instrument migrating in or out of a neurosurgical set is 50% (Bryant *et al*, 2015).113 This document contains a project report and guidance for the Department of Health (DoH) to employers on the precautions to control the risk of exposure of employees and others to TSE agents from work activities. The estimate does not appear to be supported by any evidence. However, if such a high level of migration of instruments during high-risk posterior segment surgery occurred it could potentially to promote a self-sustaining epidemic of CJD or vCJD.

### *2.7.1 Studies relating to evidence that instruments used for high-risk procedures remain in their original sets after decontamination*

The number and type of included studies are shown in Table 20.

Table 20: Characteristics of included studies

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Study | Country | Time period | Design | Strategy | Details |
| Belay *et al* (2013)115 | USA | 1998-2012 | Audit and evaluation of neurosurgery performed on CJD patients | None | An audit of the ability of specified centres to identify particular instruments and sets.  The study provides limited quantitative evidence on sets and set-splitting. |
| NICE 2016205 | England | NR | Qualitative and observational: interviews and a single site visit for neurosurgery | The implementation of guidance on maintaining set integrity | Qualitative evidence on the barriers to achieving or maintaining set integrity.  The study provides limited qualitative evidence on sets and set-splitting. |

Only two studies were identified that provided any evidence on whether instruments for high-risk procedures remain in their original sets (Belay *et al* (2013)115, NICE 2016).205 In 2013, an article was published by Belay *et al* (2013)115 reporting an audit to identify instruments and sets of instruments that might have been used on patients known to have CJD. The sample was limited to CJD cases from US hospitals and reported to the US Center for Disease Control and Prevention (CDC). The aim of the audit was to identify patients who subsequently underwent neurosurgery with the same instruments or sets. There was no reported strategy in place to maintain or to evaluate set integrity. The audit reported that a single hospital could have between one and 12 sets of instruments for neurosurgery; that 12 of the 19 affected hospitals had multiple sets; and in 11 of these 12 hospitals those sets used on a CJD patient could not be identified (see Table 21).

The second study was an unpublished report produced for NICE in 2016. The aim of the study was to explore the barriers and facilitators affecting the implementation of NICE IPG19614 on the surgical transmission of CJD. The document reported findings concerning the identification of at-risk patients and the acquisition of instruments, but also covered the principal perceived barriers to the implementation of the guidance on set integrity, which required keeping all instruments for neurosurgery within their designated sets or ‘kits’. The sample was limited to four NHS trusts in the UK. The report did not provide a detailed methodology for the study. Study participants (‘clinicians and other users’) reported multiple barriers to maintaining set integrity, i.e. guaranteeing that instruments did not migrate between sets. These are detailed in Table 21 and included: the absence of an adequate and reliable instrument tracking system; errors in scanning instruments that did have barcodes; the periodic inaccessibility of tracking systems; and their failure to be completely integrated with patient records. The study also reported, however, that set integrity had been improved in the sampled settings by stopping the use of supplementary instruments and the increased use of single-use instruments. It is important to note that the report provided no quantitative evidence on whether instruments for high-risk surgery remained in their sets, but given that participants reported many problems with identifying and tracking certain instruments, the migration of at least some instruments between neurosurgery sets is probable.

Table 21: Findings of included studies

|  |  |
| --- | --- |
| Study | Findings |
| Belay *et al* (2013)115 | * At least 12/19 (63%) hospitals had multiple neurosurgical sets, making identification of contaminated instruments nearly impossible in some hospitals by the time of CJD diagnosis. * For hospitals with available information, the number of neurosurgical sets per hospital ranged from 1 to 12. * Overall, the CJD-contaminated sets could not be identified in 11 (58%) of the 19 hospitals. In these 11 hospitals, the exact number of patients exposed to the instruments used on the index patient could not be determined. |
| NICE 2016 | Barriers that affect the implementation of the guidance on keeping instruments for high-risk surgery within specific sets:   * High cost of sets and lack of clarity over responsibility for paying for full sets; * Lack of clarity on categories of patients who are to be exposed to particular sets; * Lack of conviction regarding level of transmission risk to patients; * Less paediatric work in a hospital, less likely to have specific sets for the younger cohort; * Absence of an adequate and reliable instrument tracking system:   + Some barcoding / laser etching has been undertaken in some sites, but this can be high cost and some instruments are too small to barcode;   + There are errors in scanning;   + Tracking system is not always accessible and is not fully integrated with patient records   Facilitators that enable the implementation of the guidance:   * Use of single-use or disposal of re-usables where possible (more frequently than previously); * Reasonable cost of some disposables; * Users report that use of supplementary instruments, that might migrate between sets, has been stopped |

### *2.7.2 Discussion/ summary of evidence on set-keeping for high-risk procedures*

Very little research has been undertaken to evaluate whether instruments for high-risk neurosurgeries remain in their designated sets. The two studies identified for this systematic review reported only limited evidence on this question. One study was conducted in the USA and reported that instruments could not be identified in the vast majority of cases where they had been used on a patient who was later diagnosed with CJD, and where there were multiple sets in a hospital (Belay *et al* (2013)115). The second study was performed in the highly-relevant setting of the NHS, but is unpublished and its methodology was poorly reported (NICE 2016). It did not report quantitative evidence on whether instruments for high-risk surgery remained in their sets; rather, the evidence consisted of clinicians’ and users’ reported experiences of implementing NICE IPG196 guidance14 on keeping instruments for high-risk surgeries in their designated sets. These participants reported a range of barriers to set integrity, but also reported more frequent use of single-use instruments and anaesthetic equipment, and that supplementary instruments were no longer used. These developments reduce the absolute levels of migration of contaminated instruments between sets. Evidence to substantiate the estimated likelihood of 50% for at least one instrument migrating in or out of a neurosurgical set, posited in the DoH guidance report (Bryant *et al*, 2015113) is therefore limited, but indicates that there is a high probability that at least some if not all instruments in neurosurgery sets do migrate between sets.

## 2.8 The evidence for complication rates of single-use compared with reusable instruments for high-risk procedures

The aim of this review was to identify any published or unpublished evidence for the safety of single-use instruments compared to reusable instruments for high-risk procedures. Safety was to be determined by the relative frequency of complications. This review excluded instruments, including anaesthetic equipment, which would not normally come into contact with high-risk tissues (Rutala *et al* (2010),200 and Department of Health206) or which are now single-use (NICE 2016).205 Evidence on safety outcomes might have implications for the viability of single-use or disposable instruments as an alternative to reusable instruments for high-risk procedures.

### *2.8.1 Studies relating to evidence for complication rates of single-use compared with reusable instruments for high-risk procedures*

No relevant papers were identified pertaining to this review question.

### *2.8.2 Discussion/ summary of complication rates for single-use vs reusable instruments*

An unpublished report produced for NICE in 2016 explored the barriers and facilitators affecting the implementation of NICE IPG19614 on the surgical transmission of CJD. The report summarised the findings of an observational site visit and interviews with ‘clinicians and other users’ in a sample of four NHS trusts in the UK. The participants reported more frequent use of single-use instruments and anaesthetic equipment than previously, and that single-use instruments were increasingly relatively inexpensive. However, no published or unpublished studies were identified by this systematic review that compared complication rates for single-use instruments with the complication rates for reusable instruments employed in the designated high-risk neurosurgeries. The relative efficacy and safety of these groups of instruments or devices is therefore unknown.

## 2.9 The evidence for the likelihood of future surgery for a patient undergoing high-risk procedures

The purpose of this review was to identify relevant published and unpublished evidence to determine the risk of future surgery for a patient undergoing high-risk neurosurgical procedures. A risk assessment study performed for the Department of Health (2001) reported one factor that can have a significant impact on infection dynamics is the chance of individuals having two or more operations (especially surgery to the central nervous system or posterior eye).207 The aim of this review was to assess the potential number of high-risk tissue exposures to potentially contaminated instruments, which might then have implications for the risk of transmission of disease to patients undergoing high-risk procedures.

### *2.9.1 Studies relating to evidence for the likelihood of future surgery for a patient undergoing high-risk procedures*

Only one study was identified that provided any evidence on the risk or rate of neurosurgery after a first neurosurgical procedure (Bird *et al* (2009),208 see Table 22). The aim of the study was to assess the feasibility of post-mortem surveillance of patients who had undergone neurosurgical procedures at least five years previously in order to explore the prevalence of subclinical vCJD. To do this, the article analysed the relationship between mortality and re-operation rates by procedure. The annual incidence of mortality in this cohort five or more years after the first instance of neurosurgery was as low as 3% for certain procedures that would not be considered as not high-risk (such as primary/revision excision of a lumbar disc): whereas a greater likelihood of mortality was associated with other procedures (e.g. brain excisions and the drainage of extra- and sub-dural haematomas).

Table 22: Characteristics of included studies

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Study | Country | Time period | Design | Type of surgery | Details |
| Bird *et al* (2009)208 | UK (Scotland) | 1993-2001 | Audit and evaluation | Neurosurgery | Neurosurgery (and proportions of patients experiencing more than one procedure) and mortality |

The article reported the extraction and analysis of patient records’ data relating to the 10 most frequent neurosurgical operations performed in Scotland in the period 1993-2001, focusing on four procedures considered to present a medium- or high risk of CJD prion transmission: drainage of extra- and sub-dural haematoma; cerebral aneurysm operations; primary or revisional decompression operations; and the creation of ventricular shunts (Bird *et al* (2009)208). Two additional procedures from this paper have also been included here as potentially relevant: unspecified excision of brain, and excision of brain lesion(s) due to their low 5-yr survival rates (41.5 and 29.9 respectively). In terms of the current review, the aim was to document the potential for surgical transmission through contaminated instruments by establishing the rate of future high-risk procedures following an index procedure. It is not clear whether, in the Bird (2009)208 report, the future procedures are always the same as the index procedure (i.e. if the index procedure was concerned ventricular shunts, then the reported rates of future procedures also only related to ventricular shunts) or whether they might be a neurosurgical procedure different from the index procedure. The evidence was presented as event rates for procedures deemed to be of high or medium potential risk of vCJD transmission (see Table 23).

Table 23: Findings of Bird *et al* (2009)208 on subsequent event rates for selected neurosurgical procedures for any patient within the time period 1993-2001

|  |  |  |  |
| --- | --- | --- | --- |
| Procedure | Only one subsequent procedure after the index procedure  % (n) | More than one subsequent procedure  % (n) | Proportion of individuals with a subsequent procedure who underwent more than one% (n) |
| Drainage of extra- and sub-dural haematoma\* | 8.3 (221/2,654) | 2.4 (63/2,654) | 22.2 (63/284) |
| Cerebral aneurysm operations | 14.8 (264/1,782) | 7.1 (127/1,782) | 32.5 (127/391) |
| Creation of ventricular shunts | 21.2 (191/900) | 28.3 (255/900) | 57.2 (255/446) |
| Excision of brain – unspecified\* | 12.1 (110/911) | 6.9 (63/911) | 36.4 (63/173) |
| Excision of brain lesion- frontal etc.\* | 13.0 (139/1072) | 5.6 (60/1072) | 30.2 (60/199) |

\*Not specified as high risk

The data indicate that the proportion of individuals in this sample having a second or third procedure (or more) within 5-10 years after an initial neurosurgical procedure differed depending on the index procedure (see Table 23). This ranged from 10.7% for individuals having one of more additional procedures for the drainage of extra- and sub-dural haematoma to 49.5% for individuals having one of more additional procedures related to a ventricular shunt. In the case of ventricular shunts, a majority (57.2%) of those who had subsequent procedures were also likely to have more than one additional procedure.

### *2.9.2 Discussion/ summary of risk of future surgery in high risk procedures*

The Bird *et al* (2009)208 paper is a UK (Scotland) study analysing relatively recent patient records’ data on the actual proportions of patients undergoing one or more medium- or high-risk neurosurgical procedure. This evidence indicates that, depending on the procedure, between 50% and 90% of patients are unlikely to have a second high-risk procedure within 5-10 years of the initial procedure and that the number of patients undergoing additional procedures, with their increased risks of surgical transmission, depends heavily on the procedures involved. The potential for the Bird *et al* (2009)208 paper to inform the model is limited, however, as it did not focus solely on high-risk procedures and does not compare the risk of additional procedures with control data for those who had not undergone an index high-risk procedure.

# 3 COST EFFECTIVENESS

## 3.1 Background

Previous modelling work assessing the risks of surgical transmission of Creutzfeldt-Jakob disease (CJD) was undertaken by the School of Health and Related Research (ScHARR) culminating in a report in 2006.11 Henceforth this will be known as the ScHARR report. This report was part of the evidence base appraised by the Advisory Sub-Committee (CJDAS) who produced interventional procedures guidance (IPG) 196.209 This guidance highlighted three high-risk surgical areas: neurosurgery; posterior eye; and neuroendoscopy. It was recommended that migration of instruments between sets should be abolished and that single-use instruments were not recommended on the basis of cost-effectiveness with the exception of accessories for neuroendoscopy. A separate recommendation was made that separate sets of instruments be established for patients born since 1st January 1997, (who are unlikely to have been exposed to the bovine spongiform encephalopathy epidemic).

ScHARR have undertaken an update of the previous work focussing solely on the surgical procedures deemed to be high-risk. This update incorporates the latest evidence on key model parameters and assess a range of appropriate strategies and interventions. Reasons for updating IPG196 include: the continued evolution of high quality and less expensive single-use instruments; the lack of adoption of new decontamination methods potentially effective against human prions; the findings of abnormal prion accumulation in the appendices of patients born after 1996; and anecdotal reports that the recommendations of IPG196 have proved to be difficult to implement, or unachievable, for a number of units. The primary deliverable was a report for a NICE committee that had been convened for the purposes of providing an update to IPG196.

The analyses undertaken assess the potential transmissions of all forms of CJD, which include: sporadic CJD (sCJD); familial CJD; and iatrogenic CJD. Throughout the report, any CJD cases that have been caused by surgical transmission will be abbreviated to stCJD.

Many data relating to model parameters are subject to considerable uncertainty and were populated following two elicitation sessions, one with epidemiological experts and one with decontamination experts. At a meeting of the NICE interventional procedures (IP) committee and ScHARR in October 2017, it was decided that the elicitation related to epidemiological parameters should be re-conducted to address potential concerns relating to the lack of potential to be misdiagnosed with a different neurodegenerative disease, and with the incubation periods previously elicited. This elicitation session was undertaken on the 18th of January 2018; results of the elicitation exercise are contained in Appendix 4.

### *3.1.1 Cost-effectiveness literature searches*

The literature searches of bibliographic databases were performed on 14th August 2017 and yielded 1108 citations. Forty-eight citations were obtained for full text retrieval. Evidence from none of the papers were directly used within the model but some provide context or alternative values and have been detailed in the appropriate section.

## 3.2 The conceptual model

Within the literature review a publication by Bennett *et al.*13 was identified, which was not conceptually different from Stevenson *et al.*,12 but used a system dynamics approach. In contrast to Stevenson *et al*, Bennett *et al* commented that instrument migration did not impact on the expected number of infections. Conclusions from the Bennet et al paper was that ‘*the risk of surgical transmission of vCJD could not be dismissed*’ and that improvements to decontamination ‘*should be respectively cost-effective unless vCJD turned out to be a very rare disease*.’ A further paper by Garske *et al*.210 reported that key determinants of future cases were the number of times an instrument is re-used, the infectivity of contaminated instruments and the effectiveness of decontamination. These results came from a differential equation model which did not consider instrument migration nor the mass transferred to a patient. Neither model was deemed by the authors of this report to be preferable to that described by Stevenson *et al*.12 which was a summary of a report11 undertaken for the CJDAS, with the addition of Bayesian updating to take into account further observed data between the generation of the results and submission of the manuscript. The model structure of Stevenson et al was used as a foundation for the modelling undertaken in the report and was amended as recommended by the NICE committee, most noticeably to include the possibility that patients may be an stCJD case but could be diagnosed with an alternative neurodegenerative disease.

A schematic of the conceptual model relating to infection transmission is shown in Figure 4. Figure 4 depicts the flows of patients, instrument sets and supplementary instruments (SI) that have the potential to transmit CJD surgically. The decontamination cycle removes mass from the instruments and reduces the infectious titre where applicable. During the operation, the decontamination process, and the instrument storing process, instruments may migrate between sets. Furthermore, SIs cannot always be distinguished from similar items in the main instrument set and migration between SIs and instruments from the main set can occur. Further details are provided in following sections. The modelling unit was a geographical area representing a population 1/27 of the size of England which was assumed to have a neurosurgical centre and a posterior eye centre. A key change in the methodology is that where previously patients born after 1996 were excluded from the original ScHARR model, these were explicitly included in the updated modelling work. The rationale for the change was that it may be the case that such patients can be infectious, whereas previously this was not thought possible, and that this explicitly allows an evaluation of the health and cost implications of removing the guidance that patients born after 1996 should use different instrument sets to the remainder of the population.

Figure 5 provides the conceptual model for determining the outcomes for patients who have become infected. There has been a fundamental change in this process since the earlier work as the possibility that patients who become symptomatic following infection with CJD are misdiagnosed as having a different neurodegenerative disease is included. Further details are provided in following sections.

The model was run from January 1st 2004, the year at which a proportion of key distributions within the model were elicited, to 2018 in the calibration period. This duration includes a one-year warm-up period from January 1st 2004 to January 1st 2005, which allows for the possibility that instruments were contaminated with CJD prions at the start of 2005. The expected number of modelled CJD cases (estimated based on the number of transmissions that resulted in clinical infection and the elicited probability of correct diagnosis) between 2005 and 2018 were then compared to those potentially observed in the UK to establish plausible bounds for use within probabilistic sensitivity analyses (PSA) and then subsequently to determine likelihood ratios for each probabilistic sensitivity analysis configuration. This process is described in further detail in a later section.

Having established parameter configurations that were plausibly consistent with the number of stCJD cases potentially observed, the model was run for a further five years to look at the potential loss of health due to stCJD associated with each strategy evaluated.

The model was constructed in Simul8 2017 Professional Edition (© Simul8 Corporation). An NHS and Personal Social Services perspective was taken and both costs and benefits were discounted at 3.5% per annum as recommended by NICE.211

Figure 4: The conceptual model relating to the infection process

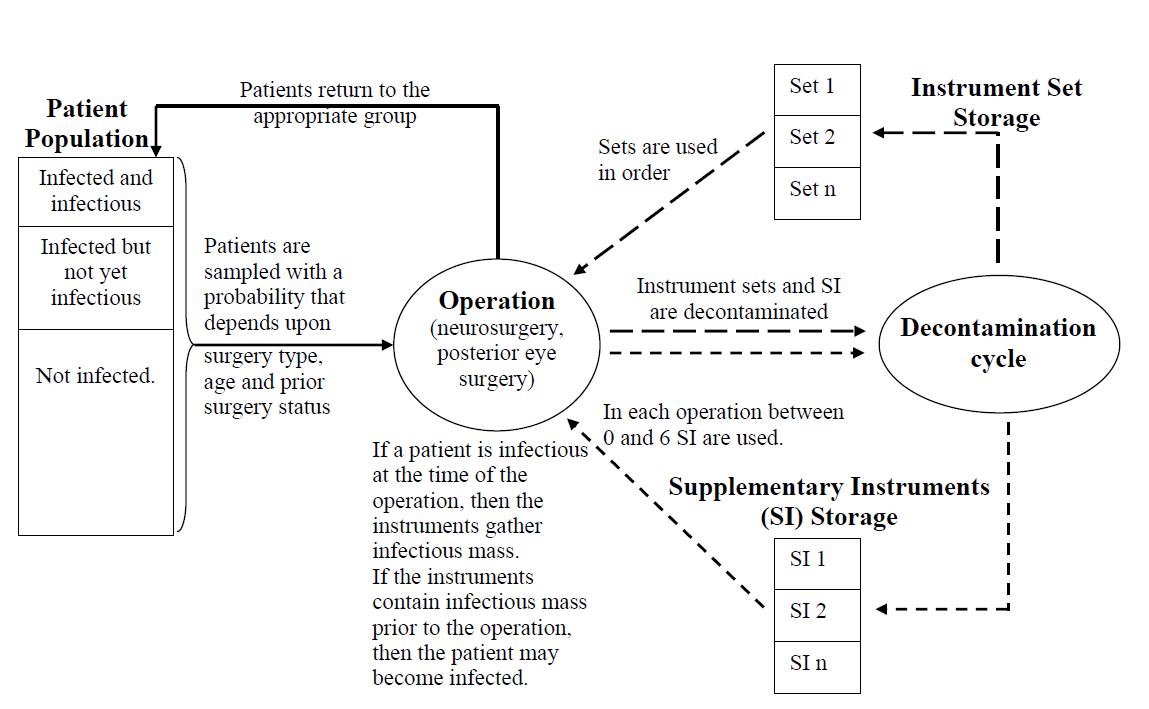


Figure 5: The conceptual model relating to patient outcome post infection



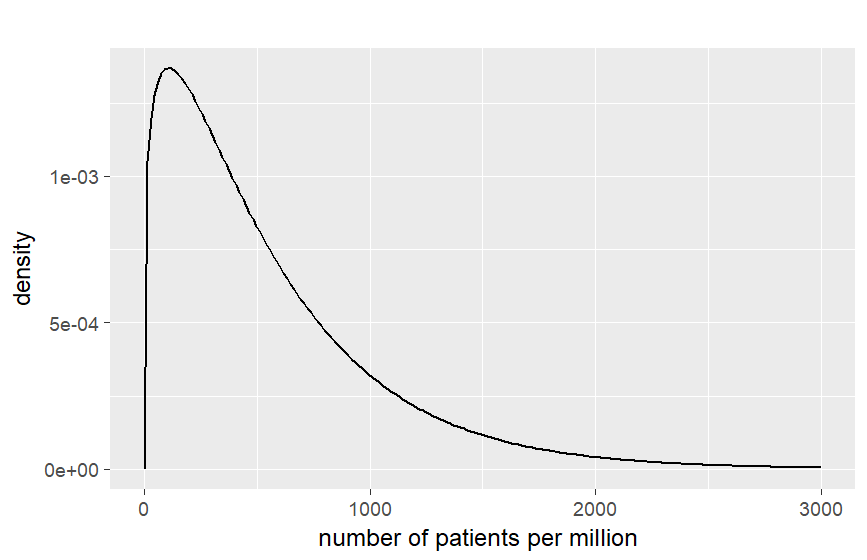
## 3.3 Key model parameters

### *3.3.1 Parameters relating to the probability and the mass of prions being transferred to surgical instruments*

3.3.1.1 The underlying probability of CJD prions within central nervous tissue in the asymptomatic population

The experts in the elicitation session indicated that the previously elicited distributions relating to the prevalence of CJD prions in all tissue for patients aged 16-39 in 2005 could still be used for the prevalence of CJD prions in central nervous tissue in 16-39 year olds in the current analysis, although they acknowledged that the range would produce an over-estimate. The experts disagreed with the previous experts in whether the prevalence would be greatest in the 16-39 year-old age group compared with the 0-15 years, 40-69 years and 70 years and over age band. The current experts believed that the elicited distribution should be used for all age groups. The distribution used to populate the model is provided in Figure 6 and represents a Beta (1.240, 2225.393) for the prevalence. The distribution provides a 95% credible interval (CrI) ranging from 26 to 1875 people per million population.

Figure 6: The prevalence of CJD prions within central nervous tissue



The NICE committee asked that two scenarios be evaluated which used different assumptions for the patients born after 1996, henceforth denoted the P96 group. In one scenario it was assumed that the P96 group were not infectious, as these were assumed unlikely to have been exposed to the bovine spongiform encephalopathy epidemic; in an alternative scenario it was assumed that the P96 group had the same probability of being infectious as the general population.

3.3.1.2 The residual mass per surgical instrument

The ScHARR report11 assumed that the mass on an individual instrument was 2.88mg of wet tissue equivalent, for instruments used for tonsillectomies, and 1.26mg of wet tissue equivalent for instruments used in general surgery. This mass was assumed to be independent of size and complexity. The source for this was ‘*provided by Professor Baxter and colleagues from the University of Edinburgh*’ with these data reported in a different form within Baxter *et al*.212 It was assumed that that the tonsillectomy value was generalisable to the residual mass on brain and posterior eye surgery. When multiplied by the number of instruments assumed in each set equated to 51.84 mg of wet tissue equivalent on brain surgery instrument sets and 25.92 mg of wet tissue equivalent on posterior eye instrument sets. Each SI would have a wet mass equivalent of 2.88mg. These values were assumed fixed.

During discussions on the parameterisation of residual mass a committee member highlighted a recently published article, Smith *et al*.191 that suggests that the residual protein mass is likely to be less than 5µg protein mass per instrument side. This is considerably less than that used in the previous ScHARR report,11 which was 576µg of protein mass (2.88mg of wet-tissue equivalent).

A preliminary inspection of articles discussing residual mass was undertaken which indicated that protein mass ranges between 163-756 µg (120 instruments) in Baxter R *et al*.187 and between 8-91µg (mean 71.67 µg; 43 instruments) in Murdoch *et al*.188 Lipscomb *et al*.190 presented further evidence based on a set each from nine NHS trusts (260 instruments in total) and reported that 66% of all instruments showed severe contamination in at least one sample area, which equates to *>4.4µg/mm2.*

Examining the data in Baxter *et al*. and Murdoch *et al*., the mean residual protein mass per instrument in 2004 was set to 200µg (95% CI 150µg to 250µg) in consultation with NICE committee members.

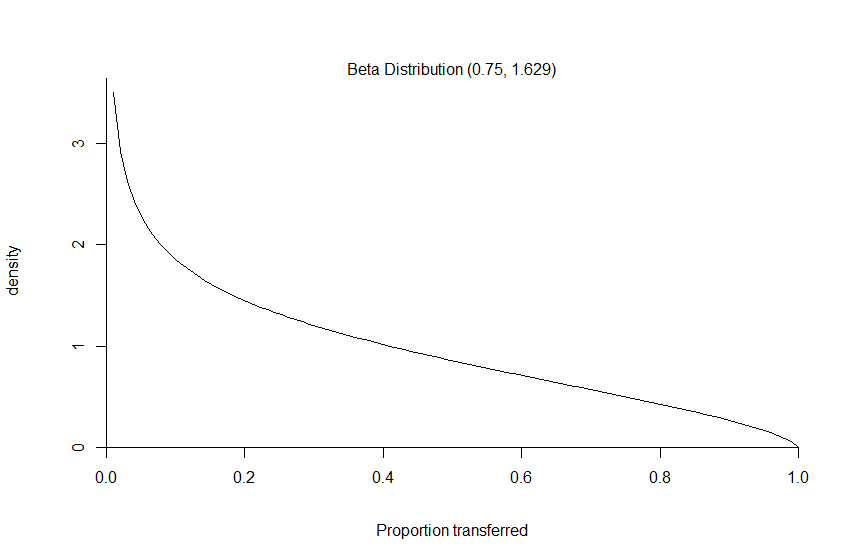
However, the data reported in Smith *et al*.191 and further data marked as academic-in-confidence obtained from a NICE committee member indicates that there has been a reduction in mass over time, for the hospitals where data has been recorded. In discussion with committee members, it was assumed that this change, which is assumed to be related to guidance on keeping instruments moist prior to decontamination, would have occurred in 2012 in line with the purchase of new instruments for those units who had adhered to IPG196. Following discussion with committee members, the mean residual mass for those units which were compliant with guidance to keep instruments moist was assumed to be 10ug. Within the 90% of units that did not adhere to IPG196 it was assumed that two-thirds of these (i.e. 60% of total units) would not keep instruments sufficiently moist, and that 200ug would remain on each instrument, with the remaining third (i.e. 30% of total units) adequately keeping instruments moist.

This conceptual model was operationalised by assuming that the mass harvested from a patient from 2012 onwards was 0.05 (10/200) that of the mass assumed harvested prior to 2012. Any infectious mass already on an instrument was assumed to remain on the instrument following measures to keep instruments moist.

3.3.1.3 The proportion of residual mass on brain and posterior instruments that is transferred to a patient

This value was estimated in the original elicitation exercise undertaken to inform the previous work undertaken by ScHARR.11 A depiction of the distribution for the proportion of residual mass transferred to the patient is provided in Figure 7. This has a mean of 31.5% and a 95% CrI of 0.4% to 87.1%, showing considerable uncertainty.

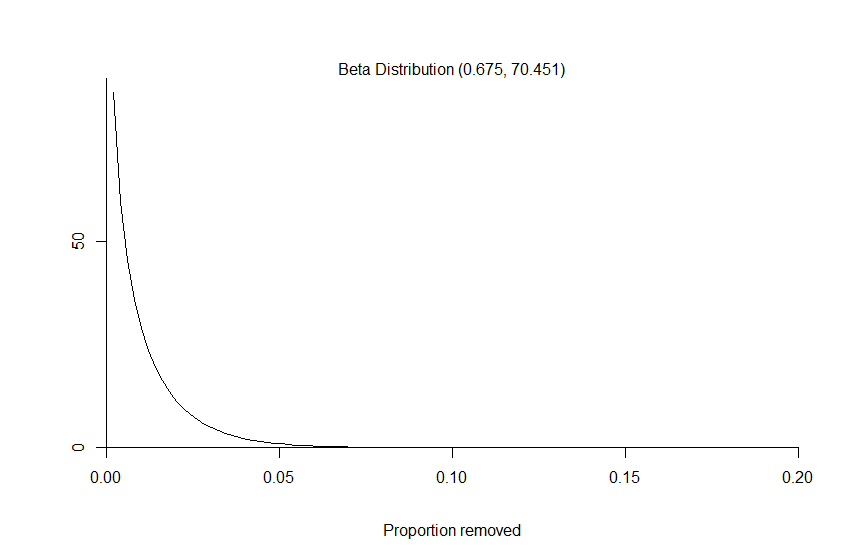
Figure 7: The proportion of residual mass transferred to a patient



3.3.1.4 The proportion of residual mass on brain and posterior instruments that is removed in a subsequent decontamination cycle

This value was estimated in the original elicitation exercise undertaken to inform the previous work undertaken by ScHARR.11 A depiction of the distribution for the proportion of mass transferred to the patient is provided in Figure 8. This has a mean of 0.9% and a 95% CrI of 0.0% to 4.0%.

Figure 8: The proportion of residual mass removed in a subsequent decontamination cycle



3.3.1.5 The proportion of mass on instruments that is replaced with new tissue per brain or posterior eye operation

In accordance with the previous ScHARR model,11 it was assumed that the residual mass on an instrument was in steady state. As such, the sum of the mass transferred to the patient and the mass removed in the next decontamination cycle equals the newly acquired mass from the operation. The mean value of the proportion of the mass removed from instruments during an operation is 32.4% with an estimated 95% CrI of 1.1% to 88.4%. Any supplementary instruments used were assumed to gather the same mass as instruments in the main set.

3.3.1.6 Residual mass, proportion transferred to a patient, proportion removed during the operation and the mass harvested during neuroendoscopy

The spreadsheet calculations that were performed to obtain the proportion of mass transferred to the patient and the proportion removed in the next decontamination cycle for rigid neuroendoscopes and flexible neuroendoscopes used in the previous modelling work11 could not be retrieved, but the values used in the PSA were available. These values have been re-used in the modelling, although it appears that there was a discrepancy between the mass transferred from a patient to a rigid neuroendoscope lumen used in the model and that reported in Table 11 of the ScHARR report,11 with the former being ten times smaller. For the updated work, we have erred on the side of caution and assumed that the greater mass is harvested per operation.

For information, key statistics on the proportion of mass harvested from a patient, the proportion of mass transferred to a patient and the proportion of mass removed in the next decontamination cycle are provided in Table 24.

Table 24: Information relating to mass transferred to a patient, mass washed off in subsequent decontamination cycles and mass harvested from a patient

|  |  |  |  |
| --- | --- | --- | --- |
| Type of neuroendoscope | Proportion of mass transferred to a patient  Mean (95% range in the PSA) | Proportion of mass that has already been decontaminated that is removed in the next decontamination cycle  Mean (95% range in the PSA) | Mass harvested from a patient (μg)  Mean (95% range in the PSA) |
| Flexible | 19.5% (3.10% to 49.73%) | 70.6% (42.10% to 91.22%) | 2.37 (0.74 to 4.21) |
| Rigid | 0.61% (0.00% to 2.99%) | 1.22% (0.00% to 5.24%) | 0.48 (0.00 to 2.24) |

### *3.3.2 Parameters relating to the decontamination of surgical instruments*

3.3.2.1 The assumed infectious titre of tissues containing CJD prions

In line with the ScHARR report,11 brain and posterior eye tissue were assumed to have 108 ID50s per gram. This value was assumed fixed and was applied from the moment the patient became infectious to the moment when clinical symptoms of CJD were observed, in which instance re-usable instruments would not be used on the patient.

Following discussion with the committee, the previous assumptions were amended to allow more heterogeneity in patients who have CJD prions in high-risk tissue. First, the mean infectious titre was varied between 107 and 109 per gram assuming a uniform distribution. Secondly, it was assumed that 20% of patients would have an infectious titre 1 log higher than the mean and that 20% of patients would have an infectious titre 1 log lower than the mean, with the remaining 60% of patients having the mean value. This approach incorporates uncertainty around the mean estimate as well as patient heterogeneity, with individual patient values ranging from 106 to 1010 ID50s per gram.

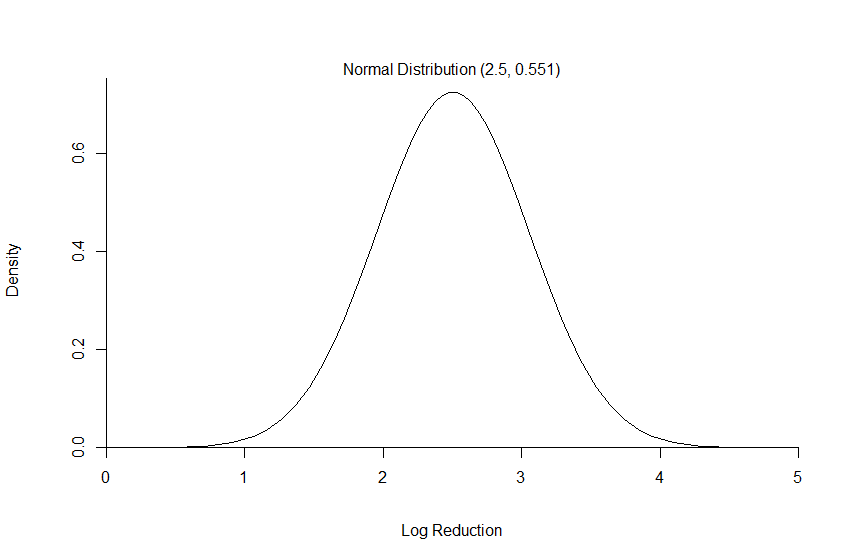
3.3.2.2 The effectiveness of current decontamination processes in reducing infectivity

The distributions produced from the elicitation exercise to inform the ScHARR report11 were considered appropriate by the NICE committee. These were split into three categories: the effectiveness of infectivity reduction in the first decontamination cycle; the effectiveness of infectivity reduction in subsequent decontamination cycles; and the mass removed in second and subsequent decontamination cycles. The model assumes that there have been no improvements in the reduction in infectivity since 2004.

3.3.2.2.1 The effectiveness of infectivity reduction in the first decontamination cycle

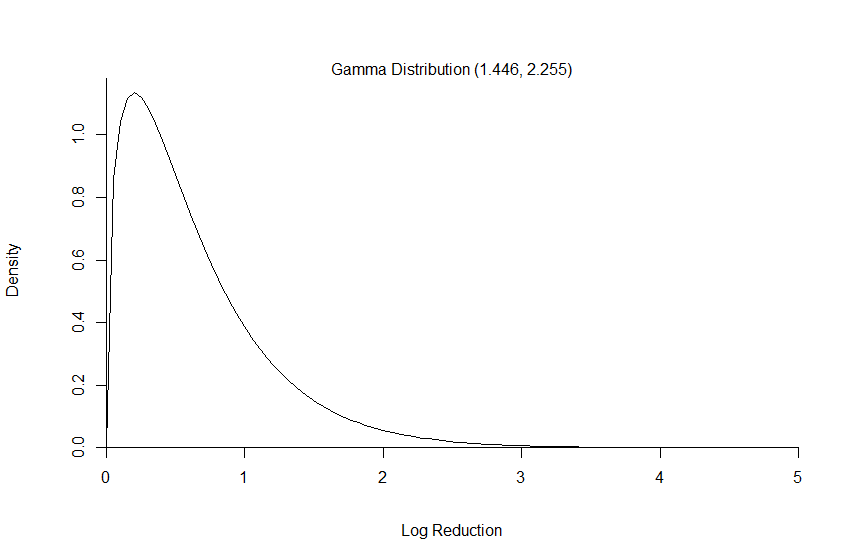
The distribution assumed for the infectivity reduction associated with the first cycle of autoclaving is displayed in Figure 9. This has a mean log reduction of 2.50 and a 95% CrI in log reduction of 1.42 to 3.58.

Figure 9: The reduction in infectivity in the first autoclaving cycle



The distribution assumed for the infectivity reduction associated with the first cycle of detergents for brain and posterior eye surgery is displayed in Figure 10. This has a mean log reduction of 0.64 and a 95% CrI in log reduction of 0.04 to 2.03. Note that detergents used in cleaning neuroendoscopes were assumed to not reduce infectivity.

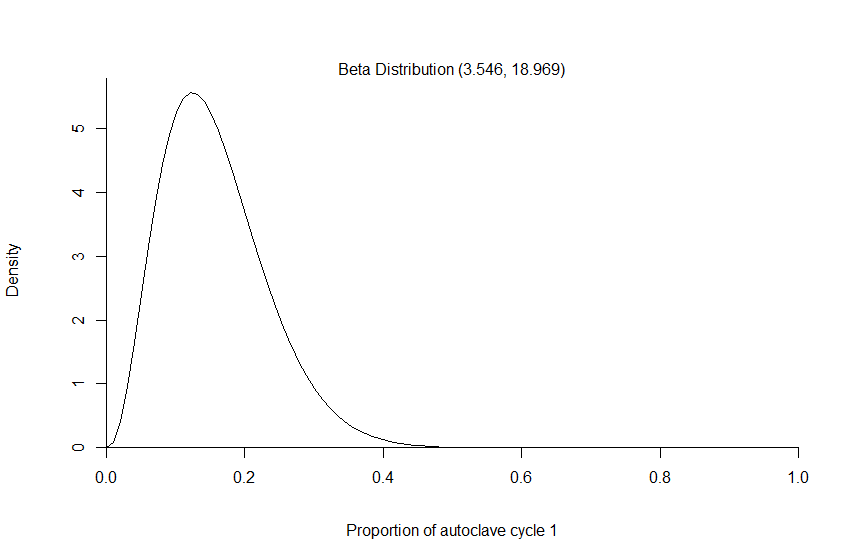
Figure 10: The reduction in infectivity in the first detergent cycle



3.3.2.2.2 The effectiveness of infectivity reduction in subsequent decontamination cycles

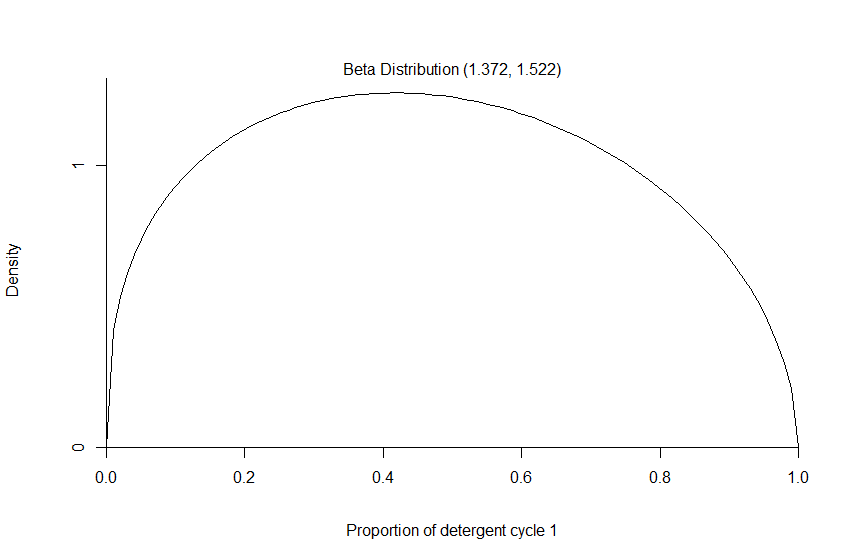
It was assumed in the ScHARR report11 that the second and third autoclaving cycle would reduce prion infectivity, although this would be to a lesser extent than the initial autoclaving cycle. The log reduction on the second and third autoclaving cycle was expressed as a proportion of the reduction estimated in the first cycle. The distribution assumed for the multiplier is shown in Figure 11. This distribution has a mean of 0.157 with a 95% CrI ranging from 0.043 to 0.330.

Figure 11: The proportion of autoclave cycle 1 log reduction achieved by cycles 2 and 3



It was assumed in the ScHARR report11 that the second detergent cycle would reduce prion infectivity, although this would be to a lesser extent than the initial autoclaving cycle. The log reduction on the second and third autoclaving cycle was expressed as a proportion of the reduction estimated in the first cycle. The distribution assumed for the multiplier is shown in Figure 12. This distribution has a mean of 0.474 with a 95% CrI ranging from 0.047 to 0.931.

Figure 9: The proportion of detergent cycle 1 log reduction achieved by cycle 2



3.3.2.2.3 The proportion of mass that has been through a decontamination cycle that is removed in subsequent decontamination cycles

This has been detailed in Section 3.3.1.4 for brain and posterior eye instruments and in Section 3.3.1.6 for neuroendoscopes.

3.3.2.3 The probability of disposing of a re-usable instrument

In the ScHARR report,11 it was assumed that following use, an instrument had a 1/250 probability of being disposed of, (range 1/200 to 1/300) with all infectious load on the instrument destroyed. For each instrument disposed of in a brain surgery set, it was assumed that between 0% and 12% (sampled from a uniform distribution) of infectious load was removed from the set. For each instrument disposed of in a posterior surgery set, it was assumed that between 0% and 25% (sampled from a uniform distribution) of infectious load was removed from the set. In discussions with the committee the probability of an instrument being disposed of was reduced to 1/2500 with a range of 1/2000 to 1/3000.

### *3.3.3 Parameters relating to instrument migration, costs and safety*

3.3.3.1 The instruments assumed on model set-up

In the modelling undertaken for the ScHARR report,11 it was assumed that there were: 12 brain surgery sets, with 18 instruments assumed to come into contact with potentially infectious mass; 12 posterior eye surgery sets, with nine instruments assumed to come into contact with potentially infectious mass; one rigid neuroendoscope and one flexible neuroendoscope both of which had a single accessory.

Following discussion with the committee, it was assumed that the number of instruments coming into contact with high-risk tissue in brain operations was lower than previously thought with the number reduced to 14 (previously 18).

For brain and posterior eye sets, the instruments sets were used in rotation. For neuroendoscopy operations, it was assumed that 75% were undertaken with rigid neuroendoscopes (which can be autoclaved) and 25% were undertaken using flexible neuroendoscopes (which cannot be autoclaved).

Brain and posterior eye sets were also complemented by six types of SI, each of which had six instruments which were used in rotation. During each operation, each SI had a 20% chance of being required.

For neuroendoscopy, IPG196209 recommended that all neuroendoscopy accessories become single-use. For simplicity, however, it was assumed that this was not followed, based on the committee’s estimation of units that had adhered to IPG196, and with an assumption that one supplementary instrument was used in all operations. If a large number of deaths was observed related to neuroendoscopy, this assumption would be amended.

3.3.3.2 Recommendations on instrument migration and use of supplementary instruments in IPG196

Maintaining the integrity of surgical instrument sets was shown to be a key parameter affecting the incremental cost-effectiveness ratios (ICERs) associated with the introduction of single-use surgical instruments.12 The ScHARR report11 made the following assumptions in relation to set integrity:

1. That the probability of an instrument being swapped with a similar instrument in a separate set was 50%, whilst the set was undergoing the decontamination process. This value was selected following ‘*discussion with clinicians and some evidence provided by Scantrack in their submission [ref not provided]*’. When instruments migrate between sets it was assumed that between 0% and 20% (sampled from a uniform distribution) of the infectious material in ‘Set A’ would move to ‘Set B’, with between 0% and 20% (sampled from a uniform distribution) of the infectious material Set B would move to Set A.
2. That when an SI was used, there was a 50% chance that this instrument would join the set with a similar instrument from the set becoming the SI. When this occurs, all infectious load on the SI is added to the set, and between 0% and 10% of the infectious load (sampled from a uniform distribution) in the set is assumed to reside on the ‘new’ SI.

The model has the facility to alter the levels of set migration following the publication of IPG196,209 which recommended that migration of instruments between sets should be abolished and that SIs that come into contact with high-risk tissues should either be single-use or should remain with the set to which they have been introduced. However, due to logistical and/or financial problems in implementing IPG196,209 these recommendations were not fully adhered to by all hospitals. The model has been set up so that it is assumed that after 2012, no SIs are used for those units that are assumed to adhere to IPG196.

3.3.3.3 The costs associated with single-use instruments

Data provided to a NICE committee member indicate that the costs of single-use sets are likely to lie in the region of £350 - £500 and that the cost of a single-use rigid neuroendoscope is £710. No cost was identified for a single-use flexible neuroendoscope.

3.3.3.4 The costs associated with re-usable instruments

In the ScHARR report,11 it was assumed that a brain surgery set costs £3500 and that a posterior eye set costs £1000. Based on the number of instruments that come into contact with high-risk tissue, the cost of an individual re-usable instrument is likely to be in the region of £100 - £200.

The ScHARR report assumed that a re-usable rigid neuroendoscope costs £397 and a re-usable flexible neuroendoscope costs £9300. More recent prices estimate that a re-usable rigid endoscope set including instruments would cost approximately £8850 with a flexible endoscope costing approximately £21,000.

3.3.3.5 The costs associated with decontaminating re-usable instruments

Data provided by a committee member indicated that the costs of decontaminating a re-usable instrument was an average of 60p in Scotland. Assuming that this result is generalisable to England, this would correspond to a decontamination cost of £8.40 for a high-risk tissue brain set and £5.40 for a high-risk tissue posterior eye set.

3.3.3.6 The costs associated with disposing of single-use sets

For simplicity, we have assumed that the costs of disposing of single-use sets are included within the purchase price. Given the relatively wide range in the costs assumed for a single-use high-risk tissue set (£350 to £500). The authors of this report deemed that this simplifying assumption would not cause significant inaccuracy.

3.3.3.7 The costs associated with keeping instruments moist

Data reported in Smith *et al*.191 state that the cost of NHS bags would be £440 per 7355 neurosurgical trays reprocessed equating to 6p per bag. Calculations based on the additional savings that could be made ‘using tap water and tray liner’ suggests that the costs of these elements are also 6p per tray. Thus it has been assumed that the cost of keeping instruments moist was 12p per set conditional on using NHS bags, tap water and tray liner.

3.3.3.8 The assumed safety of single-use instruments

In the base case it is assumed that the complication rates and outcomes are identical for re-usable instruments and single-use instruments. The NICE committee believed this assumption was reasonable.

3.3.3.9 The costs associated with systems to allow instruments to be tracked

Committee members provided data from an unpublished Society for British Neurosurgeons survey and from costs recorded at their own units that indicated that £750k across a 5-year period including necessary equipment would be a reasonable estimate. Sensitivity analyses were intended using £500,000 and £1,000,000.

### *3.3.4 Parameters relating to the probability of infection, the incubation time, and consequences if clinical symptoms appear*

3.3.4.1 The conceptual model of estimating the probability of infection when prions are transferred to the patient

In accordance with the earlier ScHARR model, the probability of infection was estimated using the mass transferred to the patient (in grams) and the infectious titre of the mass (in terms of ID50s per gram, where an ID50s is the dose required to infect 50% of the susceptible population,). It was assumed that the relationship between the number of ID50s and probability of infection was:

Probability of infection = MIN (No of ID50s transferred \* 50%, 100%)

Such that 2ID50s or more would result in a certain infection.

The mass assumed to be transferred per operation is detailed in Section 3.3.1.3, whilst the assumed infectious titre per gram is detailed in Section 3.3.2.

In a key change from the ScHARR report,11 it was assumed that all patients, regardless of age or genotype, were susceptible to CJD infection.

3.3.4.2 The incubation period following surgically-transmitted CJD infection

The incubation period associated with stCJD was elicited from clinical experts in January 2018. The results are contained in Appendix 1 but are briefly detailed here. The elicited results differed from those previously elicited in that: 1) distributions were no longer elicited for each genotype as it was assumed that a single distribution could cover all genotypes as the incubation period would be affected by the genotype of the recipient, the infecting prion, and the infectious dose provided, 2) uncertainty in the mean estimates were formally captured and 3) it was assumed that all genotypes were susceptible to CJD.

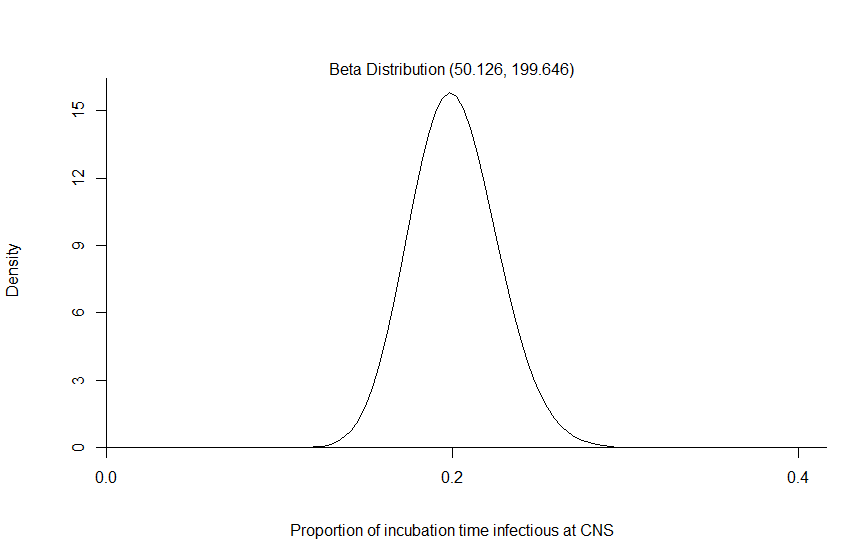
Four incubation intervals were specified; in the base case, each interval was assumed to be equally likely. These were: 0.25 to 2 years; 2 to 10 years; 10 to 20 years, and 20 to 50 years. Within each time interval, a uniform distribution was used on the assumption that each value was equally likely to occur. To allow for uncertainty around the mean incubation period, it was proposed that the first probability of being in the first three intervals would range between 10% and 40% whilst the probability of being in interval 4 (20 to 50 years) would lie between 15% and 35%.

As indicated in Figure 5, should the incubation time be less than the patient’s life expectancy (sourced from the Office For National Statistics213), the patient would display clinical symptoms. Otherwise, the patient would die without CJD symptoms. Each year a proportion of patients incubating CJD die, due to non-CJD-related reasons, in line with data reported by the Office of National Statistics.213 The probability of non-CJD related death was dynamic between 2005 to 2014, using the appropriate life table, but was assumed to use life tables from 2014 until 2023.

3.3.4.3 The infectious period following surgically-transmitted CJD infection

The proportion of the incubation period associated with stCJD for which a patient was considered infectious and able to pass CJD prions to instruments was taken from the elicitation session used to inform the earlier ScHARR report.11 This distribution is shown in Figure 12. The mean of this distribution is 20.0%, indicating that the patient is only infectious for the last 20% of the incubation period. The 95% CrI for this parameter ranged from 15.3% to 25.2%. It has been assumed that the infectious titre of CJD prions is at the maximum value for the entire infectious period.

Figure 12: The proportion of the incubation period during which the patient is infectious



3.3.4.4 Estimations of the relative likelihood of returning to high-risk surgery

Patients who are infectious can return to surgery and may do so at a quicker rate than people who have not experienced prior surgery. The earlier ScHARR report11 assumed that: 1) people who had previous brain surgery were 43 times more likely to have a further brain operation than people without a history of a brain operation; 2) people who had previous posterior eye surgery were 60 times more likely to have a further posterior eye operation than people without a history of a posterior eye operation; and 3) people who had previous neuroendoscopy were 761 times more likely to have a further neuroendoscopy than people without a history of a neuroendoscopy. These values were based on Hospital Episode Statistics (HES) data that were extracted by a third party (Northgate Information Solutions) and were assumed to be applicable for use in the updated modelling. Having performed sensitivity analyses in the construction of the model, by increasing the relative rates by 10, the model did not appear sensitive to this variable and the values were left at the values used previously.

3.3.4.5 The assumed costs and quality adjusted life years associated with CJD

Once clinical symptoms have developed, it is assumed that patients accrue no further QALYs due to the severity of the condition. The earlier ScHARR report11 used a value of £40,000 for the costs associated with treating a case of CJD. This has been updated using the inflationary indices reported in Curtis and Burns,214 and Curtis215 which estimate an inflation value of 302.3/240.9 (1.25) between 2005/6 and 2016/17 using the Hospital and Community Health Services index. Data reported in Barnett *et al*.216 indicate that costs of additional care and/or equipment was approximately £10,500 per person, from invoices received from 33 patients, although the authors of the paper state that ‘*local agencies contributions have not been quantified*’. This is lower than that assumed in the original ScHARR model which has been maintained as the base case value and is favourable to strategies to reduce future stCJD cases. For simplicity, we have assumed that the costs, from an NHS and Personal Social Services perspective, in 2017/8 for a CJD case was £50,000.

3.3.4.6 The probability that a person with CJD symptoms are not diagnosed with CJD

It is possible that patients with CJD may be diagnosed with another neurodegenerative disease. This possibility was not considered in the initial ScHARR report,11 but was requested following a meeting of the NICE committee. The distribution of patients that were presumed to be diagnosed with another neurodegenerative disease was elicited from experts in January 2018 (see Appendix 1 for full details) for two age bands: those aged below 60 years and those aged above 80 years, with the experts willing to allow the misdiagnosis in the 60 years to 80 years of age category to be the average of the two other age bands. The distribution for those patients aged under 60 years is shown in Figure 13.

The mean value is 13.0% with a 95% CrI of to 0.4% to 26.8%. The distribution for those patients aged over 80 years is shown in Figure 14. The mean value is 55.0% with a 95% CrI of to 18.6% to 88.4%. The simulated distribution for patients aged between 60 and 80 years of age inclusive is shown in Figure 13. This distribution has a mean of 34.0% with an estimated 95% CrI of 13.5% to 54.3%.

It should be noted that based on the advice of clinical experts on the committee, there has been no change in CJD case ascertainment levels since 2005. This is partially supported by data from the NCJDRSU in the UK (25th Annual Report (Figure 3217)) which showed similar age-specific mortality rates between 2005-09 and 2010-16 in those aged 60-64 years and those aged 75-79 years. However, the age-specific mortality rates were higher in the 70-74 years of age group in 2010-16 than in 2005-09, which could be indicative of better ascertainment in recent years. The assumption of equal ascertainment would favour single-use instruments.

In patients who are correctly diagnosed with CJD, the model does not explicitly distinguish between sCJD and stCJD and thus the probability node at the far right of Figure 5 is not contained in the model. However, it is appreciated that patients with stCJD may be categorised as sCJD, and these are used when calibrating the model output to the numbers of observed cases. This is described in more detail in Section 3.4.1.2.

Figure 13: The proportion of patients under 60 years with clinical CJD symptoms that are diagnosed with another neurodegenerative disease

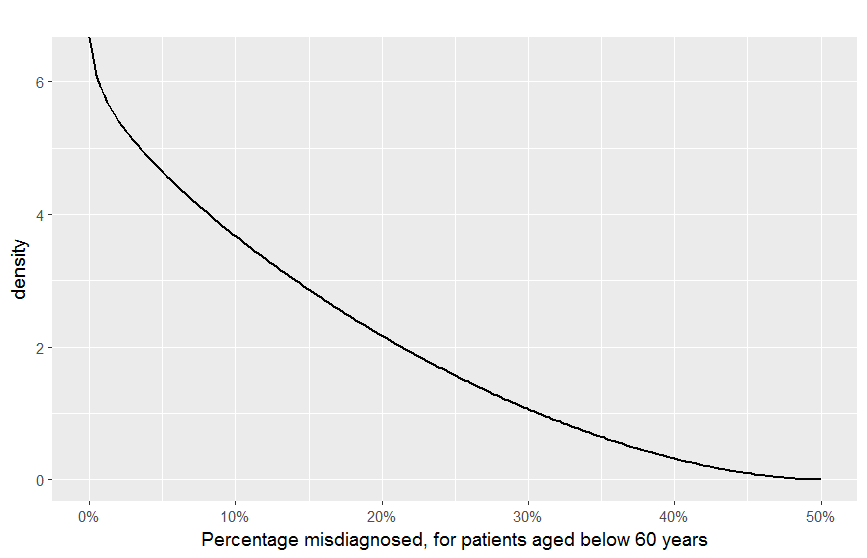


Figure 14: The proportion of patients over 80 years with clinical CJD symptoms that are diagnosed with another neurodegenerative disease



Figure 15: The simulated proportion of patients aged between 60 and 80 years inclusive with clinical CJD symptoms that are diagnosed with another neurodegenerative disease



### *3.3.5 Parameters relating to the numbers of operations that are considered to be high-risk and the characteristics of patients undergoing these operations*

3.3.5.1 The operations considered to be at risk

In consultation with NICE only high-risk operations are modelled, which have been subdivided into those related to the brain, those related to posterior eye operations and those involving neuroendoscopy. The operations, using HES data to four characters, that are considered to be high-risk were identified by an expert on the NICE committee and are contained in Appendix 2. For brain operations, an expert on the NICE committee grouped the operations into those with normal life expectancy, those where the patient would be expected to survive 18 months, and those with a 50% probability of death at 18 months and a 50% probability of a normal life expectancy.

Only the main procedure codes have been used rather than all the procedure codes, as there is a possibility that more than one high-risk HES code is undertaken within the same operation, using the same instrument set. In the modelling, the HES data have been inflated by 15% as in the ScHARR report11 to take into consideration that not all of the additional operations (between the main procedure and all procedures) are conducted simultaneously with another high-risk code, and also to incorporate operations undertaken by the private sector in non-NHS hospitals.

The estimated number of operations reported within the HES data since January 1st 2005 are provided in Table 25. For future years, the average number of operations in the last three years were assumed to continue. Operations were assumed to happen at a constant rate throughout the year. It should be noted that the values in Table 25 are those reported in the HES data as main procedures and have been increased by 15% within the model in line with the earlier modelling undertaken by ScHARR.

HES data provide age breakdowns for each code, with more granularity in the years 2012 onwards than prior to this date. Analysis of these data indicated that the age profile of patients for each of the three brain operation groupings, for neuroendoscopy, and for posterior eye operations remained relatively stable across time. As such, for simplification, the age profile within 2016-17 were assumed to apply throughout the model. Depictions of each assumed age profile are provided in Appendix C.

Table 25: The number of operations classified as high-risk by the NICE committee (HES data)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Brain 1 | Brain 2 | Brain 3 | NE | PE |
| 2005-06 | 19,554 | 5,346 | 1,684 | 302 | 4,629 |
| 2006-07 | 21,451 | 5,317 | 1,069 | 311 | 4,098 |
| 2007-08 | 19,302 | 5,517 | 1,062 | 338 | 6,164 |
| 2008-09 | 18,406 | 5,557 | 1,107 | 354 | 8,415 |
| 2009-10 | 19,404 | 5,706 | 1,101 | 389 | 7,660 |
| 2010-11 | 20,323 | 5,755 | 1,121 | 488 | 7,796 |
| 2011-12 | 21,288 | 5,889 | 1,217 | 497 | 5,081 |
| 2012-13 | 21,110 | 5,887 | 1,151 | 500 | 13,296 |
| 2013-14 | 22,497 | 5,905 | 1,110 | 539 | 13,060 |
| 2014-15 | 22,508 | 6,013 | 1,087 | 532 | 5,378 |
| 2015-16 | 22,916 | 6,106 | 1,110 | 527 | 5,226 |
| 2016-17 | 23,029 | 6,114 | 968 | 518 | 5,481 |
| Numbers assumed subsequent to 2017† | 22,818 | 6,078 | 1,055 | 526 | 5,362 |
| Brain 1 denotes operations with assumed normal life expectancy  Brain 2 denotes operations with assumed death within 12 months  Brain 3 denotes operations with a 50% chance of death within 12 months and a 50% chance of normal life expectancy.  † Estimated as an average of the numbers between 2014 and 2017  Note these data are inflated by 15% within the modelling to account for operations not coded as the main procedure and to account for operations conducted privately at non-NHS hospitals. | | | | | |

## 3.4 Calibration targets

### *3.4.1 The observed number of stCJD cases between 2005 and 2018 and the potentially unobserved number of stCJD cases*

3.4.1.1 The observed number of stCJD cases between 2005 and 2018

There have been no cases of CJD that have been categorised as stCJD during this period.

3.4.1.2 The potentially unobserved number of stCJD cases between 2005 and 2018

There are two possible ways in which patients with stCJD can be misdiagnosed. The first is that another neurodegenerative disease is diagnosed; this has been discussed in Section 3.3.3.5. The second way of misdiagnosis of stCJD is that a different form of CJD (in particular sCJD) is the presumed diagnosis. The potential number of patients misdiagnosed as a different form of CJD was investigated.

Data were supplied to a NICE committee member by the National CJD Research & Surveillance Unit (NCJDRSU) which detailed whether patients who had a diagnosis of CJD since 2005 had a history of neurosurgery or posterior eye surgery and a brief description of the operation. These data were reviewed by a NICE committee member who categorised each patient as having an operation that was of high-risk (and therefore potentially a stCJD case) or not.

For posterior eye surgery, there were potentially 24 individuals who had surgical operations that could have transmitted CJD, although only 10 of these had operations in 2005 or later. The year of the operation is important as we want to calibrate the model only to cases where the patient had been infected during the modelling period. For brain surgery operations, there were potentially 13 individuals who had operations that could have transmitted CJD. There were no dates of operation provided and thus it was assumed that the proportion of operations conducted in 2005 or later that was observed for posterior eye surgery (10/24) was applicable to neurosurgery, which equates to a possible 5 cases of stCJD since 2005. The sum of these calculations implies that there could have been 15 cases of stCJD transmitted since 2005 which had been misdiagnosed as another form of CJD, or just over 1 case per year on average.

## 3.5 Categorisation of surgical units, establishing PSA configurations that are plausible, and generating likelihood functions for plausible PSA configurations

### *3.5.1 Categorisation of surgical units*

Based on the heterogeneity in surgical units adhering to IPG196 and the analyses varying the assumption of whether the P96 group could be infectious from birth, six categories of surgical units were defined (demoted S1 to S6). These were:

* S1: A unit adheres to IPG196 and guidance on keeping instruments moist. The P96 group are infectious from birth.
* S2: A unit does not adhere to IPG196 but adheres to guidance on keeping instruments moist. The P96 group are infectious from birth.
* S3: A unit does not adhere to IPG196 nor does it adhere to guidance on keeping instruments moist. The P96 group are infectious from birth.
* S4: A unit adheres to IPG196 and guidance on keeping instruments moist. The P96 group are not infectious from birth.
* S5: A unit does not adhere to IPG196 but adheres to guidance on keeping instruments moist. The P96 group are not infectious from birth.
* S6: A unit does not adhere to IPG196 nor does it adhere to guidance on keeping instruments moist. The P96 group are not infectious from birth.

It was assumed that independent of whether the P96 group was assumed to be infectious, 10% of units adhered to IPG196 and guidance on keeping instruments moist, 30% of units adhered only to keeping instruments moist and that 60% of units neither followed IPG196 nor kept instruments moist.

### *3.5.2 Employing a heuristic to rule out PSA configurations that would produce implausible results*

Due to the time required for each run (approximately 12 seconds per ‘plausible’ (defined later) PSA configuration), the number of PSA configurations, the number of random number (RN) streams, the number of scenarios, and the number of PSA configurations that would not be compatible with the observed data, heuristics were used to generate the cost-effectiveness results. At all stages, a cautious approach was employed to ensure that potentially appropriate configurations were not prohibited. Appendix 5 describes the methodology using formal mathematical notation, with a lay description provided in the main text.

The initial step was to develop a metric to exclude PSA draws that would clearly be discrepant to the observed data (known cases of CJD that could potentially be attributed to surgical transmission) without having to run these configurations.

Here, a factor to efficiently maximise the likelihood (FML) was established and any PSA configuration with a value greater than the FML value was discarded.

FML was derived using a combination of parameters related to: infectious titre after a decontamination cycle; the mass transferred to a patient; and the prevalence of prion in tissue in asymptomatic patients.

FML = 10A x B x C, where:

A = Mean infectious titre (in log terms) x Log reduction in infectivity associated with the first autoclaving cycle x Log reduction associated with detergent on the first cycle

B = Residual mass on an instrument x (1 – the proportion of residual mass transferred to the patient)

C = The proportion of asymptomatic individuals with CJD prions in their tissue

In order to generate the FML threshold value, 2000 PSA configurations were drawn from the appropriate distributions and run using twelve RN streams for each of the following scenarios: S1, S2 and S3. Having assessed the likelihood of each of the 2000 PSA configurations producing results consistent with the observed data, it was decided that any draw with an FML value of > e12 would effectively have zero weight and could be discarded without affecting the results. Any draw with a value ≤ e12 could potentially be consistent with the observed data.

### *3.5.3 Running further analyses to remove PSA configurations that are potentially consistent with the observed data but generate an implausible number of transmissions when run through the model*

Two thousand PSA configurations with an FML ≤ e12 were sampled. For each configuration, the first RN stream was run, assuming an S3 surgical unit and determining whether there was a violation of the permissible limit (VPL) of clinical transmissions for patients aged 60 years or younger. It was noted that the clinical experts had stated that it was implausible that the correct detection rate of CJD was below 50% in this age group and that the assumed maximum number of clinically apparent cases potentially transmitted via surgery, across all ages, was 15. If there was a VPL then the PSA configuration was deemed to be inconsistent with the observed data, and the PSA run was discarded. If there was not a VPL then the next RN stream was run, with this process repeated until a maximum of 27 RN streams had been run.

The VPL threshold was dynamic and changed as the number of RN streams increased. A large VPL threshold was chosen to reduce the possibility of rejecting viable PSA configurations whilst also acknowledging that there was also the probability that clinical transmissions had occurred in older patients. The initial threshold for VPL was 36 transmissions, which was constant for the cumulative total across the first six RN streams. Between RN streams 7 to 13 the VPL threshold was increased to 40; to 45 for RN streams 14 to 17; to 55 for RN streams 18 to 23; and 66 for RN streams 24 to 27. This resulted in 509 of the 2000 PSA runs that all had an FML ≤ e12, being potentially consistent with the observed data. These are denoted ‘plausible’ PSA configurations.

### *3.5.4 Calculating the likelihood of each plausible PSA configuration being consistent with the observed data*

Approximate Bayesian computation methods were used to estimate the likelihood of a PSA configuration being consistent with the observed data. Full details are provided in Appendix 5. A likelihood ranges from 1, where the simulated number of transmissions that are clinically detected are entirely consistent with the number of observed cases, to 0 where the simulated number of transmissions that are clinically detected cannot be consistent with the number of observed cases. Within this decision problem, any PSA configuration that produces 15 or fewer transmissions that result in clinical symptoms would have a likelihood of 1, whereas any PSA configuration that produced more than 30 transmissions that result in clinical symptoms, in patients that are younger than 60 years, would have a likelihood of zero.

The likelihoods for each PSA configuration are shown in Figure 16. These have been ranked in descending order and have been curtailed at 250 of the 509 PSA configurations. A large proportion of the PSA configurations that were not rejected have likelihoods close to zero which offers support to the belief that it was unlikely that potentially appropriate PSA configurations were discarded. For information, the lowest likelihood was 10-12 where the P96 group was assumed to be infectious and 10-13 where the P96 group was assumed not to be infectious.

Figure 16: The likelihoods of the PSA configurations being compatible with the observed data (curves are drawn on top of each other)

### *3.5.5 Generating estimates of the expected numbers of future stCJD deaths, life years lost, QALYs lost*

The likelihoods associated with each PSA sample was multiplied by the results (future stCJD deaths; life years lost; and QALYs lost) produced when using that PSA sample and these were added together and divided by the sum of the likelihood to produce expectations for the combined results.

### *3.5.6 Exploring the uncertainty in the results produced within the base case analyses.*

In order to explore more pessimistic scenarios, the maximum value across all of the 509 PSA configurations of the number of QALYs simulated to be lost multiplied by the likelihood of the PSA was also calculated. These values are necessarily greater than the expectations which average across all PSA configurations. Generating CIs around the mean of each output was more complex due to the use of likelihoods as not all of the 509 scenarios were weighted equally. In order to provide an indication of the width of the CI (which would need to be halved if only looking at increasing or decreasing the value from the mean) an approximation was made, which is detailed in Appendix 7, that involved simulation to translate each PSA likelihood into either zero or one, and then using statistical techniques to estimate a CI.

### *3.5.7 Exploring the probability that each type of surgical unit was the most cost-effective.*

Exploratory analyses were undertaken to provide indicative probabilities that each surgical unit type, (either S1, S2 and S3, or S4, S5 and S6) or moving to single-use instruments were most cost-effective across a range of cost per QALY thresholds. This analysis assumed that a surgical centre was an S3 (S6), so that expenditure was required to move to S1 or S2 (S4 or S5). The probabilities were calculated assuming that the weight applied to each of the 509 PSA values would be provided to the surgical unit or single-use instrument, scenario which was most cost-effective at a chosen cost-per QALY threshold. The summated total of weights for each option was divided by the sum of the total weights to provide a probability of being most cost-effective, which summate to 1.

### *3.5.8 Exploring the changes in the results produced with alternative assumptions relating to the assumed distribution of surgical units between the assumed decontamination levels.*

In the base case analyses, it was assumed that: 10% of surgical units would both follow IPG196 and keep instruments moist; 30% would not follow IPG196; and that 60% of surgical units neither kept instruments moist nor followed IPG196. The NICE appraisal committee requested that a scenario analysis be run that changed these proportions to: 50%; 30%; and 20%. Thus, in this scenario analysis half of surgical units both followed IPG196 and kept instruments moist.

## 3.6 Strategies modelled

In consultation with the NICE committee, the following strategies were run:

1. Do nothing, assuming that the current situation is maintained
2. Adherence to IPG196, and guidance on keeping instruments moist for those units where this is not followed.
3. Adherence to keeping instruments moist for those units where this is not followed.
4. Removal of the requirements to have separate instrument sets for the P96 group
5. Modelling interventions which prohibit the possibility of stCJD. These are likely to take the form of the introduction single-use instruments or the introduction of a decontamination product during the sterilisation process that is 100% effective.

Within this report ‘adherence to IPG196’ is a slight misnomer as the modelled scenario does not assume that neuroendoscopy instruments are single-use. However, for brevity, we have used the term ‘adherence to IPG196’.

Based on advice provided by the NICE committee it was assumed that the quality of single-use and re-usable instruments were equivalent.

## 3.7 Epidemiological results

For each PSA scenario, the number of transmissions by age group that resulted in clinical symptoms, whether correctly diagnosed as CJD or not, the number of life years lost and the number of discounted QALYs lost were simulated through the mathematical model. These results were then weighted by the likelihood with the sum of these values divided by the sum of the likelihoods.

The epidemiological results presented are based on an individual surgical unit. Units are denoted S1 to S6 (defined in Section 3.5.1) to represent the combinations of: the unit’s adherence to IPG196 whether instruments are kept moist; and whether it is assumed that the P96 group is infectious or not. It has been assumed that there are 27 units in England.

It is assumed that the answers produced will contain Monte Carlo sampling error and that further RN streams and PSA configurations would provide more accurate answers. However, we believe that the results presented are sufficiently robust to draw conclusions. The base case results assume that there may have been up to 15 deaths attributable to stCJD between 2005 and 2018.

### *3.7.1 Base case results*

The base case results are provided in Table 26 and relate to the period 2019 – 2023, as agreed with the NICE committee. The estimated values are presented in columns 2-4: these are calculated using all PSA configurations (509), and all RN streams (27). The values of simulated deaths due to CJD infection weighted by their likelihood that the transmissions of CJD modelled between 2005 and 2018 matched the observed data. The final column contains a value which represents the maximum value across the PSA configurations of the simulated deaths in that PSA multiplied by the likelihood of that PSA. Note that the maximum deaths across the P96 and the non-P96 group may not equal the maximum values for both the P96 group and the non-P96 group individually.

Table 26: Base case results per surgical unit

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Average future deaths caused by infections between 2019 and 2023. Total (Non-P96 group / P96 group) \* | Average future undiscounted life years lost due to infections between 2019 and 2023 | Average future discounted QALYs lost due to infections between 2019 and 2023 | Maximum across the PSAs of future deaths caused by infections between 2019 and 2023 multiplied by likelihood Total (Non-P96 group / P96 group) \* |
| S1 | 0.052 (0.036 / 0.016) | 1.548 | 0.459 | 0.519 (0.519 / 0.000) |
| S2 | 0.087 (0.068 / 0.020) | 2.699 | 0.874 | 1.741 (1.481 / 0.259) |
| S3 | 0.430 (0.339 / 0.091) | 12.438 | 4.009 | 4.259 (3.704 / 0.556) |
| S4 | 0.038 (0.038 / 0.000) | 0.741 | 0.275 | 0.519 (0.519 / 0.000) |
| S5 | 0.078 (0.036 / 0.015) | 2.276 | 0.736 | 1.741 (1.481 / 0.259) |
| S6 | 0.389 (0.314 / 0.075) | 10.809 | 3.485 | 4.259 (3.704 / 0.556) |
| See text for definitions of S1 to S6. \*Numbers may appear discrepant due to rounding. | | | | |

3.7.1.1 Interpretation of the base case results

As anticipated, fewer deaths due to stCJD were anticipated when IPG196 were followed, and when residual mass was reduced. Thus, in terms of future deaths due to stCJD, S1 < S2 < S3 and S4 < S5 < S6. Further, as anticipated, when the P96 group was assumed not to be infectious there were fewer projected deaths due to stCJD; that is, S1 > S4, S2 > S5 and S3 > S6.

Those units which followed IPG196 and kept instruments moist (S1 and S4) had 0.052 and 0.038 future deaths caused by stCJD respectively. Where IPG196 was not followed but instruments were kept moist, there was an increase in future deaths due to stCJD of 0.035 and 0.040 depending on whether the p96 group was deemed infectious or not. When it was assumed that a unit neither followed IPG196 and instruments were not kept moist the estimated numbers of future deaths, compared with not following IPG196 increased by 0.343 and 0.310 depending on whether the P96 group was deemed infectious or not. From these results, it is apparent that ensuring that instruments are kept moist has a large impact on the risk of future transmissions.

It is of note that the numbers of potential stCJD infections in the P96 group is not necessarily zero even when these patients are assumed not to be infectious. This can occur when a P96 patient is infected via an operation prior to 2012, the date at which the new instrument sets for the P96 patients were introduced. Such a patient could then have a further high-risk operation whilst in the sub-clinical, but infectious, period which could have infected P96 patients.

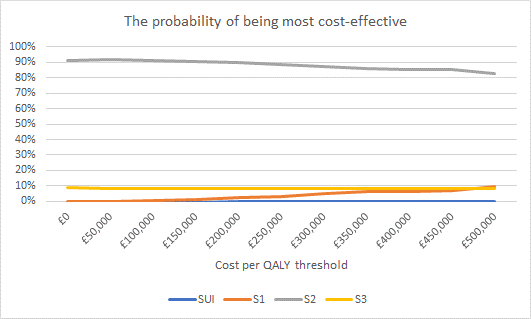
The circumstances in which the maximum future deaths predicted within the model were explored. A high number of future deaths was associated with the prevalence of CJD prions in the tissue being very low: less than 1 per 200,000 people. In these PSA runs, no infectious people had entered the system between 2004 and 2018 resulting in no infections, and thus have a likelihood of 1 of matching the observed data. In the 2019 – 2023 period, infectious people were simulated to have an operation in some RN streams which resulted in infections and deaths. The numbers of deaths were greater where IPG196 was not followed and where instruments were not kept moist. The maximum number of future deaths multiplied by the likelihood is expected to be associated with approximately ten times more deaths than the expectation. For completeness the best case scenario would be that there were no further deaths, which applies for all types of surgical unit.

Uncertainty in the mean number of QALYs gained was explored as described in Section 3.5.6 and Appendix 7. The width of the CI around the mean estimate of QALY loss was estimated to be: 0.25 for S1 units; 0.58 for S2 units; 2.07 for S3 units; 0.19 for S4 units; 0.58 for S5 units; and 1.89 for S6 units. To explore the relationship between the number of PSA samples and the width of the CI a randomly selected PSA was removed with the remaining 508 split into two groups of 254. The widths of the CIs were: 0.32 and 0.40 for S1; 0.87 and 0.78 for S2; 3.02 and 2.85 for S3; 0.25 and 0.29 for S4; 0.78 and 0.87 for S5; and 2.76 to 2.62 for S6. This indicated that approximately doubling the number of PSA configurations had led to a reduction in the width of the CIs by approximately 30%. These CIs produced with 509 PSA configurations were not seen by the authors of this report to be significant large such that the conclusions of the analyses are endangered and that further reductions in the width of the CIs, through running further PSAs were not required.

3.7.1.2 Estimating the probabilities that each type of surgical unit, or using single use instruments are the most cost-effective assuming that a centre does not currently follow IPG196 nor keep instruments moist

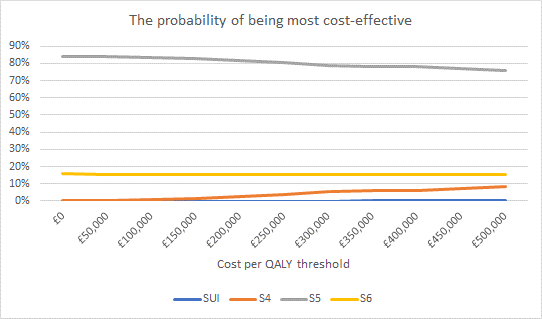
The probability of each surgical unit and using single-use instruments being most cost-effective are provided in Figure 17 when it is assumed that the P96 group are infectious, and in Figure 18 when it is assumed the P96 group are not infectious. These results assume that all surgical units are currently S3 or S6. Both figures have similar characteristics in that S2/S5 (units that keep instruments moist but do not follow IPG196) has the highest probability of being cost-effective, followed by remaining ignoring IPG196 and not keeping instruments moist. Even at high cost per QALY thresholds the probability that single-use instruments are the most cost-effective is negligible. The probability of being most cost-effective accord with the scenarios (S2 and S5) which are estimated to be the most cost-effective.

Figure 17: The probabilities that S1, S2, S3 and single-use instruments are most cost-effective at a range of cost per QALY thresholds



SUI: single-use instruments.

Figure 18: The probabilities that S4, S5, S6 and single-use instruments are most cost-effective at a range of cost per QALY thresholds



SUI: single-use instruments.

### *3.7.2 Scenario analyses using the base case as the foundation*

Eight scenario analyses were run, with the change within a unit being assumed to happen instantly at midnight on the 31st December 2018. These scenarios were comprised of strategies to follow IPG196 and/or reduce the residual mass on instruments and, additionally, of estimating the impact of removing the guidance on having different instrument sets for the P96 group from the remaining patients. The results of the scenario analyses are presented in Table 27.

Table 27: Results of the scenario analyses per surgical unit using the base case as the foundation

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Average future deaths caused by infections between 2019 and 2023 Total (Not P96 group / P96 group) \* | Average future undiscounted life years lost due to infections between 2019 and 2023 | Average future discounted QALYs lost due to infections between 2019 and 2023 | Maximum across the PSAs of future deaths caused by infections between 2019 and 2023 multiplied by likelihood Total (Non-P96 group / P96 group) \* |
| S2 to S1 | 0.045 (0.037 / 0.008) | 1.127 | 0.359 | 0.519 (0.519 / 0.000) |
| S3 to S1 | 0.047 (0.039 / 0.008) | 1.159 | 0.371 | 0.519 (0.519 / 0.000) |
| S3 to S2 | 0.073 (0.073 / 0.000) | 2.894 | 0.825 | 1.741 (1.481 / 0.259) |
| S5 to S4 | 0.038 (0.038 / 0.000) | 0.744 | 0.271 | 0.519 (0.519 / 0.000) |
| S6 to S4 | 0.040 (0.040 / 0.000) | 0.782 | 0.285 | 0.519 (0.519 / 0.000) |
| S6 to S5 | 0.058 (0.058 / 0.000) | 2.238 | 0.627 | 1.741 (1.481 / 0.259) |
| S1✝ | 0.041 (0.041 / 0.000) | 1.661 | 0.484 | 0.556 (0.444 / 0.111) |
| S4✝ | 0.037 (0.037 / 0.000) | 1.543 | 0.451 | 0.556 (0.444 / 0.111) |
| See text for definitions of S1 to S6. \*Numbers may appear discrepant due to rounding.  ✝ Removing the necessity for the P96 group to have to use a different instrument set. | | | | |

3.7.2.1 Interpretation of the scenario analyses results using the base case as the foundation

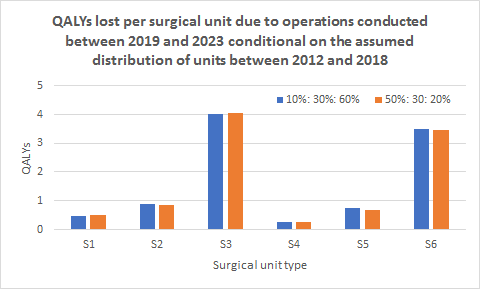
These results are subject to Monte Carlo sampling error, particularly in relation to the random numbers exhausted within a simulation. For example, in the scenario analysis which changed a unit from S2 to S1, at the start of 2019 this model run will have used significantly more random numbers than a comparison with S1 alone. This is due to the random numbers required in selecting from 2012 onwards the supplementary instruments used in an operation and the migration of instruments between sets (which is a feature of S2 but not of S1). This misalignment of random numbers between runs will result in different simulated outcomes.

Despite the presence of Monte Carlo sampling error, the results generated are broadly consistent between comparable units, offering support that the values are relatively robust. Caution is advised however, in trying to interpret differences in the results of the scenario analyses (Table 27) and the base case results (Table 26) as these differences could be artefacts of the random numbers selected. Significantly more computational time would be required to provide an accurate comparison of the scenario analyses and the base case results that was beyond the timescales of the project.

### *3.7.3 Scenario analyses using an alternative distribution of surgical unit compliance with following IPG196 and keeping instruments moist*

As described in Section 3.5.7 the distribution assumed in relation to following IPG196 and guidance on keeping instruments moist was changed to provide an indication of the sensitivity of the epidemiological results to these parameters. The results in terms of the expected number of QALYs lost due to infections occurring between 2019 and 2023 are shown for the base case and the alternative scenario in Figure 19. The results are very similar, as will be the costs associated with each strategy, and as such no analyses of the alternative scenario will be provided, as these are highly comparable to those of the base case.

Figure 19: Comparing the QALYS lost produced within the base case and when using an alternative assumption related to the distribution of surgical units following IPG196 and in keeping instruments moist



S1 and S4 are assumed to both follow IPG196 and guidance on keeping instruments moist

S2 and S5 are assumed to keep instruments moist

S3 and S6 are assumed to neither follow IPG196 nor keep instruments moist.

The three numbers in the legend relate to the proportion of units that are S1/S4: S2/S5: S3/S6.

## 3.8 Cost-effectiveness results

The presented results have been grouped by type of surgical unit (from S1 to S6). Within each category, evaluated strategies are compared incrementally if appropriate. In addition to the base case results, sensitivity analyses have been run changing the values of parameters, and additionally threshold analyses have been performed to determine at what price a single-use kit, or cleaning solution that was 100% effective, the cost per QALY gained would equal the chosen cost-effectiveness threshold.

In all analyses, the additional costs have been calculated considering the following elements: the costs of single-use sets; the disposal costs of re-usable instruments; the costs of autoclaving re-usable instruments; and the costs associated with stCJD that produced clinical symptoms.

When cost per QALY values have been calculated, these are compared with threshold values used within common NICE evaluations. These are: £30,000 within a standard technology appraisal, although this can potentially be raised to approximately £50,000 if the end of life criteria are met,211 and between £100,000 and £300,000 for highly specialised technologies.218

### *3.8.1 Parameter values within the base case cost-effectiveness results*

The parameter values used within the base case estimate of the cost-effectiveness of various strategies are shown in Table 28. It is noted that the number of operations were discounted such that sensitivity analyses on the values could be performed without re-running the model. On completion of the runs it was discovered that the number of instruments disposed of within the run was not saved to file. As such, an estimate of this was calculated rather than being directly taken from the model; it is unlikely that this limitation will influence the results due to the relatively small values involved.

Table 28: Parameter values used within the cost-effectiveness analyses

|  |  |  |
| --- | --- | --- |
|  | Base case value | Intended values for use in the sensitivity analyses |
| Discounted number of brain operations performed between 2019 and 2023 | 5199.84 | Assumed fixed |
| Discounted number of posterior eye operations performed between 2019 and 2023 | 904.92 | Assumed fixed |
| Discounted number of neuroendoscopies performed between 2019 and 2023 | 58.7 | Assumed fixed |
| Cost of an average single-use set, including disposal costs | £425 | £350; £500 |
| Cost of a replacement re-usable instrument | £150 | £100; £200 |
| Assumed number of new instruments bought per surgical unit between 2019 and 2023 | 32 | Assumed fixed |
| Assumed cost associated with a clinically CJD transmission (diagnosed correctly or not) | £50,000 | £30,000; £70,000 |
| Cost of an autoclaving cycle (per instrument) | £0.60 | Assumed fixed |
| Cost of keeping an instrument set moist | £0.12 | Assumed fixed |
| Cost of increasing standards to adhere to IPG196 – set-up costs (running costs per year) | £750,000 | £500,000; £1,000,000 |
| Assumed cost-effectiveness threshold (per QALY) | £30,000 | £50,000; £100,000; £300,000 |

### *3.8.2 The base case cost-effectiveness of strategies for reducing the likelihood of stCJD*

3.8.2.1 Results for S1 and S4 units

For surgical units that are adhering to IPG196 and also keeping instruments moist, the only strategy currently available to reduce the potential for stCJD is to use single-use instruments. Based on the values reported in Table 28, it is estimated for an S1 unit that the additional net costs of single-use instruments per unit would be £2,564,139 which would produce an expected 0.459 QALYs, thereby resulting in a cost per QALY gained of £5,585,484. For an S4 unit, the net costs were similar (£2,564,545) with fewer QALYs gained (0.275) resulting in a cost per QALY of £9,322,717. Both cost per QALY estimates are markedly higher than the thresholds commonly used by NICE.

3.8.2.2 Results for S2 and S5 units

For surgical units that are not adhering to IPG196 but are keeping instruments moist, two strategies are currently available to reduce the potential for stCJD: the use of single-use instruments; and adhering to IPG196.

Based on the values reported in Table 28, it is estimated for an S2 unit that the additional net costs of single-use instruments per unit would be £2,562,829 which would produce an expected 0.874 QALYs, thereby resulting in a cost per QALY gained of £2,933,530. For an S5 unit, the net costs were similar (£2,563,238) with fewer QALYs gained (0.736) resulting in a cost per QALY of £3,484,476. Both cost per QALY estimates are markedly higher than the thresholds commonly used by NICE.

For an S2 unit, adherence to IPG196 is estimated to cost approximately £750,000 (net) and provide an increase in QALYs of 0.415 resulting in a cost per QALY of approximately £1.8 million. For an S5 unit, these values are a net cost of approximately £750,000 an increase in QALYs of 0.461 resulting in a cost per QALY in the region of £1.6 million. Both cost per QALY estimates are markedly higher than the thresholds commonly used by NICE.

3.8.2.3 Results for S3 and S6 units

For surgical units that are neither adhering to IPG196 nor keeping instruments moist, three strategies are currently available to reduce the potential for stCJD: the use of single-use instruments; adhering to IPG196 and keeping instruments moist; and keeping instruments moist.

Based on the values reported in Table 28, it is estimated for an S3 unit that the additional costs of single-use instruments per unit would be £2,550,760 which would produce an expected 4.009 QALYs, thereby resulting in a cost per QALY gained of £636,292. For an S6 unit the costs were similar (£2,552,043) with fewer QALYs gained (3.485) resulting in a cost per QALY of £732,364. Both cost per QALY estimates are markedly higher than the thresholds commonly used by NICE.

For an S3 unit, keeping instruments moist is estimated to produce a cost saving (as the costs of potential prevented CJD cases outweighed those associated with keeping the instruments moist) and to provide an increase of 3.135 QALYs, suggesting that keeping instruments moist is a dominant strategy (lower costs and more health produced). For an S6 unit, there was also an expected cost saving, an increase in QALYs of 2.749 resulting in the strategy of keeping instruments moist being dominant.

For an S3 unit, having initially kept instruments moist, the cost-effectiveness of adhering to IPG196 would be similar to that of moving from S2 to S1, that is in the region of £1.8 million per QALY gained. For an S6 unit, having moved to an S5, the cost per QALY of adhering to IPG196 would be in the region of £1.6 million.

### *3.8.3 Sensitivity Analyses performed on the base case results*

Having observed the incremental cost-effectiveness ratios (ICERs) presented in terms of cost per QALY gained produced in the base case, the sensitivity analyses performed explored using a combination of all of the values that were more favourable to single-use instruments. Thus, the cost of a CJD case was increased to £70,000, the average cost of a re-usable instrument was assumed to be £200 and the cost of a single-use set was assumed to be £350. Note that these sensitivity analyses change the costs only and that the benefits in QALYs are assumed constant.

3.8.3.1 Sensitivity analyses results for S1 and S4 units

The ICER for single-use instruments for an S1 unit became £4,573,372, whilst the ICER for an S4 unit became £7,634,262. Neither value was below commonly used NICE thresholds.

3.8.3.2 Sensitivity analyses results for S2 and S5 units

The ICER for single-use instruments for an S2 unit became £2,401,091, whilst the ICER for an S5 unit became £2,852,364. Neither value was below commonly used NICE thresholds.

For an S2 unit, adherence to IPG196 is estimated to have an ICER of approximately £1.2 million. For an S5 unit, this ICER was approximately £1.1 million. Neither value was below commonly used NICE thresholds.

3.8.3.3 Sensitivity analyses results for S3 and S6 units

For an S3 unit, keeping instruments moist remains a dominant strategy. This is also the case for an S6 unit.

For an S3 unit, having initially kept instruments moist, the cost-effectiveness of adhering to IPG196 would be similar to that of moving from S2 to S1, that is in the region of £1.2 million per QALY gained. For an S6 unit, the cost per QALY of adhering to IPG196 would be in the region of £1.1 million which is moving from an S5 to an S4. These values are similar rather than identical as there may be more infectious material on instruments in the S3 and S6 units than in S2 and S5 units.

### *3.8.4 Threshold analyses on the costs of single-use sets or a completely effective cleaning solution*

Analyses were performed to indicate the cost at which a single-use set (including disposal costs), or a cleaning solution which was 100% effective at removing CJD prions would be at a chosen cost per QALY threshold. These results are presented for each unit type, by four cost per QALY thresholds, and for the base case and for a scenario analysis which was more favourable to re-usable instruments and completely effective cleaning solutions. The results are presented in Table 29. Caution must be used in interpreting these results as options other than single-use instruments or completely effective cleaning solution exist. For example, moving from an S6 to an S5 (or S3 to an S2) is estimated to be a dominant strategy and thus the thresholds for single-use sets for an S6 unit or an S3 unit is redundant; although these have been presented for information.

Table 29: Threshold analyses on the cost of single-use sets (including disposal costs) and a completely effective cleaning solution

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  |  | Cost per QALY threshold | | | |
| Unit Type | Assumptions | £30,000 | £50,000 | £100,000 | £300,000 |
| S1 | Base Case | £11.21 | £12.70 | £16.43 | £31.32 |
|  | Favourable | £11.60 | £13.09 | £16.81 | £31.71 |
| S2 | Base Case | £13.44 | £16.28 | £23.36 | £51.71 |
|  | Favourable | £13.91 | £16.75 | £23.83 | £52.18 |
| S3 | Base Case | £30.66 | £43.67 | £76.19 | £206.27 |
|  | Favourable | £31.91 | £44.92 | £77.44 | £207.53 |
| S4 | Base Case | £10.25 | £11.14 | £13.37 | £22.30 |
|  | Favourable | £10.61 | £11.50 | £13.73 | £22.66 |
| S5 | Base Case | £12.70 | £15.09 | £21.06 | £44.93 |
|  | Favourable | £13.15 | £15.53 | £21.50 | £45.37 |
| S6 | Base Case | £27.90 | £39.21 | £67.48 | £180.55 |
|  | Favourable | £29.07 | £40.38 | £68.65 | £181.72 |
| Favourable denotes assumptions that are more favourable to single-use and effective detergents | | | | | |

It is seen that in units where instruments were kept moist that a single-use set price would need in the region of £50 to have a cost per QALY below £300,000; to be below a cost per QALY of £30,000, the cost of a single-use kit would need to be in the region of £10.

### *3.8.5 Threshold analyses on the costs of adhering to IPG196*

Analyses were performed to indicate for S2 and S5 units the cost at which adhering to IPG196 would produce an ICER equal to a chosen threshold. These results are presented for the S2 and S5 unit types, by four cost per QALY thresholds, and for the base case and for the scenario more favourable to re-usable instruments and completely effective cleaning solutions. The results are presented in Table 30.

Table 30: Threshold analyses on the cost of implementing IPG196

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  |  | Cost per QALY threshold | | | |
| Unit Type | Assumptions | £30,000 | £50,000 | £100,000 | £300,000 |
| S2 | Base Case | £13,746 | £22,038 | £42,766 | £125,678 |
|  | Favourable | £14,270 | £22,561 | £43,290 | £126,202 |
| S5 | Base Case | £15,122 | £24,333 | £47,360 | £139,466 |
|  | Favourable | £15,645 | £24,856 | £47,882 | £139,988 |
| Favourable denotes assumptions that are more favourable to single-use and effective detergents | | | | | |

The estimated costs of fully tracking instruments per unit is estimated to be £750,000 which is greater than the threshold values provided in Table 30.

### *3.8.6 Estimating the cost-effectiveness of removing the need for the P96 group to be operated on with separate instrument sets*

The data reported in Table 26 and in Table 27 indicate that there would be fewer deaths and QALYs lost when the recommendation that the P96 group are operated on using different instrument sets is removed. These results lack face-validity, particularly in relation to QALYs lost as younger patients can lose more QALYs, and is caused by Monte Carlo sampling error due to the misalignment of random numbers. The computational time required to provide an accurate estimate for both number of deaths (which may be equal in both scenarios) and in QALYs lost is far beyond the resources assigned to this work. As such, the results should be interpreted with caution, although currently there is no indication that removing the recommendation related to separate instrument sets would greatly influence the numbers of predicted CJD cases.

# 4 DISCUSSION AND CONCLUSIONS

The purpose of the systematic reviews was to summarise the most up-to-date published evidence about CJD with regards to risk of transmission by surgery. As the reviews are largely descriptive, rather than summative, with no attempt to rank evidence, formal critical appraisal of study quality was not deemed to be useful. Direct evidence to inform the literature review questions was limited due to the rare nature of CJD. As a result, the eight systematic reviews are heavily reliant on historical cases of surgically transmitted CJD, observational data, case-control study designs and animal data.

The review has included evidence from all forms of CJD, whereas the decision problem was focused on vCJD in the previous work conducted by ScHARR in 2005. The apparent increase in sCJD cases noted in several papers is speculated to be due to improved case ascertainment, population increases and an ageing population. Whilst the vCJD epidemic appears to have subsided, evidence indicates that CJD is an iatrogenic risk from sporadic and genetic forms. The recent Appendix III study has identified the presence of abnormal prion deposits in cohorts who were not considered to have had significant exposure the BSE epidemic. Studies using advanced detection assays also highlight wide vCJD involvement in the peripheral tissues of a preclinical patient. However, some studies indicate that prions can accumulate in peripheral tissues such as appendices without transmission to the CNS. Therefore, the assumption that a prevalence of non-clinical prion accumulation in peripheral tissue represents disease that will go on to become clinical CJD has yet to be substantiated. As CJD detection methods advance, more accurate confirmation of CJD pathology will be possible from autopsy and excised tissue samples. Data on the likely incubation periods of CJD are limited to retrospective data from iatrogenic CJD, vCJD or Kuru cases. These data indicate that very long incubation periods which exceed life expectancy are possible. Whilst sCJD cannot be considered to have an incubation period, as the precise time of disease onset cannot be ascertained, on the basis of having the highest incidence, sCJD (rather than vCJD or gCJD) is likely to pose the greatest risk to surgery.

In the period covered by the reviews no observed cases surgically transmitted CJD have been published. Whilst many studies aim to retrospectively suggest a relationship between prior surgery and risk of developing CJD, these case-control designs are known to be prone to bias and confounding. Few data to supersede the original review conducted by ScHARR regarding infectious dose required to transmit CJD but some animal studies using advanced detection methods indicate that infectious doses greater than 108 ID50s are possible.

Evidence on decontamination of surgical instruments is fragmented with no single study assessing the efficacy of all strategies including: reducing residual mass, keeping instruments moist, autoclaving and sterilisation. Comparison of included studies is also problematic due to being conducted under different conditions and in laboratory settings which limit their external validity to the clinical setting. As empirical data on instrument set-keeping and single-use instruments were not retrieved, no evidence to substantiate or refute anecdotal claims about the drawbacks and merits of reusable versus single-use instruments is available. Data on the likelihood of future surgery in those undergoing high-risk procedures is limited in its potential to inform the model as it did not focus solely on high-risk procedures and does not compare the risk of additional procedures with control data for those who had not undergone an index high-risk procedure.

The mathematical model followed, as much as possible, guidance provided by NICE.211 This recommends the use of QALYs. However, at least one committee member was critical of the use of QALYs and stated that “*Personally I reject the idea that the value of ensuring safety of neurosurgery is in the QALYs saved from future CJD patients. This is rather an issue of infection control/ perceptions of safety which cannot be estimated in this way. Similarly, this method doesn’t take into account the harm of CJD Incidents and notifications.*” Ideally, any benefits not captured in the model would attempted to be quantified either in terms of QALYs, or in monetary terms via a willingness to pay approach, whilst additional costs deemed appropriate considered. Given the large ICERs for the strategies the additional QALYs that would need to be gained through an improved perceptions of infection control would have to be very large to bring the ICERs for strategies below the thresholds commonly used by NICE.

Whilst simplifications were made in the modelling process all decisions were made in consultation with the NICE appraisal committee meaning that it is likely that all key aspects were included. Whilst running a greater number of probabilistic sensitivity analysis configurations would increase the accuracy in the ICER related to uncertainty in parameter estimates and running more random number streams would increase the accuracy for a given PSA configuration, it is believed that the results are suitable for robust decision making, given that (1) the estimated uncertainty in the mean QALYs lost is relatively small and (2) that keeping instruments moist is a dominant strategy, and that all other ICERs are in excess of £1 million per QALY gained.

The decision problem was complex due to the paucity of robust data on key modelling parameters such as: the efficacy of current decontamination methods and the incubation period associated with stCJD; the lack of observed stCJD cases; the possibility for patients with stCJD to be misdiagnosed as having a different neurodegenerative disease; and the number of model runs required to produce accurate results for the scenarios evaluated. In order to provide additional data to populate the model output from elicitation sessions were used alongside heuristics that increased the efficiency of the available computational time. The results produced suggest that whilst there is a possibility that stCJD cases are observed between 2019 and 2023 these are unlikely to be large in number.

The results of the mathematical model indicate that keeping instruments moist is a dominant strategy in that there would be an increase in population health as well as a decrease in costs. Keeping instruments moist is also aligned with guidance from Department of Health and Social Care (2016).198. Assuming that instruments are kept moist then the cost-effectiveness of other strategies evaluated with an aim of reducing the future risk of stCJD cases were in excess of £1,000,000 per QALY. These values are greater than the cost-effectiveness thresholds reported by NICE.

Threshold analyses undertaken indicate that the cost of single-use instruments (per cycle) or the cost per set of using a completely effective decontamination method would need to be in the region of £50 to be cost-effective at a threshold of £300,000 per QALY. Assuming a lower cost per QALY threshold of £30,000 meant that the single-use sets or decontamination method would need to be in the region of £10 per set. Threshold analyses were also undertaken to determine the maximum cost to a unit, over a five-year period, of following IPG196. Assuming a cost per QALY threshold of £300,000 and £30,000 these costs were approximately £125,000 and £15,000 respectively.

Further, the analyses run indicated that there would be no marked increase in the risk of stCJD cases when the requirement that P96 patients need to be operated on with separate instruments were removed.

As such, the authors of this report believe that (1) implementing measures to ensure that instruments are kept moist should be of paramount importance, (2) if surgical units do not currently prevent instrument migration then the costs of ensuring this does not happen has ICERs greater than all of NICE’s published thresholds, and (3) if surgical units that treat both the P96 group and the non-P96 group have not instigated procedures to ensure that separate instruments are used in the P96 group, then the expenditure require to ensure such segregation has an ICER greater all of NICE’s published thresholds. These results appeared robust to assumptions regarding the current standard of decontamination amongst surgical units.

# Acknowledgements

This study was funded by the NIHR HTA programme (reference number 17/48/01). The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

We would like to thank the NICE Committee members who provided feedback and data during the research. We would like to thank Andrea Shippam for help in extracting data and in formatting the report, and Paul Tappenden for providing a peer-review of a draft.

Contributions of the authors

Matt Stevenson led the project, undertook the review of cost-effectiveness literature, constructed the mathematical model, interpreted the results. Lesley Uttley and Christopher Carroll undertook the review of clinical literature, and reviewed a proportion of the cost-effectiveness literature review to ensure consistency. Jeremy Oakley led the elicitation session and devised the methods to produce the likelihoods for PSA configurations, and to approximate the width of the confidence intervals. Stephen Chick provided simulation advice throughout the project. Ruth Wong updated and performed the literature searches of electronic databases.

Conflicts

No author declares any conflict of interest.

# REFERENCES

1. The University of Edinburgh. The National CJD Research & Surveilance Unit (NCJDRSU). 2017. <http://www.cjd.ed.ac.uk/> (Accessed 11.07.2017).

2. National CJD Research & Surveillance Unit. Creutzfeldt-Jakob Disease Surveillance in the UK: 25th Annual Report 2016: The National CJD Research & Surveillance Unit, Western General Hospital, Edinburgh, EH4 2XU; 2016 <https://www.cjd.ed.ac.uk/sites/default/files/report25.pdf>.

3. Brown P, Brandel JP, Sato T, Nakamura Y, MacKenzie J, Will RG*, et al.* Iatrogenic Creutzfeldt-Jakob disease, final assessment. *Emerging Infectious Diseases* 2012;18:901-7.

4. World Health Organization. WHO infection control guidelines for transmissible spongiform encephalopathies: report of a WHO consultation, Geneva, Switzerland, 23-26 March 1999. 2000.

5. World Health Organization. WHO Tables on Tissue Infectivity Distribution in Transmissible Spongiform Encephalopathies. World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland; 2010 <http://www.who.int/bloodproducts/tablestissueinfectivity.pdf>.

6. Brown P, Farrell M. A practical approach to avoiding iatrogenic CJD from invasive instruments. *Prion* 2015;9:S98.

7. Hilton DA, Ghani AC, Conyers L, Edwards P, McCardle L, Ritchie D*, et al.* Prevalence of lymphoreticular prion protein accumulation in UK tissue samples. *The Journal of Pathology* 2004;203:733-9.

8. Ghani AC, Ferguson NM, Donnelly CA, Anderson RM. Factors determining the pattern of the variant Creutzfeldt-Jakob disease (vCJD) epidemic in the UK. *Proceedings of the Royal Society of London B: Biological Sciences* 2003;270:689-98.

9. Clarke P, Ghani AC. Projections of the future course of the primary vCJD epidemic in the UK: inclusion of subclinical infection and the possibility of wider genetic susceptibility. *Journal of the Royal Society Interface* 2005;2:19-31.

10. Lloyd Jones M, Stevenson M, Sutton A. Patient safety and reduction of risk of transmission of Creutzfeldt– Jakob disease (CJD) via interventional procedures. Systematic literature reviews final report. National Institute for Health and Care Excellence: School of Health and Related Research, University of Sheffield; 2006 <https://www.nice.org.uk/guidance/ipg196/documents/ipg196-patient-safety-and-reduction-of-risk-of-transmission-of-creutzfeldtjakob-disease-cjd-via-interventional-procedures-systematic-review2>.

11. Stevenson M, Oakley J, Chick SE. Patient safety and reduction of risk of transmission of Creutzfeldt–Jakob disease (CJD) via interventional procedures—final report: School of Health and Related Research, University of Sheffield; 2006 <https://www.nice.org.uk/guidance/ipg196/documents/ipg196-patient-safety-and-reduction-of-risk-of-transmission-of-creutzfeldtjakob-disease-cjd-via-interventional-procedures-final-report2>.

12. Stevenson MD, Oakley JE, Chick SE, Chalkidou K. The cost-effectiveness of surgical instrument management policies to reduce the risk of vCJD transmission to humans. *Journal of the Operational Research Society* 2009;60:506-18.

13. Bennett P, Hare A, Townshend J. Assessing the risk of vCJD transmission via surgery: models for uncertainty and complexity. *Journal of the Operational Research Society* 2005;56:202-13.

14. National Institute for Health and Care Excellence. NICE interventional procedure guidance 196. Patient safety and reduction of risk of transmission of Creutzfeldt–Jakob disease (CJD) via interventional procedures.; 2008. <https://www.nice.org.uk/guidance/ipg196/documents/ipg196-patient-safety-and-reduction-of-risk-of-transmission-of-creutzfeldtjakob-disease-cjd-via-interventional-procedures-guidance2> (Accessed 02.02.2018).

15. Public Health England. Summary results of the third national survey of abnormal prion prevalence in archived appendix specimens; 2016 <https://app.box.com/s/hhhhg857fjpu2bnxhv6e/file/91796156506>.

16. Advisory Committee on Dangerous Pathogens TSE Subgroup. Updated position statement on occurrence of vCJD and prevalence of infection in the UK; 2016 <https://app.box.com/s/hhhhg857fjpu2bnxhv6e/file/30140977007>.

17. Jaunmuktane Z, Quaegebeur A, Taipa R, Viana-Baptista M, Barbosa R, Koriath C*, et al.* Evidence of amyloid-β cerebral amyloid angiopathy transmission through neurosurgery. *Acta Neuropathologica* 2018:1-9.

18. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Plos Medicine* 2009;6:e1000097.

19. Creutzfeldt-Jakob Disease International Surveillance Network formerly EuroCJD. CJD Surveillance Data 1993-2017. 2017. <http://www.eurocjd.ed.ac.uk/surveillance%20data%201.html> (Accessed 23.01.18).

20. Jeon BH, Kim J, Kim GK, Park SC, Kim S, Cheong HK. Estimation of the size of the iatrogenic Creutzfeldt-Jakob disease outbreak associated with cadaveric dura mater grafts in Korea. *Epidemiology and Health* 2016;19:19.

21. US Centres for Disease Control and Prevention (CDC). Creutzfeldt-Jakob Disease, Classic (CJD) Occurrence and Transmission. 2018. <https://www.cdc.gov/prions/cjd/occurrence-transmission.html> (Accessed 23.01.18).

22. Yamada M, Hamaguchi T, Sakai K, Nozaki I, Noguchi-Shinohara M, Sanjo N*, et al.* Epidemiological and clinical features of human prion diseases in Japan: Prospective 17-year surveillance. *Prion* 2016;10:S10-S1.

23. Klug GM, Boyd A, Sarros S, Stehmann C, Simpson M, McLean CA*, et al.* Creutzfeldt-Jakob disease surveillance in Australia: update to December 2015. *Communicable Diseases Intelligence Quarterly Report* 2016;40:E368-E76.

24. Begue C, Martinetto H, Schultz M, Rojas E, Romero C, D'Giano C*, et al.* Creutzfeldt-Jakob disease surveillance in Argentina, 1997-2008. *Neuroepidemiology* 2011;37:193-202.

25. Lu CJ, Sun Y, Chen SS. Incidence of Creutzfeldt-Jakob disease in Taiwan: a prospective 10-year surveillance. *European Journal of Epidemiology* 2010;25:341-7.

26. Gao C, Shi Q, Tian C, Chen C, Han J, Zhou W*, et al.* The epidemiological, clinical, and laboratory features of sporadic Creutzfeldt-Jakob disease patients in China: surveillance data from 2006 to 2010. *PLoS ONE [Electronic Resource]* 2011;6:e24231.

27. Molesworth A, Yates P, Hewitt P, Mackenzie J, Ironside J, Galea G*, et al.* vCJD associated with organ or tissue transplantation in the UK: A lookback study. *Prion* 2013;7:60.

28. Isotalo J, Gardberg M, Verkkoniemi-Ahola A, Paetau A, Martikainen MH, Korpela J*, et al.* Phenotype and incidence of Creutzfeldt-Jakob disease in Finland in 1997-2013. *Duodecim* 2015;131:465-74.

29. Chen SS. Surveillance of prion diseases in Taiwan. *Prion* 2016;10:S11.

30. Van Everbroeck B, Michotte A, Sciot R, Godfraind C, Deprez M, Quoilin S*, et al.* Increased incidence of sporadic Creutzfeldt-Jakob disease in the age groups between 70 and 90 years in Belgium. *European Journal of Epidemiology* 2006;21:443-7.

31. Ae R, Nakamura Y, Takumi I, Sanjo N, Kitamoto T, Yamada M*, et al.* Epidemiologic features of human prion diseases in Japan: A prospective 15-year surveillance study. *Prion* 2016;10:S103-S4.

32. Rus T, Caks Jager N, Popovic M, Blasko Markic M, Kramberger Gregoric M. High incidence of sporadic Creutzfeldt-Jakob disease in Slovenia in 2015. *European Journal of Neurology* 2016;23:602.

33. Mok T, Jaunmuktane Z, Joiner S, Campbell T, Morgan C, Wakerley B*, et al.* Variant Creutzfeldt–Jakob Disease in a Patient with Heterozygosity at PRNP Codon 129. *New England Journal of Medicine* 2017;376:292-4.

34. Urwin PJM, Mackenzie JM, Knight RSG, Will RG, Molesworth AM. Is sporadic CJD an acquired disease? A review of the UK CJD cases. *Prion* 2016;10:S77.

35. Shi J, Chen Q, Chen X, Zhang J. Case Report Clinical scenarios in creutzfeldt-jakob disease (CJD): report of nine cases. *Int J Clin Exp Pathol* 2016;9:2744-51.

36. Baig M, M., Phillips M. A case of Creutzfeldt-Jakob disease: diagnostic dilemmas of a rapidly fatal disease. *Infectious Disease Reports* 2013;5:e10.

37. Maddox RA, Holman RC, Folkema AM, Gambetti P, Zou WQ, Minino AM*, et al.* Creutzfeldt-Jakob disease among blacks in the United States, 1994-2007. *Prion* 2010;4 (3):161.

38. Holman RC, Belay ED, Christensen KY, Maddox RA, Minino AM, Folkema AM*, et al.* Human prion diseases in the United States. *PLoS ONE [Electronic Resource]* 2010;5:e8521.

39. Maddox RA, Holman RC, Minino AM, Blevins JE, Schonberger LB, Belay ED. Prion disease among Asians and Pacific Islanders in the United States, 2003-2009. *Prion* 2013;7:60.

40. Nakatani E, Nishimura T, Zhou B, Kaneda H, Teramukai S, Nagai Y*, et al.* Temporal and regional variations in sporadic Creutzfeldt-Jakob disease in Japan, 2001-2010. *Epidemiology & Infection* 2015;143:1073-8.

41. Klug GM, Wand H, Boyd A, Law M, Whyte S, Kaldor J*, et al.* Enhanced geographically restricted surveillance simulates sporadic Creutzfeldt-Jakob disease cluster. *Brain* 2009;132:493-501.

42. Brandel JP, Peckeu L, Haik S. The French surveillance network of Creutzfeldt-Jakob disease. Epidemiological data in France and worldwide. *Transfusion Clinique et Biologique* 2013;20:395-7.

43. Mitrova E, Kosorinova D, Gajdos M, Sebekova K, Tomeckova I. A pilot study of a genetic CJD risk factor (E200K) in the general Slovak population. *European Journal of Epidemiology* 2014;29:595-7.

44. Ladogana A, Puopolo M, Croes EA, Budka H, Jarius C, Collins S*, et al.* Mortality from Creutzfeldt-Jakob disease and related disorders in Europe, Australia, and Canada. *Neurology* 2005;64:1586-91.

45. Tuskan-Mohar L, Legac M, Prunk DA, Bucuk M, Perkovic O, Antoncic I. The frequency of creutzfeldtjakob disease in primorsko-goranska county. *Acta Clinica Croatica, Supplement* 2012;51:83-4.

46. Kosier N. Why won't she talk? A case of Creutzfeldt-Jakob disease masquerading as psychiatric decompensation. *Journal of the American Geriatrics Society* 2017;65:S25.

47. Litzroth A, Cras P, De Vil B, Quoilin S. Overview and evaluation of 15 years of Creutzfeldt-Jakob disease surveillance in Belgium, 1998-2012. *Bmc Neurology* 2015;15:250.

48. Brett FM, Looby S, Chalissery A, Chen D, Heaney C, Heffernan J*, et al.* Brain biopsies requiring Creutzfeldt-Jakob disease precautions in the Republic of Ireland 2005-2016. *Irish Journal of Medical Science* 2017;12:12.

49. Loftus T, Chen D, Looby S, Chalissery A, Howley R, Heaney C*, et al.* CJD surveillance in the Republic of Ireland from 2005 to 2015: a suggested algorithm for referrals. *Clinical Neuropathology* 2017;36:188-94.

50. Ali A, Abbas M, Ahmed S, Ejaz K. Creutzfeldt-Kajob Disease (CJD) rare stroke mimic. *Cerebrovascular Diseases* 2015;39:147.

51. Hirst CL. Sporadic Creutzfeldt-Jakob disease presenting as a stroke mimic590. *British Journal of Hospital Medicine* 2011;72:590-1.

52. Hanumanthu R, Alchaki A, Nyaboga A, Ghuman H, Chen J, Feinstein E. An unusual case of sporadic Creutzfeld Jacob disease presenting as acute neuropathy. *Movement Disorders* 2017;32:563-4.

53. Karatas H, Dericioglu N, Kursun O, Saygi S. Creutzfeldt-Jakob disease presenting as hyperparathyroidism and generalized tonic status epilepticus. *Clinical EEG & Neuroscience: Official Journal of the EEG & Clinical Neuroscience Society (ENCS)* 2007;38:203-6.

54. Kher M, Rao MY, Acharya PT, Mahadevan A, Shankar SK. Heidenhain variant of Creutzfeldt-Jakob disease: An autopsy study from India. *Annals of Indian Academy of Neurology* 2009;12:48-51.

55. Neville JL, Fichtenbaum C. 'Rapidly progressive dementia: Sometimes it is a zebra'. *Journal of General Internal Medicine* 2012;27:S508.

56. Pachalska M, Kurzbauer H, Forminska-Kapuscik M, Urbanik A, Bierzynska-Macyszyn G, Wlaszczuk P. Atypical features of dementia in a patient with Creutzfeldt-Jakob disease. *Medical Science Monitor* 2007;13:CS9-19.

57. Patrawala S, Soltani M, Zulauf M. A rare case of ataxia and rapidly progressing dementia. *Journal of General Internal Medicine* 2014;29:S280-S1.

58. Krystina C, Abbas A, Hall A, Khadjooi K, Elhag RA, Rostami K. Sporadic CJD presenting with aphasia diagnosed in medical admissions unit. *European Journal of Internal Medicine* 2011;22:S111.

59. Sann AA, Zaw MM, Choie TL. Creutzfeldt-Jakob disease presenting predominantly with movement disorder: A case report. *Movement Disorders* 2016;31:S577-S8.

60. Bruton C, Bruton R, Gentleman S, Roberts G. Diagnosis and incidence of prion (Creutzfeldt-Jakob) disease: a retrospective archival survey with implications for future research. *Neurodegeneration* 1995;4:357-68.

61. Urwin P, Thanigaikumar K, Ironside JW, Molesworth A, Knight RS, Hewitt PE*, et al.* Sporadic Creutzfeldt-Jakob Disease in 2 Plasma Product Recipients, United Kingdom. *Emerging Infectious Diseases* 2017;23:893.

62. Shepherd KJ, Barker BR. A common presentation of a rare disease: Sporadic CJD. *Journal of General Internal Medicine* 2016;1):S500-S1.

63. Galeno R, Di Bari MA, Nonno R, Cardone F, Sbriccoli M, Graziano S*, et al.* Prion Strain Characterization of a Novel Subtype of Creutzfeldt-Jakob Disease. *Journal of Virology* 2017;91:01.

64. Rudge P, Jaunmuktane Z, Adlard P, Bjurstrom N, Caine D, Lowe J*, et al.* Iatrogenic CJD due to pituitary-derived growth hormone with genetically determined incubation times of up to 40 years. *Brain* 2015;138:3386-99.

65. Sanchez-Juan P, Bishop MT, Croes EA, Knight RSG, Will RG, van Duijn CM*, et al.* A polymorphism in the regulatory region of PRNP is associated with increased risk of sporadic Creutzfeldt-Jakob disease. *BMC Medical Genetics* 2011;12.

66. Brandner S, Jaunmuktane Z. Prion disease: experimental models and reality. *Acta Neuropathologica* 2017;133:197-222.

67. Giaccone G, Capellari S, Ingrosso L, Ferrari S, Imperiale D, Taraglio S*, et al.* An update of the epidemiology of sporadic Creutzfeldt-Jakob disease in Italy based on neuropathologic and molecular typing of a large cohort of patients. *Clinical Neuropathology* 2009;28 (3):229.

68. Ironside JW, Bishop MT, Connolly K, Hegazy D, Lowrie S, Le Grice M*, et al.* Variant Creutzfeldt-Jakob disease: prion protein genotype analysis of positive appendix tissue samples from a retrospective prevalence study. Erratum appears in BMJ. 2006 Aug 26;333(7565):416. *BMJ* 2006;332:1186-8.

69. Gill ON, Spencer Y, Richard-Loendt A, Kelly C, Dabaghian R, Boyes L*, et al.* Prevalent abnormal prion protein in human appendixes after bovine spongiform encephalopathy epizootic: large scale survey. *BMJ* 2013;347:f5675.

70. Mead S, Whitfield J, Poulter M, Shah P, Uphill J, Beck J*, et al.* Genetic susceptibility, evolution and the kuru epidemic. *Philosophical Transactions of the Royal Society of London - Series B: Biological Sciences* 2008;363:3741-6.

71. Kaski D, Mead S, Hyare H, Cooper S, Jampana R, Overell J*, et al.* Variant CJD in an individual heterozygous for PRNP codon 129. *The Lancet* 2009;374:2128.

72. Peden A, McCardle L, Head MW, Love S, Ward HJT, Cousens SN*, et al.* Variant CJD infection in the spleen of a neurologically asymptomatic UK adult patient with haemophilia. *Haemophilia* 2010;16:296-304.

73. Peden AH, Head MW, Diane LR, Jeanne EB, James WI. Preclinical vCJD after blood transfusion in a PRNP codon 129 heterozygous patient. *The Lancet* 2004;364:527-9.

74. Bishop MT, Hart P, Aitchison L, Baybutt HN, Plinston C, Thomson V*, et al.* Predicting susceptibility and incubation time of human-to-human transmission of vCJD. *Lancet Neurology* 2006;5:393-8.

75. Nagoshi K, Sadakane A, Nakamura Y, Yamada M, Mizusawa H. Duration of prion disease is longer in Japan than in other countries. *Journal of Epidemiology* 2011;21:255-62.

76. Pennington C, Knight R. The clinicopathological phenotype of genetic CJD due to the E200K mutation in the UK. *Prion* 2010;4 (3):197.

77. Coulthart MB, Geschwind MD, Qureshi S, Phielipp N, Demarsh A, Abrams JY*, et al.* A case cluster of variant Creutzfeldt-Jakob disease linked to the Kingdom of Saudi Arabia. *Brain* 2016;139:2609-16.

78. Chohan G, Llewelyn C, Mackenzie J, Cousens S, Kennedy A, Will R*, et al.* Variant Creutzfeldt-Jakob disease in a transfusion recipient: coincidence or cause? *Transfusion* 2010;50:1003-6.

79. Davidson LR, Llewelyn CA, Mackenzie JM, Hewitt PE, Will RG. Variant CJD and blood transfusion: are there additional cases? *Vox Sanguinis* 2014;107:220-5.

80. Molesworth A, Yates P, Hewitt PE, Mackenzie J, Ironside JW, Galea G*, et al.* Investigation of variant Creutzfeldt-Jakob disease implicated organ or tissue transplantation in the United Kingdom. *Transplantation* 2014;98:585-9.

81. Ward HJT, Will RG, Ghani A, Ironside JW. An update on variant CJD (vCJD), secondary transmission and prevalence. *European Journal of Neurology* 2006;13:306-7.

82. Urwin PJ, Mackenzie JM, Llewelyn CA, Will RG, Hewitt PE. Creutzfeldt-Jakob disease and blood transfusion: updated results of the UK Transfusion Medicine Epidemiology Review Study. *Vox Sanguinis* 2016;110:310-6.

83. Ward HJ, MacKenzie JM, Llewelyn CA, Knight RS, Hewitt PE, Connor N*, et al.* Variant Creutzfeldt-Jakob disease and exposure to fractionated plasma products. *Vox Sanguinis* 2009;97:207-10.

84. Diack AB, Will RG, Manson JC. Public health risks from subclinical variant CJD. *PLoS Pathogens* 2017;13:e1006642.

85. Diack AB, Head MW, McCutcheon S, Boyle A, Knight R, Ironside JW*, et al.* Variant CJD. 18 years of research and surveillance. *Prion* 2014;8:286-95.

86. Ritchie DL, Boyle A, McConnell I, Head MW, Ironside JW, Bruce ME. Transmissions of variant Creutzfeldt-Jakob disease from brain and lymphoreticular tissue show uniform and conserved bovine spongiform encephalopathy-related phenotypic properties on primary and secondary passage in wild-type mice. *Journal of General Virology* 2009;90:3075-82.

87. Diack AB, Boyle A, Ritchie DL, Rabano A, De Pedro-Cuesta J, Brandel JP*, et al.* Variant CJD: Lessons in public health. *Prion* 2016;10:S82-S3.

88. Gill ON, Spencer Y, Richard-Loendt A, Kelly C, Dabaghian R, Boyes L*, et al.* Prevalent abnormal prion protein in human appendixes after bovine spongiform encephalopathy epizootic: large scale survey. *BMJ* 2013;347:f5675.

89. Olsen SB, Sheikh A, Peck D, Darzi A. Variant Creutzfeldt-Jakob disease: a cause for concern. Review of the evidence for risk of transmission through abdominal lymphoreticular tissue surgery. *Surgical Endoscopy* 2005;19:747-50.

90. de Marco MF, Linehan J, Gill ON, Clewley JP, Brandner S. Large-scale immunohistochemical examination for lymphoreticular prion protein in tonsil specimens collected in Britain. *Journal of Pathology* 2010;222:380-7.

91. Clewley JP, Kelly CM, Andrews N, Vogliqi K, Mallinson G, Kaisar M*, et al.* Prevalence of disease related prion protein in anonymous tonsil specimens in Britain: cross sectional opportunistic survey. *BMJ* 2009;338:b1442.

92. McGowan CR, Viens AM. Coroners and the obligation to protect public health: the case of the failed UK vCJD study. *Public Health* 2011;125:234-7.

93. McGowan C, Viens A. Death investigation systems and disease surveillance. *Epidemiology & Infection* 2011;139:986-90.

94. Terasaka S, Asaoka K, Yamaguchi S, Kobayashi H, Motegi H, Houkin K. A significant correlation between delayed cure after microvascular decompression and positive response to preoperative anticonvulsant therapy in patients with hemifacial spasm. *Neurosurgical Review* 2016;39:607-13.

95. Kobayashi A, Parchi P, Yamada M, Brown P, Saverioni D, Matsuura Y*, et al.* Iatrogenic transmission of Creutzfeldt-Jakob disease. *Prion* 2016;10:S5.

96. Kobayashi A, Parchi P, Yamada M, Brown P, Saverioni D, Matsuura Y*, et al.* Transmission properties of atypical Creutzfeldt-Jakob disease: a clue to disease etiology? *Journal of Virology* 2015;89:3939-46.

97. Gnanajothy R, Umashanker D, Vega MC, Wu BJ. A case of Creutzfeldt-Jakob disease following cataract surgery: sporadic versus iatrogenic cause. *Connecticut Medicine* 2013;77:335-7.

98. Tuck K, Mass M. Sporadic creutzfeld jakob disease in a 33 year old male with prior cerebral instrumentation. *Neurology Conference: 65th American Academy of Neurology Annual Meeting San Diego, CA United States Conference Publication:* 2013;80.

99. Moreno MJ, Escriche D, Romero J, Macineiras JL, Corredera E, Castro MD*, et al.* Creutzfeldt-Jakob disease cluster in the health area of Meixoeiro Hospital. *Acta Neurologica Scandinavica* 2013;127:38-45.

100. Puopolo M, Ladogana A, Vetrugno V, Pocchiari M. Transmission of sporadic Creutzfeldt-Jakob disease by blood transfusion: risk factor or possible biases. *Transfusion* 2011;51:1556-66.

101. de Pedro-Cuesta J, Mahillo-Fernandez I, Rabano A, Calero M, Cruz M, Siden A*, et al.* Nosocomial transmission of sporadic Creutzfeldt-Jakob disease: results from a risk-based assessment of surgical interventions. *Journal of Neurology, Neurosurgery & Psychiatry* 2011;82:204-12.

102. Mahillo-Fernandez I, de Pedro-Cuesta J, Bleda MJ, Cruz M, Molbak K, Laursen H*, et al.* Surgery and risk of sporadic Creutzfeldt-Jakob disease in Denmark and Sweden: registry-based case-control studies. *Neuroepidemiology* 2008;31:229-40.

103. Hamaguchi T, Noguchi-Shinohara M, Nozaki I, Nakamura Y, Sato T, Kitamoto T*, et al.* The risk of iatrogenic Creutzfeldt-Jakob disease through medical and surgical procedures. *Neuropathology* 2009;29:625-31.

104. Hamaguchi T, Noguchi-Shinohara M, Nozaki I, Nakamura Y, Sato T, Kitamoto T*, et al.* Medical procedures and risk for sporadic Creutzfeldt-Jakob disease, Japan, 1999-2008. *Emerging Infectious Diseases* 2009;15:265-71.

105. Ruegger J, Stoeck K, Amsler L, Blaettler T, Zwahlen M, Aguzzi A*, et al.* A case-control study of sporadic Creutzfeldt-Jakob disease in Switzerland: analysis of potential risk factors with regard to an increased CJD incidence in the years 2001-2004. *BMC Public Health* 2009;9:18.

106. Ward HJ, Everington D, Cousens SN, Smith-Bathgate B, Leitch M, Cooper S*, et al.* Risk factors for variant Creutzfeldt-Jakob disease: a case-control study. *Annals of Neurology* 2006;59:111-20.

107. Ward HJ, Everington D, Cousens SN, Smith-Bathgate B, Gillies M, Murray K*, et al.* Risk factors for sporadic Creutzfeldt-Jakob disease. *Annals of Neurology* 2008;63:347-54.

108. de Pedro Cuesta J, Ruiz Tovar M, Ward H, Calero M, Smith A, Verduras CA*, et al.* Sensitivity to biases of case-control studies on medical procedures, particularly surgery and blood transfusion, and risk of Creutzfeldt-Jakob disease. *Neuroepidemiology* 2012;39:1-18.

109. Alcalde-Cabero E, Almazan-Isla J, Brandel J-P, Breithaupt M, Catarino J, Collins S*, et al.* Health professions and risk of sporadic Creutzfeldt-Jakob disease, 1965 to 2010. *Eurosurveillance* 2012;17.

110. de Pedro-Cuesta J, Mahillo-Fernandez I, Calero M, Rabano A, Cruz M, Siden A*, et al.* Towards an age-dependent transmission model of acquired and sporadic Creutzfeldt-Jakob disease. *PLoS ONE [Electronic Resource]* 2014;9:e109412.

111. Cruz M, Mahillo-Fernandez I, Rabano A, Siden A, Calero M, Laursen H*, et al.* Late-in-life surgery associated with Creutzfeldt-Jakob disease: a methodological outline for evidence-based guidance. *Emerging Themes in Epidemiology* 2013;10:5.

112. Kobayashi A. Mechanisms of transmission of prion diseases. *Clinical Neurology* 2016;56:S84.

113. Bryant G, Hewitt P, Hope J, Howard C, Ironside J, Knight R*, et al.* Minimise transmission risk of CJD and vCJD in healthcare settings. Report on the Prevention of CJD and vCJD by Advisory Committee on Dangerous Pathogens' Transmission Spongiform Encephalopathy (ACDP TSE) Subgroup. 2015.

114. Hall V, Brookes D, Nacul L, Gill ON, Connor N, Panel CJDI. Managing the risk of iatrogenic transmission of Creutzfeldt-Jakob disease in the UK. *Journal of Hospital Infection* 2014;88:22-7.

115. Belay ED, Blase J, Sehulster LM, Maddox RA, Schonberger LB. Management of neurosurgical instruments and patients exposed to Creutzfeldt-Jakob disease. *Infection Control & Hospital Epidemiology* 2013;34:1272-80.

116. Thomas JG, Chenoweth CE, Sullivan SE. Iatrogenic Creutzfeldt-Jakob disease via surgical instruments. *Journal of Clinical Neuroscience* 2013;20:1207-12.

117. Orrú CD, Yuan J, Appleby BS, Li B, Li Y, Winner D*, et al.* Prion seeding activity and infectivity in skin samples from patients with sporadic Creutzfeldt-Jakob disease. *Science Translational Medicine* 2017;9.

118. Zou W, Orru CD, Yuan J, Appleby BS, Li Y, Rarick J*, et al.* PrP<sup>Sc</sup> in the skin of CJD patients. *Prion* 2016;10:S29.

119. Notari S, Moleres FJ, Hunter SB, Belay ED, Schonberger LB, Cali I*, et al.* Multiorgan detection and characterization of protease-resistant prion protein in a case of variant CJD examined in the United States. *PLoS ONE [Electronic Resource]* 2010;5:e8765.

120. Davanipour Z, Sobel E, Ziogas A, Smoak C, Bohr T, Doram K*, et al.* Ocular Tonometry and Sporadic Creutzfeldt - Jakob Disease (sCJD): A Confirmatory Case-Control Study. *British Journal of Medicine & Medical Research* 2014;4:2322-33.

121. Tullo AB, Buckley RJ, Kelly T, Head MW, Bennett P, Armitage WJ*, et al.* Transplantation of ocular tissue from a donor with sporadic Creutzfeldt-Jakob disease. *Clinical & Experimental Ophthalmology* 2006;34:645-9.

122. Jirsova K, Krabcova I, Novakova J, Hnathova I, Koukolik F, Kubesova B*, et al.* The assessment of pathogenic prions in the brains of eye tissue donors: 2-years experience in the Czech Republic. *Cornea* 2010;29:996-9.

123. Maddox RA, Belay ED, Curns AT, Zou WQ, Nowicki S, Lembach RG*, et al.* Creutzfeldt-Jakob disease in recipients of corneal transplants. *Cornea* 2008;27:851-4.

124. Bourvis N, Boelle PY, Cesbron JY, Valleron AJ. Risk assessment of transmission of sporadic Creutzfeldt-Jakob disease in endodontic practice in absence of adequate prion inactivation. *PLoS ONE [Electronic Resource]* 2007;2:e1330.

125. Everington D, Smith AJ, Ward HJ, Letters S, Will RG, Bagg J. Dental treatment and risk of variant CJD--a case control study. *British Dental Journal* 2007;202:E19; discussion 470-1.

126. Azarpazhooh A, Fillery ED. Prion disease: the implications for dentistry. *Journal of Endodontics* 2008;34:1158-66.

127. Collinge J, Whitfield J, McKintosh E, Frosh A, Mead S, Hill AF*, et al.* A clinical study of kuru patients with long incubation periods at the end of the epidemic in Papua New Guinea. *Philosophical Transactions of the Royal Society of London - Series B: Biological Sciences* 2008;363:3725-39.

128. Collinge J. Review. Lessons of kuru research: background to recent studies with some personal reflections. *Philosophical Transactions of the Royal Society of London - Series B: Biological Sciences* 2008;363:3689-96.

129. Collinge J, Whitfield J, McKintosh E, Beck J, Mead S, Thomas DJ*, et al.* Kuru in the 21st century--an acquired human prion disease with very long incubation periods. *Lancet* 2006;367:2068-74.

130. Collinge J, Alpers MP. Incubation period of human prion disease - Author's reply. *Lancet* 2006;368:914-5.

131. Haik S, Brandel JP. Infectious prion diseases in humans: cannibalism, iatrogenicity and zoonoses. *Infection, Genetics & Evolution* 2014;26:303-12.

132. Hamaguchi T. Clinical manifestations and epidemiology of prion diseases in Japan. *Rinsho Shinkeigaku - Clinical Neurology* 2013;23:1246-8.

133. Heath CA, Barker RA, Esmonde TF, Harvey P, Roberts R, Trend P*, et al.* Dura mater-associated Creutzfeldt-Jakob disease: experience from surveillance in the UK. *Journal of Neurology, Neurosurgery & Psychiatry* 2006;77:880-2.

134. Hirst C. Iatrogenic Creutzfeldt-Jakob disease presenting 24 years after human growth hormone administration. *British Journal of Hospital Medicine* 2005;66:592-3.

135. Meissner B, Kallenberg K, Sanchez-Juan P, Ramljak S, Krasnianski A, Heinemann U*, et al.* MRI and clinical syndrome in dura mater-related Creutzfeldt-Jakob disease. *Journal of Neurology* 2009;256:355-63.

136. Ritchie DL, Barria MA, Peden AH, Yull HM, Kirkpatrick J, Adlard P*, et al.* UK Iatrogenic Creutzfeldt–Jakob disease: investigating human prion transmission across genotypic barriers using human tissue-based and molecular approaches. *Acta Neuropathologica* 2017;133:579-95.

137. Wroe SJ. Clinical presentation and pre-mortem diagnosis of variant Creutzfeldt–Jakob disease associated with blood transfusion: a case report. *Lancet* 2006;368:2061-7.

138. Ironside JW. Variant Creutzfeldt-Jakob disease. *Haemophilia* 2010;16 Suppl 5:175-80.

139. Hamaguchi T, Sakai K, Noguchi-Shinohara M, Nozaki I, Takumi I, Sanjo N*, et al.* Insight into the frequent occurrence of dura mater graft-associated Creutzfeldt-Jakob disease in Japan. *Journal of Neurology, Neurosurgery & Psychiatry* 2013;84:1171-5.

140. Ibrahim-Verbaas C, Engelen-Lee JY, Spliet W, Mondria T, Willems S, Van Duijn C*, et al.* CJD with numerous Abeta plaques in a 58-year old patient 28 years after dura mater grafting. *Prion* 2012;6:131-2.

141. Kobayashi A, Teruya K, Matsuura Y, Shirai T, Nakamura Y, Yamada M*, et al.* The influence of PRNP polymorphisms on human prion disease susceptibility: an update. *Acta Neuropathologica* 2015;130:159-70.

142. Makarava N, Savtchenko R, Alexeeva I, Rohwer RG, Baskakov IV. Fast and ultrasensitive method for quantitating prion infectivity titre. *Nature Communications* 2012;3:741.

143. Halliez S, Reine F, Herzog L, Jaumain E, Haik S, Rezaei H*, et al.* Accelerated, spleen-based titration of variant Creutzfeldt-Jakob disease infectivity in transgenic mice expressing human prion protein with sensitivity comparable to that of survival time bioassay. *Journal of Virology* 2014;88:8678-86.

144. Ironside JW. Variant Creutzfeldt-Jakob disease: an update. *Folia Neuropathologica* 2012;50:50-6.

145. Bishop MT, Diack AB, Ritchie DL, Ironside JW, Will RG, Manson JC. Prion infectivity in the spleen of a PRNP heterozygous individual with subclinical variant Creutzfeldt-Jakob disease. *Brain* 2013;136:1139-45.

146. Cali I, Cohen I, Blevins J, Castellani R, Al-Shekhlee A, Yuan J*, et al.* The co-existence of PrPSc type 1 and 2 in sporadic creutzfeldt-jakob disease affects the phenotype and PrPSc conformation. *Journal of Neuropathology and Experimental Neurology* 2009;68 (5):553.

147. Parchi P, Strammiello R, Notari S, Giese A, Langeveld JP, Ladogana A*, et al.* Incidence and spectrum of sporadic Creutzfeldt-Jakob disease variants with mixed phenotype and co-occurrence of PrPSc types: an updated classification. *Acta Neuropathologica* 2009;118:659-71.

148. Bishop MT, Will RG, Manson JC. Defining sporadic Creutzfeldt-Jakob disease strains and their transmission properties. *Proceedings of the National Academy of Sciences* 2010;107:12005-10.

149. Uro-Coste E, Cassard H, Simon S, Lugan S, Bilheude JM, Perret-Liaudet A*, et al.* Beyond PrP9res) type 1/type 2 dichotomy in Creutzfeldt-Jakob disease. *PLoS Pathogens* 2008;4:e1000029.

150. Jansen C, Parchi P, Capellari S, Ibrahim-Verbaas CA, Schuur M, Strammiello R*, et al.* Human prion diseases in the Netherlands (1998-2009): clinical, genetic and molecular aspects. *PLoS ONE [Electronic Resource]* 2012;7:e36333.

151. Mackay G, Yull H, Ironside J, Head M, Knight R. Unravelling the mysteries of sporadic CJD. *Journal of Neurology, Neurosurgery and Psychiatry Conference: Association of British Neurologists, ABN Joint Meeting with the Royal College of Physicians, RCP* 2013;84.

152. Iwasaki Y, Mimuro M, Yoshida M, Hashizume Y, Kitamoto T, Sobue G. Clinicopathologic characteristics of five autopsied cases of dura mater-associated Creutzfeldt-Jakob disease. *Neuropathology* 2008;28:51-61.

153. Sakai K, Hamaguchi T, Noguchi-Shinohara M, Nozaki I, Takumi I, Sanjo N*, et al.* Graft-related disease progression in dura mater graft-associated Creutzfeldt-Jakob disease: a cross-sectional study. *BMJ Open* 2013;3:e003400.

154. Beringue V, Le Dur A, Tixador P, Reine F, Lepourry L, Perret-Liaudet A*, et al.* Prominent and persistent extraneural infection in human PrP transgenic mice infected with variant CJD. *PLoS ONE [Electronic Resource]* 2008;3:e1419.

155. Beringue V, Vilotte JL, Laude H. Prion agent diversity and species barrier. *Veterinary Research* 2008;39:47.

156. Cali I, Miller CJ, Parisi JE, Geschwind MD, Gambetti P, Schonberger LB. Distinct pathological phenotypes of Creutzfeldt-Jakob disease in recipients of prion-contaminated growth hormone. *Acta Neuropathologica Communications* 2015;3:37.

157. Peden AH, Kirkpatrick JRM, Head MW, Ironside JW. Comparison of the in vitro seeding activity of UK iatrogenic and sporadic Creutzfeldt-Jakob disease subtypes by real time quaking induced conversion. *Prion* 2016;10:S50-S1.

158. Bougard D, Brandel JP, Belondrade M, Beringue V, Segarra C, Fleury H*, et al.* Detection of prions in the plasma of presymptomatic and symptomatic patients with variant Creutzfeldt-Jakob disease. *Science Translational Medicine* 2016;8:370ra182.

159. Mead S, Wadsworth JD, Porter MC, Linehan JM, Pietkiewicz W, Jackson GS*, et al.* Variant Creutzfeldt-Jakob disease with extremely low lymphoreticular deposition of prion protein. *JAMA Neurology* 2014;71:340-3.

160. Peden AH, McGuire LI, Appleford NE, Mallinson G, Wilham JM, Orrú CD*, et al.* Sensitive and specific detection of sporadic Creutzfeldt–Jakob disease brain prion protein using real-time quaking-induced conversion. *Journal of General Virology* 2012;93:438-49.

161. Douet JY, Lacroux C, Aron N, Head MW, Lugan S, Tillier C*, et al.* Distribution and Quantitative Estimates of Variant Creutzfeldt-Jakob Disease Prions in Tissues of Clinical and Asymptomatic Patients. *Emerging Infectious Diseases* 2017;23:946-56.

162. Bishop MT, Diack A, Cancellotti E, Will R, Manson J. Variant cjd strain remains stable after secondary transmission. *Prion* 2010;4 (3):143.

163. Wadsworth JD, Dalmau-Mena I, Joiner S, Linehan JM, O'Malley C, Powell C*, et al.* Effect of fixation on brain and lymphoreticular vCJD prions and bioassay of key positive specimens from a retrospective vCJD prevalence study. *Journal of Pathology* 2011;223:511-8.

164. Ritchie DL, Gibson SV, Abee CR, Kreil TR, Ironside JW, Brown P. Blood transmission studies of prion infectivity in the squirrel monkey (Saimiri sciureus): the Baxter study. *Transfusion* 2016;56:712-21.

165. Brown P, Ritchie D, Ironside J, Abee C, Kreil T, Gibson S. Blood transmission of prion infectivity in the squirrel monkey: The Baxter study. Prion, abstract no. 10260, p. S98-S.

166. Moore RA, Head MW, Ironside JW, Ritchie DL, Zanusso G, Choi YP*, et al.* The Distribution of Prion Protein Allotypes Differs Between Sporadic and Iatrogenic Creutzfeldt-Jakob Disease Patients. Erratum appears in PLoS Pathog. 2016 Mar;12(3):e1005496 Note: Pyo Choi, Young corrected to Choi, Young Pyo ; PMID: 26954665. *PLoS Pathogens* 2016;12:e1005416.

167. House of Commons. Science and Technology Committee. After the storm? UK blood safety and the risk of variant Creutzfeldt-Jakob Disease. Second Report of Session. 2014. <https://publications.parliament.uk/pa/cm201415/cmselect/cmsctech/327/32706.htm#a7> (Accessed 15.03.2018).

168. Lehmann S, Pastore M, Rogez-Kreuz C, Richard M, Belondrade M, Rauwel G*, et al.* New hospital disinfection processes for both conventional and prion infectious agents compatible with thermosensitive medical equipment. *Journal of Hospital Infection* 2009;72:342-50.

169. Lemmer K, Mielke M, Kratzel C, Joncic M, Oezel M, Pauli G*, et al.* Decontamination of surgical instruments from prions. II. In vivo findings with a model system for testing the removal of scrapie infectivity from steel surfaces. *Journal of General Virology* 2008;89:348-58.

170. Rogez-Kreuz C, Yousfi R, Soufflet C, Quadrio I, Yan ZX, Huyot V*, et al.* Inactivation of animal and human prions by hydrogen peroxide gas plasma sterilization. *Infection Control & Hospital Epidemiology* 2009;30:769-77.

171. Belondrade M, Nicot S, Béringue V, Coste J, Lehmann S, Bougard D. Rapid and highly sensitive detection of variant Creutzfeldt-Jakob disease abnormal prion protein on steel surfaces by protein misfolding cyclic amplification: application to prion decontamination Studies. *PLoS ONE [Electronic Resource]* 2016;11:e0146833.

172. Lawson VA, Stewart JD, Masters CL. Enzymatic detergent treatment protocol that reduces protease-resistant prion protein load and infectivity from surgical-steel monofilaments contaminated with a human-derived prion strain. *Journal of General Virology* 2007;88:2905-14.

173. Beekes M, Lemmer K, Thomzig A, Joncic M, Tintelnot K, Mielke M. Fast, broad-range disinfection of bacteria, fungi, viruses and prions. *Journal of General Virology* 2010;91:580-9.

174. Bellon A, Comoy E, Simoneau S, Mornac S, Dehen C, Perrin A*, et al.* Decontamination of prions in a plasma product manufacturing environment. *Transfusion* 2014;54:1028-36.

175. Fichet G, Antloga K, Comoy E, Deslys JP, McDonnell G. Prion inactivation using a new gaseous hydrogen peroxide sterilisation process. *Journal of Hospital Infection* 2007;67:278-86.

176. Herve R, Kong M, Comoy E, Deslys JP, Keevil B. Cold atmospheric plasma for the decontamination of reusable surgical instruments. *Prion* 2010;4 (3):218.

177. Herve R, Keevil CW. Current limitations about the cleaning of luminal endoscopes. *Journal of Hospital Infection* 2013;83:22-9.

178. Howlin RP, Khammo N, Secker T, McDonnell G, Keevil CW. Application of a fluorescent dual stain to assess decontamination of tissue protein and prion amyloid from surgical stainless steel during simulated washer-disinfector cycles. *Journal of Hospital Infection* 2010;75:66-71.

179. Edgeworth JA, Sicilia A, Linehan J, Brandner S, Jackson GS, Collinge J. A standardized comparison of commercially available prion decontamination reagents using the Standard Steel-Binding Assay. *Journal of General Virology* 2011;92:718-26.

180. Jackson GS, McKintosh E, Flechsig E, Prodromidou K, Hirsch P, Linehan J*, et al.* An enzyme-detergent method for effective prion decontamination of surgical steel. *Journal of General Virology* 2005;86:869-78.

181. Peretz D, Supattapone S, Giles K, Vergara J, Freyman Y, Lessard P*, et al.* Inactivation of prions by acidic sodium dodecyl sulfate. *Journal of Virology* 2006;80:322-31.

182. Giles K, Supattapone S, Peretz D, Glidden DV, Baron H, Prusiner SB. Disinfection of Prions. *New Biocides Development: Combined Approach of Chemistry and Microbiology* 2007;967:52-74.

183. Baxter HC, Campbell GA, Whittaker AG, Jones AC, Aitken A, Simpson AH*, et al.* Elimination of transmissible spongiform encephalopathy infectivity and decontamination of surgical instruments by using radio-frequency gas-plasma treatment. *Journal of General Virology* 2005;86:2393-9.

184. Giles K, Glidden DV, Beckwith R, Seoanes R, Peretz D, DeArmond SJ*, et al.* Resistance of bovine spongiform encephalopathy (BSE) prions to inactivation. *PLoS Pathogens* 2008;4:e1000206.

185. McKintosh E, Jackson G, Flechsig E, Prodromidou K, Hirsch P, Linehan J*, et al.* A detergent-enzyme method for effective prion decontamination of surgical steel. *Proceedings of the 13th World Congress of Neurological Surgery, Vols 1 and 2* 2005, <Go to ISI>://WOS:000233429700179:923-7.

186. Herve RC, Keevil CW. Persistent residual contamination in endoscope channels; a fluorescence epimicroscopy study. *Endoscopy* 2016;48:609-16.

187. Baxter RL, Baxter HC, Campbell GA, Grant K, Jones A, Richardson P*, et al.* Quantitative analysis of residual protein contamination on reprocessed surgical instruments. *Journal of Hospital Infection* 2006;63:439-44.

188. Murdoch H, Taylor D, Dickinson J, Walker JT, Perrett D, Raven ND*, et al.* Surface decontamination of surgical instruments: an ongoing dilemma. *Journal of Hospital Infection* 2006;63:432-8.

189. Lipscomb IP, Sihota AK, Botham M, Harris KL, Keevil CW. Rapid method for the sensitive detection of protein contamination on surgical instruments. *Journal of Hospital Infection* 2006a;62:141-8.

190. Lipscomb IP, Sihota AK, Keevil CW. Comparative study of surgical instruments from sterile-service departments for presence of residual gram-negative endotoxin and proteinaceous deposits. *Journal of Clinical Microbiology* 2006b;44:3728-33.

191. Smith A, Winter S, Lappin D, Sherriff A, McIvor I, Philp P*, et al.* Reducing the risk of iatrogenic CJD by improving the cleaning of neurosurgical instruments. *Journal of Hospital Infection* 2018;epub.

192. Baxter HC, Campbell GA, Richardson PR, Jones AC, Whittle IR, Casey M*, et al.* Surgical instrument decontamination: Efficacy of introducing an argon : oxygen RF gas-plasma cleaning step as part of the cleaning cycle for stainless steel instruments. *Ieee Transactions on Plasma Science* 2006;34:1337-44.

193. Baxter HC, Jones AC, Baxter RL. Application of epifluorescence scanning for monitoring the efficacy of protein removal by RF gas-plasma decontamination. *Prion* 2009;4 (3):204-5.

194. Secker TJ, Pinchin HE, Herve RC, Keevil CW. Efficacy of humidity retention bags for the reduced adsorption and improved cleaning of tissue proteins including prion-associated amyloid to surgical stainless steel surfaces. *Biofouling* 2015;31:535-41.

195. Secker TJ, Herve R, Keevil CW. Adsorption of prion and tissue proteins to surgical stainless steel surfaces and the efficacy of decontamination following dry and wet storage conditions. *Journal of Hospital Infection* 2011;78:251-5.

196. Lipscomb IP, Pinchin H, Collin R, Keevil CW. Effect of drying time, ambient temperature and pre-soaks on prion-infected tissue contamination levels on surgical stainless steel: concerns over prolonged transportation of instruments from theatre to central sterile service departments. *Journal of Hospital Infection* 2007;65:72-7.

197. Secker TJ, Hervea R, Keevil CW. Wet versus dry: Do environmental conditions have an effect on prion decontamination? *Prion* 2010;4 (3):213-4.

198. Department of Health and Social Care. CFPP-01-01: Decontamination of surgical instruments (HTM 01-01) Health Technical Memorandum (HTM) 01-01: management and decontamination of surgical instruments (medical devices) used in acute care. Part B: Common elements. 2016.

199. Bonda DJ, Manjila S, Mehndiratta P, Khan F, Miller BR, Onwuzulike K*, et al.* Human prion diseases: surgical lessons learned from iatrogenic prion transmission. *Neurosurgical Focus* 2016;41:E10.

200. Rutala WA, Weber DJ, Society for Healthcare Epidemiology of A. Guideline for disinfection and sterilization of prion-contaminated medical instruments. *Infection Control & Hospital Epidemiology* 2010;31:107-17.

201. Dickinson J, Murdoch H, Dennis MJ, Hall GA, Bott R, Crabb WD*, et al.* Decontamination of prion protein (BSE301V) using a genetically engineered protease. *Journal of Hospital Infection* 2009;72:65-70.

202. Fichet G, Comoy E, Duval C, Antloga K, Dehen C, Charbonnier A*, et al.* Novel methods for disinfection of prion-contaminated medical devices. *The Lancet* 2004;364:521-6.

203. Rochefort F. The role of detergents in prevention of transmission of Creutzfeldt-Jakob disease. German, English. *Zentralsterilisation - Central Service* 2010;18:395-400+1-5.

204. Herve R, Secker TJ, Keevil CW. Current risk of iatrogenic Creutzfeld-Jakob disease in the UK: efficacy of available cleaning chemistries and reusability of neurosurgical instruments. *Journal of Hospital Infection* 2010;75:309-13.

205. National Institute for Health and Care Excellence. Adoption and Impact Programme. IPG196 Adoption Scoping Report. 2016.

206. Department of Health and Social Care U. Minimise transmission risk of CJD and vCJD in healthcare settings. 2012. <https://www.gov.uk/government/publications/guidance-from-the-acdp-tse-risk-management-subgroup-formerly-tse-working-group> (Accessed 23.01.18).

207. Department of Health: Economics and Operational Research Division (EOR4). Risk Assessment for Transmission of vCJD via Surgical Instruments: A Modelling Approach and Numerical Scenarios; 2001

208. Bird SM, Merrall EL, Ward HJ, Will RG. Survival and re-operation rates after neurosurgical procedures in Scotland: implications for targeted surveillance of sub-clinical variant Creutzfeldt-Jakob disease. *Neuroepidemiology* 2009;33:1-11.

209. National Institute for Health and Care Excellence. Patient safety and reduction of risk of transmission of Creutzfeldt-Jakob (CJD) via interventional procedures. . 2006, <https://www.nice.org.uk/Guidance/IPG196> Accessed 7th March 2018.

210. Garske T, Ward HJ, Clarke P, Will RG, Ghani AC. Factors determining the potential for onward transmission of variant Creutzfeldt-Jakob disease via surgical instruments. *Journal of the Royal Society Interface* 2006;3:757-66.

211. National Institute for Health and Care Excellence. Guide to the methods of technology appraisal 2013. 2013. <https://www.nice.org.uk/article/pmg9/> (Accessed 19.03.2018).

212. Baxter R, Baxter H, Campbell G, Grant K, Jones A, Richardson P*, et al.* Quantitative analysis of residual protein contamination on reprocessed surgical instruments. *J Hosp Infect* 2006;63:439-44.

213. Office for National Statistics. National life tables: United Kingdom. 2017, <https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesunitedkingdomreferencetables>. Accessed 12th March 2018.

214. Curtis LA, Burns A. Unit Costs of Health and Social Care 2017. . University of Kent; 2017 <https://doi.org/10.22024/UniKent/01.02/65559>

215. Curtis L. Unit Costs of Health & Social Care 2014. . University of Kent.; 2014 <https://www.pssru.ac.uk/pub/uc/uc2014/full-with-covers.pdf> Accessed 12th March 2018

216. Barnett F, McLean G. Care management of Creutzfeldt-Jakob Disease within the United Kingdom. *Journal of Nursing Management* 2005;13:111-8.

217. Creutzfeldt-Jakob Disease Surveillance in the UK. 24th Annual Report 2015. Edinburgh: The National CJD Research & Surveillance Unit, Western General Hospital, Edinburgh, EH4 2XU; 2015 <http://www.cjd.ed.ac.uk/sites/default/files/Report24.pdf> Accessed 19th March 2018. .

218. National Institute for Health and Care Excellence. Interim Process and Methods of the Highly Specialised Technologies Programme Updated to reflect 2017 changes. 2017, <https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-highly-specialised-technologies-guidance/HST-interim-methods-process-guide-may-17.pdf>. [Accessed 1st March 2018].

# **Appendix 1**: Clinical Effectiveness Search Strategies

**MEDLINE, MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations: Ovid, 1946 to 2017**

14th August 2017

|  |  |
| --- | --- |
| **#** | **Searches** |
| 1 | exp Creutzfeldt-Jakob Syndrome/ |
| 2 | ((creutzfeldt jakob or creutzfeldt-jakob) adj (disease or syndrome)).tw. |
| 3 | (cjd or vcjd or v-cjd).tw. |
| 4 | exp Prion Diseases/ |
| 5 | exp Prions/ |
| 6 | ((transmissible or spong\*) adj encephalopath\*).tw. |
| 7 | (prion\* or tse).tw. |
| 8 | prp.tw. |
| 9 | or/1-8 |
| 10 | exp Incidence/ |
| 11 | exp Prevalence/ |
| 12 | incidence.tw. |
| 13 | prevalence.tw. |
| 14 | or/10-13 |
| 15 | incubat\*.tw. |
| 16 | 9 and (14 or 15) |
| 17 | limit 16 to yr="2005 -Current" |
| 18 | exp Creutzfeldt-Jakob Syndrome/ |
| 19 | ((creutzfeldt jakob or creutzfeldt-jakob) adj (disease or syndrome)).tw. |
| 20 | (cjd or vcjd or v-cjd).tw. |
| 21 | exp Prion Diseases/ |
| 22 | exp Prions/ |
| 23 | ((transmissible or spong\*) adj encephalopath\*).tw. |
| 24 | (prion\* or tse).tw. |
| 25 | prp.tw. |
| 26 | or/18-25 |
| 27 | ((transmission or transmit\* or iatrogenic or transfer\*) adj5 (creutzfeldt or cjd or vcjd or v-cjd or encephalopath\* or prion\* or tse or prp)).tw. |
| 28 | exp Surgical Instruments/ |
| 29 | exp Decontamination/ |
| 30 | exp Sterilization/ |
| 31 | 28 and (29 or 30) |
| 32 | ((surgery or surgical\* or instrument\* or device\* or equipment\*) adj5 (decontaminat\* or reprocess\* or disinfect\* or wash\* or clean\* or steril\* or contaminat\* or prerinse or pre-rinse or inactivat\*)).tw. |
| 33 | 31 or 32 |
| 34 | 26 and (27 or 33) |
| 35 | limit 34 to yr="2005 -Current" |
| 36 | exp Surgical Instruments/ |
| 37 | exp Decontamination/ |
| 38 | exp Sterilization/ |
| 39 | 36 and (37 or 38) |
| 40 | ((surgery or surgical\* or instrument\* or device\* or equipment\*) adj5 (decontaminat\* or reprocess\* or disinfect\* or wash\* or clean\* or steril\* or contaminat\* or prerinse or pre-rinse or inactivat\*)).tw. |
| 41 | 39 or 40 |
| 42 | Neurosurgery/ |
| 43 | Neurosurgical Procedures/ |
| 44 | (neurosurgery or neurological surgery).tw. |
| 45 | exp Brain/su [Surgery] |
| 46 | exp Meninges/su [Surgery] |
| 47 | exp Pituitary Gland/su [Surgery] |
| 48 | Pineal Gland/su [Surgery] |
| 49 | ((brain or meninges or cerebral or pituitary or pineal) adj5 (surgery or surgical\* or excision or lesion or ablation or operation\* or neurostimulation or connection or destruction)).tw. |
| 50 | exp Cranial Nerves/su [Surgery] |
| 51 | ((cranial or dura) adj5 (graft\* or transection or destruction or lesion or repair\* or decompress\* or neurostimulation or exploration or operation\*)).tw. |
| 52 | Ophthalmologic Surgical Procedures/ |
| 53 | ((eye or vitreous or retina) adj5 (surgery or surgical\* or excision or operation\* or photocoagulation or destruction)).tw. |
| 54 | Eye/su [Surgery] |
| 55 | Vitreous Body/su [Surgery] |
| 56 | exp Retina/su [Surgery] |
| 57 | or/42-56 |
| 58 | 41 and 57 |
| 59 | limit 58 to yr="2005 -Current" |
| 60 | (disposable or dispose\* or nondispos\* or non-dispos\* or reus\* or re-us\* or "single use" or "single-use").mp. |
| 61 | Disposable Equipment/ |
| 62 | exp Equipment Reuse/ |
| 63 | (ultrasonic aspirator or aneurysm clip applicator or rhoton dissectors or microsurgical scissors or upcut rongeurs or budde halo or retraction system or self-retaining retractors or neuroendoscope\*).mp. |
| 64 | or/60-63 |
| 65 | Neurosurgery/ |
| 66 | Neurosurgical Procedures/ |
| 67 | (neurosurgery or neurological surgery).tw. |
| 68 | exp Brain/su [Surgery] |
| 69 | exp Meninges/su [Surgery] |
| 70 | exp Pituitary Gland/su [Surgery] |
| 71 | Pineal Gland/su [Surgery] |
| 72 | ((brain or meninges or cerebral or pituitary or pineal) adj5 (surgery or surgical\* or excision or lesion or ablation or operation\* or neurostimulation or connection or destruction)).tw. |
| 73 | exp Cranial Nerves/su [Surgery] |
| 74 | ((cranial or dura) adj5 (graft\* or transection or destruction or lesion or repair\* or decompress\* or neurostimulation or exploration or operation\*)).tw. |
| 75 | Ophthalmologic Surgical Procedures/ |
| 76 | ((eye or vitreous or retina) adj5 (surgery or surgical\* or excision or operation\* or photocoagulation or destruction)).tw. |
| 77 | Eye/su [Surgery] |
| 78 | Vitreous Body/su [Surgery] |
| 79 | exp Retina/su [Surgery] |
| 80 | or/65-79 |
| 81 | complication\*.mp. |
| 82 | co.fs. |
| 83 | exp Postoperative Complications/ |
| 84 | exp Intraoperative Complications/ |
| 85 | or/81-84 |
| 86 | 64 and 80 and 85 |
| 87 | limit 86 to yr="2005 -Current" |
| 88 | \*Reoperation/ |
| 89 | reoperat\*.tw. |
| 90 | ((repeat or revision) adj3 (surgery or surgical\* or operat\*)).tw. |
| 91 | or/88-90 |
| 92 | Neurosurgery/ |
| 93 | Neurosurgical Procedures/ |
| 94 | (neurosurgery or neurological surgery).tw. |
| 95 | exp Brain/su [Surgery] |
| 96 | exp Meninges/su [Surgery] |
| 97 | exp Pituitary Gland/su [Surgery] |
| 98 | Pineal Gland/su [Surgery] |
| 99 | ((brain or meninges or cerebral or pituitary or pineal) adj5 (surgery or surgical\* or excision or lesion or ablation or operation\* or neurostimulation or connection or destruction)).tw. |
| 100 | exp Cranial Nerves/su [Surgery] |
| 101 | ((cranial or dura) adj5 (graft\* or transection or destruction or lesion or repair\* or decompress\* or neurostimulation or exploration or operation\*)).tw. |
| 102 | Ophthalmologic Surgical Procedures/ |
| 103 | ((eye or vitreous or retina) adj5 (surgery or surgical\* or excision or operation\* or photocoagulation or destruction)).tw. |
| 104 | Eye/su [Surgery] |
| 105 | Vitreous Body/su [Surgery] |
| 106 | exp Retina/su [Surgery] |
| 107 | or/92-106 |
| 108 | 91 and 107 |
| 109 | 17 or 35 or 59 or 87 or 108 |

**Embase 1974 to 2017 August 11**

14th August 2017

|  |  |
| --- | --- |
| **#** | **Searches** |
| 1 | exp Creutzfeldt Jakob disease/ |
| 2 | ((creutzfeldt jakob or creutzfeldt-jakob) adj (disease or syndrome)).tw. |
| 3 | (cjd or vcjd or v-cjd).tw. |
| 4 | exp prion disease/ |
| 5 | exp prion/ |
| 6 | ((transmissible or spong\*) adj encephalopath\*).tw. |
| 7 | (prion\* or tse).tw. |
| 8 | prp.tw. |
| 9 | or/1-8 |
| 10 | exp incidence/ |
| 11 | exp prevalence/ |
| 12 | incidence.tw. |
| 13 | prevalence.tw. |
| 14 | or/10-13 |
| 15 | incubat\*.tw. |
| 16 | 9 and (14 or 15) |
| 17 | limit 16 to yr="2005 -Current" |
| 18 | ((transmission or transmit\* or iatrogenic or transfer\*) adj5 (creutzfeldt or cjd or vcjd or v-cjd or encephalopath\* or prion\* or tse or prp)).tw. |
| 19 | exp surgical equipment/ |
| 20 | instrument sterilization/ |
| 21 | 19 and 20 |
| 22 | ((surgery or surgical\* or instrument\* or device\* or equipment\*) adj5 (decontaminat\* or reprocess\* or disinfect\* or wash\* or clean\* or steril\* or contaminat\* or prerinse or pre-rinse or inactivat\*)).tw. |
| 23 | 21 or 22 |
| 24 | 9 and (18 or 23) |
| 25 | limit 24 to yr="2005 -Current" |
| 26 | exp surgical equipment/ |
| 27 | instrument sterilization/ |
| 28 | 26 and 27 |
| 29 | ((surgery or surgical\* or instrument\* or device\* or equipment\*) adj5 (decontaminat\* or reprocess\* or disinfect\* or wash\* or clean\* or steril\* or contaminat\* or prerinse or pre-rinse or inactivat\*)).tw. |
| 30 | 28 or 29 |
| 31 | neurosurgery/ |
| 32 | (neurosurgery or neurological surgery).tw. |
| 33 | exp brain/su [Surgery] |
| 34 | exp meninx/su [Surgery] |
| 35 | exp hypophysis/su [Surgery] |
| 36 | pineal body/su [Surgery] |
| 37 | ((brain or meninges or cerebral or pituitary or pineal) adj5 (surgery or surgical\* or excision or lesion or ablation or operation\* or neurostimulation or connection or destruction)).tw. |
| 38 | exp cranial nerve/su [Surgery] |
| 39 | ((cranial or dura) adj5 (graft\* or transection or destruction or lesion or repair\* or decompress\* or neurostimulation or exploration or operation\*)).tw. |
| 40 | eye surgery/ |
| 41 | ((eye or vitreous or retina) adj5 (surgery or surgical\* or excision or operation\* or photocoagulation or destruction)).tw. |
| 42 | eye/su [Surgery] |
| 43 | vitreous body/su [Surgery] |
| 44 | exp retina/su [Surgery] |
| 45 | or/31-44 |
| 46 | 30 and 45 |
| 47 | limit 46 to yr="2005 -Current" |
| 48 | (disposable or dispose\* or nondispos\* or non-dispos\* or reus\* or re-us\* or "single use" or "single-use").mp. |
| 49 | disposable equipment/ |
| 50 | exp recycling/ |
| 51 | (ultrasonic aspirator or aneurysm clip applicator or rhoton dissectors or microsurgical scissors or upcut rongeurs or budde halo or retraction system or self-retaining retractors or neuroendoscope\*).mp. |
| 52 | or/48-51 |
| 53 | neurosurgery/ |
| 54 | (neurosurgery or neurological surgery).tw. |
| 55 | exp brain/su [Surgery] |
| 56 | exp meninx/su [Surgery] |
| 57 | exp hypophysis/su [Surgery] |
| 58 | pineal body/su [Surgery] |
| 59 | ((brain or meninges or cerebral or pituitary or pineal) adj5 (surgery or surgical\* or excision or lesion or ablation or operation\* or neurostimulation or connection or destruction)).tw. |
| 60 | exp cranial nerve/su [Surgery] |
| 61 | ((cranial or dura) adj5 (graft\* or transection or destruction or lesion or repair\* or decompress\* or neurostimulation or exploration or operation\*)).tw. |
| 62 | eye surgery/ |
| 63 | ((eye or vitreous or retina) adj5 (surgery or surgical\* or excision or operation\* or photocoagulation or destruction)).tw. |
| 64 | eye/su [Surgery] |
| 65 | vitreous body/su [Surgery] |
| 66 | exp retina/su [Surgery] |
| 67 | or/53-66 |
| 68 | complication\*.mp. |
| 69 | co.fs. |
| 70 | exp postoperative complication/ |
| 71 | exp peroperative complication/ |
| 72 | or/68-71 |
| 73 | 52 and 67 and 72 |
| 74 | limit 73 to yr="2005 -Current" |
| 75 | \*reoperation/ |
| 76 | reoperat\*.tw. |
| 77 | ((repeat or revision) adj3 (surgery or surgical\* or operat\*)).tw. |
| 78 | or/75-77 |
| 79 | neurosurgery/ |
| 80 | (neurosurgery or neurological surgery).tw. |
| 81 | exp brain/su [Surgery] |
| 82 | exp meninx/su [Surgery] |
| 83 | exp hypophysis/su [Surgery] |
| 84 | pineal body/su [Surgery] |
| 85 | ((brain or meninges or cerebral or pituitary or pineal) adj5 (surgery or surgical\* or excision or lesion or ablation or operation\* or neurostimulation or connection or destruction)).tw. |
| 86 | exp cranial nerve/su [Surgery] |
| 87 | ((cranial or dura) adj5 (graft\* or transection or destruction or lesion or repair\* or decompress\* or neurostimulation or exploration or operation\*)).tw. |
| 88 | eye surgery/ |
| 89 | ((eye or vitreous or retina) adj5 (surgery or surgical\* or excision or operation\* or photocoagulation or destruction)).tw. |
| 90 | eye/su [Surgery] |
| 91 | vitreous body/su [Surgery] |
| 92 | exp retina/su [Surgery] |
| 93 | or/79-92 |
| 94 | 78 and 93 |
| 95 | 17 or 25 or 47 or 74 or 94 |
| 96 | remove duplicates from 95 |

**Science Citation Index (SCI-E) and Conference Proceedings Citation Index (CPCI): Web of Science, 1990 to 2017**

14th August 2017

|  |  |
| --- | --- |
| **#** | **Searches** |
| # 1 | TS=(creutzfeldt jakob NEAR/1 disease) OR TS=(creutzfeldt jakob NEAR/1 syndrome) OR TS=(creutzfeldt-jakob NEAR/1 disease) OR TS=(creutzfeldt-jakob NEAR/1 syndrome) |
| # 2 | TS=((cjd or vcjd or v-cjd)) |
| # 3 | TS=(transmissible NEAR/1 encephalopath\*) OR TS=(spong\* NEAR/1 encephalopath\*) |
| # 4 | TS=(prion\* or tse or prp) |
| # 5 | #4 OR #3 OR #2 OR #1 |
| # 6 | TS= (incidence) |
| # 7 | TS= (prevalence) |
| # 8 | TS= (incubat\*) |
| # 9 | #8 OR #7 OR #6 |
| # 10 | #9 AND #5 Timespan=2005-2017 |
| # 11 | TS=(creutzfeldt jakob NEAR/1 disease) OR TS=(creutzfeldt jakob NEAR/1 syndrome) OR TS=(creutzfeldt-jakob NEAR/1 disease) OR TS=(creutzfeldt-jakob NEAR/1 syndrome) |
| # 12 | TS=((cjd or vcjd or v-cjd)) |
| # 13 | TS=(transmissible NEAR/1 encephalopath\*) OR TS=(spong\* NEAR/1 encephalopath\*) |
| # 14 | TS=(prion\* or tse or prp) |
| # 15 | #14 OR #13 OR #12 OR #11 |
| # 16 | TS=(((transmission or transmit\* or iatrogenic or transfer\*) NEAR/5 (creutzfeldt or cjd or vcjd or v-cjd or encephalopath\* or prion\* or tse or prp))) |
| # 17 | TS=(((surgery or surgical\* or instrument\* or device\* or equipment\*) NEAR/5 (decontaminat\* or reprocess\* or disinfect\* or wash\* or clean\* or steril\* or contaminat\* or prerinse or pre-rinse or inactivat\*))) |
| # 18 | #17 OR #16 |
| # 19 | #18 AND #15 Timespan=2005-2017 |
| # 20 | TS=(((surgery or surgical\* or instrument\* or device\* or equipment\*) NEAR/5 (decontaminat\* or reprocess\* or disinfect\* or wash\* or clean\* or steril\* or contaminat\* or prerinse or pre-rinse or inactivat\*))) |
| # 21 | TS=((neurosurgery or neurological surgery)) |
| # 22 | TS=(((brain or meninges or cerebral or pituitary or pineal) NEAR/5 (surgery or surgical\* or excision or lesion or ablation or operation\* or neurostimulation or connection or destruction))) |
| # 23 | TS=(((cranial or dura) NEAR/5 (graft\* or transection or destruction or lesion or repair\* or decompress\* or neurostimulation or exploration or operation\*))) |
| # 24 | TS=(((eye or vitreous or retina) NEAR/5 (surgery or surgical\* or excision or operation\* or photocoagulation or destruction))) |
| # 25 | #24 OR #23 OR #22 OR #21 |
| # 26 | #25 AND #20 Timespan=2005-2017 |
| # 27 | TS=((disposable or dispose\* or nondispos\* or non-dispos\* or reus\* or re-us\* or "single use" or "single-use")) |
| # 28 | TS=((ultrasonic aspirator or aneurysm clip applicator or rhoton dissectors or microsurgical scissors or upcut rongeurs or budde halo or retraction system or self-retaining retractors or neuroendoscope\*)) |
| # 29 | #28 OR #27 |
| # 30 | TS=((neurosurgery or neurological surgery)) |
| # 31 | TS=(((brain or meninges or cerebral or pituitary or pineal) NEAR/5 (surgery or surgical\* or excision or lesion or ablation or operation\* or neurostimulation or connection or destruction))) |
| # 32 | TS=(((cranial or dura) NEAR/5 (graft\* or transection or destruction or lesion or repair\* or decompress\* or neurostimulation or exploration or operation\*))) |
| # 33 | TS=(((eye or vitreous or retina) NEAR/5 (surgery or surgical\* or excision or operation\* or photocoagulation or destruction))) |
| # 34 | #33 OR #32 OR #31 OR #30 |
| # 35 | #34 AND #29 |
| # 36 | TS=(complication\*) |
| # 37 | #36 AND #35 Timespan=2005-2017 |
| # 38 | TS=(reoperat\*) |
| # 39 | TS=(((repeat or revision) NEAR/3 (surgery or surgical\* or operat\*))) |
| # 40 | #39 OR #38 |
| # 41 | TS=((neurosurgery or neurological surgery)) |
| # 42 | TS=(((brain or meninges or cerebral or pituitary or pineal) NEAR/5 (surgery or surgical\* or excision or lesion or ablation or operation\* or neurostimulation or connection or destruction))) |
| # 43 | TS=(((cranial or dura) NEAR/5 (graft\* or transection or destruction or lesion or repair\* or decompress\* or neurostimulation or exploration or operation\*))) |
| # 44 | TS=(((eye or vitreous or retina) NEAR/5 (surgery or surgical\* or excision or operation\* or photocoagulation or destruction))) |
| # 45 | #44 OR #43 OR #42 OR #41 |
| # 46 | #45 AND #40 |
| # 47 | #46 OR #37 OR #26 OR #19 OR #10 |

**Supplementary search in October 2017**

**MEDLINE, MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations: Ovid, 1946 to 2017**

2nd October 2017

|  |  |
| --- | --- |
| **#** | **Searches** |
| 1 | exp Creutzfeldt-Jakob Syndrome/ |
| 2 | ((creutzfeldt jakob or creutzfeldt-jakob) adj (disease or syndrome)).tw. |
| 3 | (cjd or vcjd or v-cjd).tw. |
| 4 | exp Prion Diseases/ |
| 5 | exp Prions/ |
| 6 | ((transmissible or spong\*) adj encephalopath\*).tw. |
| 7 | (prion\* or tse).tw. |
| 8 | prp.tw. |
| 9 | or/1-8 |
| 10 | (surgery or surgical\* or operat\*).tw. |
| 11 | risk\*.mp. |
| 12 | 9 and 10 and 11 |
| 13 | limit 12 to yr="2005 -Current" |

**Embase 1974 to 2017 October**

2nd October 2017

|  |  |
| --- | --- |
| **#** | **Searches** |
| 1 | exp Creutzfeldt Jakob disease/ |
| 2 | ((creutzfeldt jakob or creutzfeldt-jakob) adj (disease or syndrome)).tw. |
| 3 | (cjd or vcjd or v-cjd).tw. |
| 4 | exp prion disease/ |
| 5 | exp prion/ |
| 6 | ((transmissible or spong\*) adj encephalopath\*).tw. |
| 7 | (prion\* or tse).tw. |
| 8 | prp.tw. |
| 9 | or/1-8 |
| 10 | (surgery or surgical\* or operat\*).tw. |
| 11 | risk\*.mp. |
| 12 | 9 and 10 and 11 |
| 13 | limit 12 to yr="2005 -Current" |

**Science Citation Index (SCI-E) and Conference Proceedings Citation Index (CPCI): Web of Science, 1990 to 2017**

2nd October 2017

|  |  |
| --- | --- |
| **#** | **Searches** |
| # 1 | TS=(creutzfeldt jakob NEAR/1 disease) OR TS=(creutzfeldt jakob NEAR/1 syndrome) OR TS=(creutzfeldt-jakob NEAR/1 disease) OR TS=(creutzfeldt-jakob NEAR/1 syndrome) |
| # 2 | TS=((cjd or vcjd or v-cjd)) |
| # 3 | TS=(transmissible NEAR/1 encephalopath\*) OR TS=(spong\* NEAR/1 encephalopath\*) |
| # 4 | TS=(prion\* or tse or prp) |
| # 5 | #4 OR #3 OR #2 OR #1 |
| # 6 | TOPIC: ((surgery or surgical\* or operat\*)) |
| # 7 | TOPIC: ((risk\*)) |
| # 8 | #7 AND #6 AND #5 |
| # 9 | #7 AND #6 AND #5 Refined by: PUBLICATION YEARS: ( 2006 OR 2012 OR 2016 OR 2015 OR 2007 OR 2013 OR 2005 OR 2009 OR 2010 OR 2017 OR 2014 OR 2011 OR 2008 ) |

# **Appendix 2**: Cost Effectiveness Search Strategies

**MEDLINE, MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations: Ovid, 1946 to 2017**

7th June 2017

|  |  |
| --- | --- |
| **#** | **Searches** |
| 1 | exp Creutzfeldt-Jakob Syndrome/ |
| 2 | ((creutzfeldt jakob or creutzfeldt-jakob) adj (disease or syndrome)).tw. |
| 3 | (cjd or vcjd or v-cjd).tw. |
| 4 | exp Prion Diseases/ |
| 5 | exp PRIONS/ |
| 6 | ((transmissible or spong\*) adj encephalopath\*).tw. |
| 7 | (prion\* or tse).tw. |
| 8 | prp.tw. |
| 9 | or/1-8 |
| 10 | exp "Costs and Cost Analysis"/ |
| 11 | Economics/ |
| 12 | exp Economics, Hospital/ |
| 13 | exp Economics, Medical/ |
| 14 | Economics, Nursing/ |
| 15 | exp models, economic/ |
| 16 | Economics, Pharmaceutical/ |
| 17 | exp "Fees and Charges"/ |
| 18 | exp Budgets/ |
| 19 | budget$.tw. |
| 20 | ec.fs. |
| 21 | cost$.ti. |
| 22 | (cost$ adj2 (effective$ or utilit$ or benefit$ or minimi$)).ab. |
| 23 | (economic$ or pharmacoeconomic$ or pharmaco-economic$).ti. |
| 24 | (price$ or pricing$).tw. |
| 25 | (financial or finance or finances or financed).tw. |
| 26 | (fee or fees).tw. |
| 27 | (value adj2 (money or monetary)).tw. |
| 28 | quality-adjusted life years/ |
| 29 | (qaly or qalys).af. |
| 30 | (quality adjusted life year or quality adjusted life years).af. |
| 31 | or/10-30 |
| 32 | 9 and 31 |
| 33 | limit 32 to yr="2004 -Current" |

**Embase 1974 to 2017 June 6**

7th June 2017

|  |  |
| --- | --- |
| **#** | **Searches** |
| 1 | exp Creutzfeldt Jakob disease/ |
| 2 | ((creutzfeldt jakob or creutzfeldt-jakob) adj (disease or syndrome)).tw. |
| 3 | (cjd or vcjd or v-cjd).tw. |
| 4 | exp prion disease/ |
| 5 | exp prion/ |
| 6 | ((transmissible or spong\*) adj encephalopath\*).tw. |
| 7 | (prion\* or tse).tw. |
| 8 | prp.tw. |
| 9 | or/1-8 |
| 10 | Socioeconomics/ |
| 11 | Cost benefit analysis/ |
| 12 | Cost effectiveness analysis/ |
| 13 | Cost of illness/ |
| 14 | Cost control/ |
| 15 | Economic aspect/ |
| 16 | Financial management/ |
| 17 | Health care cost/ |
| 18 | Health care financing/ |
| 19 | Health economics/ |
| 20 | Hospital cost/ |
| 21 | (fiscal or financial or finance or funding).tw. |
| 22 | Cost minimization analysis/ |
| 23 | (cost adj estimate$).mp. |
| 24 | (cost adj variable$).mp. |
| 25 | (unit adj cost$).mp. |
| 26 | or/10-25 |
| 27 | 9 and 26 |
| 28 | limit 27 to yr="2004 -Current" |

**Science Citation Index (SCI-E) and Conference Proceedings Citation Index (CPCI): Web of Science, 1990 to 2017**

11th July 2017

|  |  |
| --- | --- |
| **#** | **Searches** |
| # 1 | TS=(creutzfeldt jakob NEAR/1 disease) OR TS=(creutzfeldt jakob NEAR/1 syndrome) OR TS=(creutzfeldt-jakob NEAR/1 disease) OR TS=(creutzfeldt-jakob NEAR/1 syndrome) |
| # 2 | TS=((cjd or vcjd or v-cjd)) |
| # 3 | TS=(transmissible NEAR/1 encephalopath\*) OR TS=(spong\* NEAR/1 encephalopath\*) |
| # 4 | TS=(prion\* or tse or prp) |
| # 5 | #4 OR #3 OR #2 OR #1 |
| # 6 | TS=((cost\* and (effective\* or utilit\* or benefit\* or minimi\*))) OR TI=((cost\*)) OR TS=((economic\* or pharmacoeconomic\* or pharmaco-economic\*)) OR TS=((price\* or pricing\*)) OR TS=((financial or finance or finances or financed)) OR TS=((economic\* and (hospital or medical or nursing or pharmaceutical))) OR TS=(("quality adjusted life year" or "quality adjusted life years")) OR TS=((qaly or qalys)) OR TS=((budget\*)) |
| # 7 | #6 AND #5 Refined by: PUBLICATION YEARS: ( 2015 OR 2017 OR 2011 OR 2014 OR 2016 OR 2008 OR 2013 OR 2007 OR 2009 OR 2005 OR 2012 OR 2004 OR 2010 OR 2006 ) |

# Appendix 3: Excluded studies from the clinical reviews with reasons for exclusion

|  |  |
| --- | --- |
| Reference | Primary reason for exclusion |
| Adam, A. M. and O. Akuku (2005). "Creutzfeldt-Jakob disease in Kenya." Tropical Medicine & International Health 10(7): 710-712. | Data for pre-2005 |
| Allen, C. T., et al. (2007). "Washington statewide pathology surveillance for prion disease." Annals of Neurology 61(4): 371-372. | Superceded data |
| Amour, J. (2010). "Comparison of Single-use and Reusable Metal Laryngoscope Blades for Orotracheal Intubation during Rapid Sequence Induction of Anesthesia: A Multicenter Cluster Randomized Study." Anaesthesiology 112: 325-332. | Not high-risk surgery |
| Brandel, J. P., et al. (2009). "Epidemiological surveillance of Creutzfeldt-Jakob in France." Revue Neurologique 165(8-9): 684-693. | Review with no original data |
| Chandra, S. R., et al. (2016). "Creutzfeldt-Jakob Disease Phenotype and Course: Our Experience from a Tertiary Center." Indian Journal of Psychological Medicine 38(5): 438-442. | No usable data for any review question |
| Checchi, M., et al. (2016). "Ten-year follow-up of two cohorts with an increased risk of variant CJD: donors to individuals who later developed variant CJD and other recipients of these at-risk donors." Vox Sanguinis 111(4): 325-332. | No usable data for any review question |
| Chen, C. C., et al. (2013). "Consumption of bovine spongiform encephalopathy (BSE) contaminated beef and the risk of variant Creutzfeldt-Jakob disease." Risk Analysis 33(11): 1958-1968. | No usable data for any review question |
| de Pedro-Cuesta, J., et al. (2006). "Classification of surgical procedures for epidemiologic assessment of sporadic Creutzfeldt-Jakob disease transmission by surgery." European Journal of Epidemiology 21(8): 595-604. | Wrong outcome |
| Frontzek, K., et al. (2015). "Iatrogenic and sporadic Creutzfeldt-Jakob disease in 2 sisters without mutation in the prion protein gene." Prion 9(6): 444-448. | No usable data for any review question |
| Graziano, S. and M. Pocchiari (2009). "Management and prevention of human prion diseases." Current Neurology & Neuroscience Reports 9(6): 423-429. | Review with no original data |
| Gregori, L., et al. (2012). "Estimation of variant Creutzfeldt-Jakob disease infectivity titers in human blood." Prion 6: 139. | No usable data for any review question |
| Gubbels, S., et al. (2012). "Description and analysis of 12 years of surveillance for Creutzfeldt-Jakob disease in Denmark, 1997 to 2008." Euro Surveillance: Bulletin Europeen sur les Maladies Transmissibles = European Communicable Disease Bulletin 17(15): 12. | Superceded data |
| Hamaguchi, T. (2013). "Clinical manifestations and epidemiology of prion diseases in Japan." Rinsho Shinkeigaku - Clinical Neurology 23(11): 1246-1248. | Superceded data |
| Ironside, J. W., et al. (2010). "Asymptomatic vCJD infection detected at autopsy in a UK haemophilic patient." Haemophilia 16: 29. | Superceded data |
| Karhade, A. V., et al. (2016). "Thirty-day readmission and reoperation after surgery for spinal tumors: a National Surgical Quality Improvement Program analysis." Neurosurgical Focus 41(2). | Wrong outcome |
| Klug, G. M., et al. (2009). "Surveillance of Creutzfeldt-Jakob disease in Australia: 2009 update." Communicable Diseases Intelligence Quarterly Report 33(2): 188-191. | Superceded data |
| Kobayashi, A., et al. (2016). "Sporadic Creutzfeldt-Jakob Disease MM1+2C and MM1 are Identical in Transmission Properties." Brain Pathology 26(1): 95-101. | Review with no original data |
| Kobayashi, A., et al. (2015). "The influence of PRNP polymorphisms on human prion disease susceptibility: an update." Acta Neuropathologica 130(2): 159-170. | Review with no original data |
| Kovacs, G. G. and K. Majtenyi (2005). "Creutzfeldt-Jakob disease in Hungary." Folia Neuropathologica 43(4): 279-285. | Superceded data |
| Maddox, R. A., et al. (2016). "Unusually young prion disease cases in the United States, 1979-2014." Prion 10: S98-S99. | No usable data for any review question |
| Maheshwari, A., et al. (2015). "Recent US Case of Variant Creutzfeldt-Jakob Disease-Global Implications." Emerging infectious diseases 21(5): 750-759. | Superceded data |
| Mei, L. L., et al. (2015). "Effectiveness of 2D barcode tracking in recording instrument sterilization & avoiding spread of infection in operating theatre." Journal of Microbiology, Immunology and Infection 1): S68. | Wrong outcome |
| Mikol, J., et al. (2012). "Creutzfeldt-Jakob disease with unusually extensive neuropathology in a child treated with native human growth hormone." Clinical Neuropathology 31(3): 127-134. | Superceded data |
| Papacostas, S., et al. (2008). "Ten-year mortality from Creutzfeldt-Jakob disease in Cyprus." Eastern Mediterranean Health Journal 14(3): 715-719. | Data for pre-2005 |
| Parchi, P. (2009). "Molecular-phenotypic correlation in sporadic and genetic Creutzfeldt-Jakob disease: Insights from recent studies." Clinical Neuropathology 28 (3): 235-236. | Review with no original data |
| Ritchie, D. L., et al. (2017). "Amyloid-beta accumulation in human growth hormone related iatrogenic CJD patients in the UK." Neuropathology and Applied Neurobiology 43: 39. | Not CJD related |
| Rohan, Z., et al. (2015). "Human prion diseases in the Czech Republic." Epidemiologie Mikrobiologie Imunologie 64(3): 115-120. | No usable data for any review question |
| Saba, R. and S. A. Booth (2013). "The genetics of susceptibility to variant Creutzfeldt-Jakob disease." Public Health Genomics 16(1-2): 17-24. | No usable data for any review question |
| Sawyer, E. B., et al. (2015). "Preclinical detection of infectivity and disease-specific PrP in blood throughout the incubation period of prion disease." Scientific Reports 5: 17742. | No usable data for any review question |
| Takeuchi, A., et al. (2013). "Characterization of variant Creutzfeldt-Jakob disease prions in prion protein-humanized mice carrying distinct codon 129 genotypes." Journal of Biological Chemistry 288(30): 21659-21666. | No usable data for any review question |

# Appendix 4: Elicitation exercise relating to epidemiological parameters. Conducted 18th January 2018

**1 List of participants**

**Participating experts**

(In alphabetical order of surname)

Dr David Hilton – Consultant Neuropathologist, Plymouth Hospitals NHS Trust

Professor Simon Mead - Professor of Neurology, University College London

Professor Graham Medley – Professor of Infectious Disease Modelling, London School of Hygiene & Tropical Medicine

Dr Katy Sinka – Creutzfeldt-Jacob disease (CJD) Section Head, Public Health England

Note that this order does not correspond to Experts A, B, C and D: we have chosen to anonymise individual responses and comments in this record.

**Facilitator**

Professor Jeremy Oakley – Professor of Statistics, University of Sheffield.

**2 Parameters related to misdiagnoses of the cause of death in patients who die due to CJD**

The quantity of interest is the percentage of patients whose death was due to CJD that are misdiagnosed as having died from another neurodegenerative disease, since 2005.

A separate percentage is considered for each of three age categories:

1. < 60 years old
2. 60-79 years old
3. ≥ 80 years old

It was decided to elicit distributions for age categories (1) and (3), and assume that the percentage for age category (2) would be the mean of these two.

**2.1 Parameter 1 definition:** the percentage of patients, aged less than 60, whose death was due to CJD, that are misdiagnosed as having died from another neurodegenerative disease, since 2005.

**2.1.1 Individual judgements**

Without conferring, the experts made the following probability judgements for Parameter 1

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Expert | Plausible lower limit | 25th percentile | median | 75th  percentile | Plausible upper limit |
| A | 0% | 0.5% | 1% | 3% | 10% |
| B | 0% | 2.5% | 5% | 7.5% | 15% |
| C | 0% | 10% | 20% | 30% | 50% |
| D | 0% | 1% | 5% | 10% | 20% |

**2.1.2 Group discussion and consensus judgements**

Expert C argued that correct diagnosis would be dependent on whether the patient was referred to Neurology; a higher misdiagnosis rate could occur if the referral rate were lower. Where patients were misdiagnosed, a possible diagnosis would be early onset dementia.

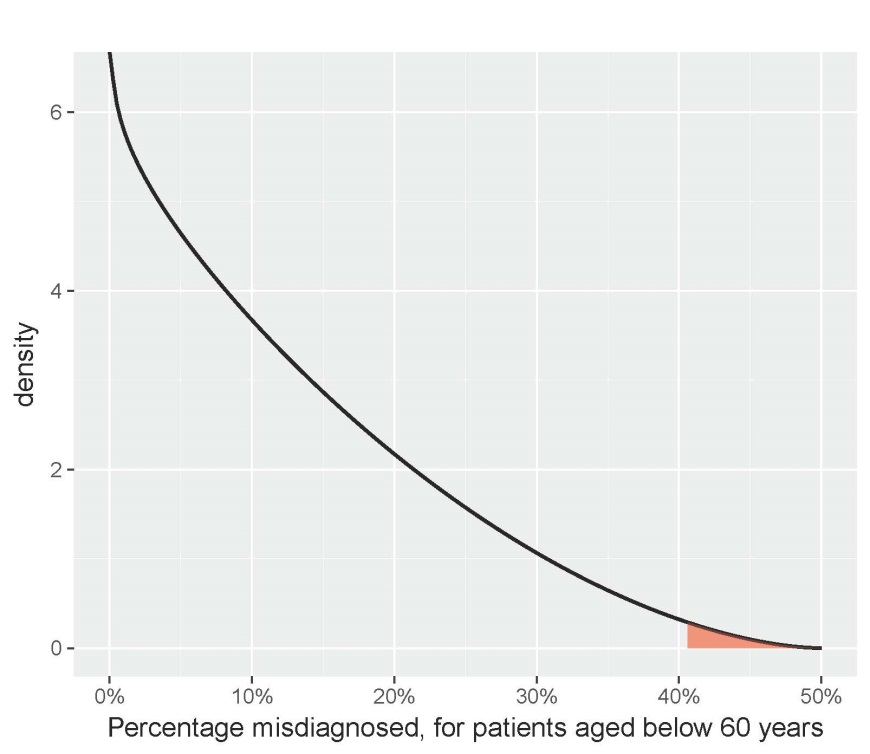
Expert A was willing to revise their own judgements upwards somewhat, but thought Expert C’s view was pessimistic.

It was agreed that Expert C’s arguments were valid, but not overwhelming; for the consensus distribution, the experts agreed on quartiles supporting higher values, but set somewhat lower than those originally proposed by Expert C.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Plausible lower limit | 25th percentile | median | 75th  percentile | Plausible upper limit |
| 0% | 5% | 10% | 20% | 50% |

**2.1.3 Fitted distribution for Parameter 1**

A Beta (0.952, 2.71) distribution, scaled to the interval [0, 50%], was fitted to the consensus judgements.



*Figure 1: the distribution chosen to represent the experts’ consensus judgements for Parameter 1: the percentage of patients, aged less than 60, whose death was due to CJD, that are misdiagnosed as having died from another neurodegenerative disease, since 2005.* *The red shaded region indicates that, given this choice of distribution, a probability of about 0.99 has been assumed that the percentage misdiagnosed will be less than 40%.*

Percentiles from the fitted Beta distribution

|  |  |  |  |
| --- | --- | --- | --- |
| 1st | 5th | 95th | 99th |
| 0.1% | 0.8% | 33.0% | 40.6% |

**2.2 Parameter 2 definition:** the percentage of patients, aged 80 years and above, whose death was due to CJD, that are misdiagnosed as having died from another neurodegenerative disease, since 2005.

**2.2.1 Individual judgements**

Without conferring, the experts made the following probability judgements for Parameter 2

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Expert | Plausible lower limit | 25th percentile | median | 75th  percentile | Plausible upper limit |
| A | 5% | 30% | 50% | 60% | 70% |
| B | 10% | 25% | 50% | 75% | 90% |
| C | 20% | 50% | 80% | 90% | 100% |
| D | 0% | 20% | 50% | 60% | 75% |

**2.2.2 Group discussion and consensus judgements**

Expert C argued for higher percentage based on Figures 2 and 3 from the 25th Annual Report on CJD surveillance in the UK[[1]](#footnote-1). The argument was that mortality rates from sporadic CJD have been observed to increase over time in the higher age categories, and that this is a consequence of changes in diagnostics; it is plausible that this trend will continue, suggesting that the current percentage of misdiagnoses could be high. The remaining experts accepted a higher median and 25th percentile as consensus judgements, but thought that percentages close to 100% would be unlikely, agreeing a 75th percentile closer to the median.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Plausible lower limit | 25th percentile | median | 75th  percentile | Plausible upper limit |
| 0% | 40% | 60% | 65% | 100% |

**2.2.3 Fitted distribution for Parameter 2**

A Beta (3.36, 2.75) distribution was fitted to the consensus judgements.



*Figure 2: the distribution chosen to represent the experts’ consensus judgements for Parameter 2: the percentage of patients, aged 80 and above, whose death was due to CJD, that are misdiagnosed as having died from another neurodegenerative disease, since 2005.* *The red shaded region indicates that, given this choice of distribution, a probability of about 0.98 has been assumed that the percentage misdiagnosed will be between 14% and 92%.*

Percentiles from the fitted Beta distribution

|  |  |  |  |
| --- | --- | --- | --- |
| 1st | 5th | 95th | 99th |
| 14% | 23% | 85% | 92% |

**2.3 Parameter 3 definition:** the percentage of patients, aged 60-79 years whose death was due to CJD, that are misdiagnosed as having died from another neurodegenerative disease, since 2005.

This parameter is assumed to be the mean of Parameters 1 and 3 (the percentages for the two age groups: below 60, and 80 and above). Its implied distribution can be obtained by simulation.



*Figure 3: the distribution chosen to represent the experts’ consensus judgements for Parameter 3: the percentage of patients, aged between 60 and 79 years, whose death was due to CJD, that are misdiagnosed as having died from another neurodegenerative disease, since 2005.*

Percentiles of this distribution are estimated by simulation.

|  |  |  |  |
| --- | --- | --- | --- |
| 1st | 5th | 95th | 99th |
| 10% | 16% | 51% | 58% |

**3 Distributions related to incubation periods**

Previous analysis had used different incubation periods for different recipient genotypes. It was thought that incubation period would depend on both the genotypes of host and recipient and also the infecting prion, and that a more manageable elicitation task would be to consider a single distribution of incubation periods, for genotype unspecified.

**3.1 Distribution definition:**

The uncertain object of interest here is not a single parameter, but instead a *distribution* of incubation periods: the distribution of incubation period in years, in all patients, following infection with prion via surgery (posterior eye, brain, neuroendoscopy, and intradural spinal surgery), genotype unknown for each patient.

**3.2 Individual estimates of the uncertain distribution.**

Without conferring, each expert gave estimates of three quantiles of the uncertain distribution, together with suggested lower and upper limits.

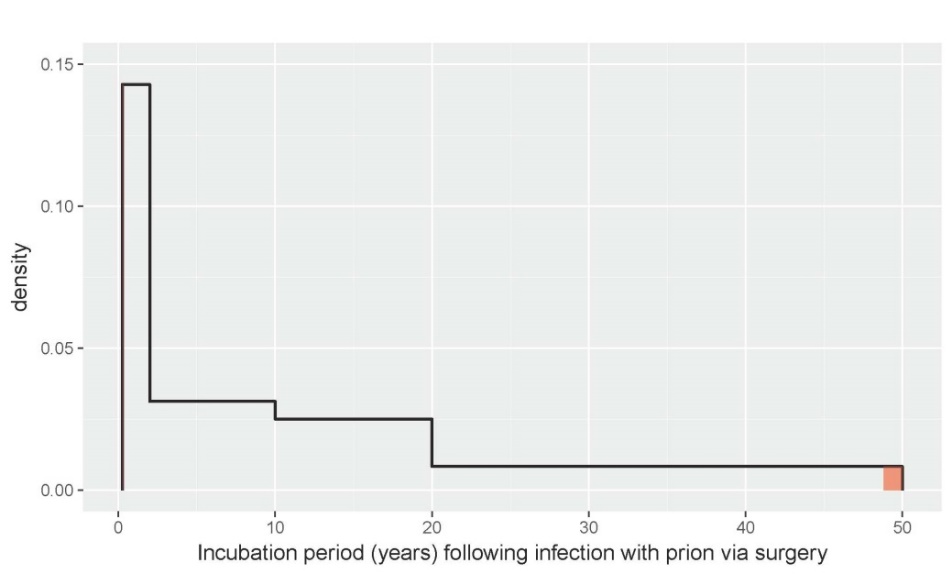
|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Expert | Plausible lower limit | 25th percentile | median | 75th  percentile | Plausible upper limit |
| A | 0.5 | 2 | 4 | 10 | 50 |
| B | 0.25 | 3 | 7.5 | 10 | 40 |
| C | 0.2 | 1 | 12 | 20 | 50 |
| D | 0.5 | 3 | 12 | 30 | 70 |

**3.3 Group discussion, and quantifying uncertainty about the distribution**

It was proposed to quantify uncertainty about the distribution of incubation periods as follows. First four intervals were specified, based on the estimates provided at the individual stage

|  |  |  |  |
| --- | --- | --- | --- |
| Interval 1 | Interval 2 | Interval 3 | Interval 4 |
| 0.25-2 years | 2-10 years | 10-20 years | 20-50 years |

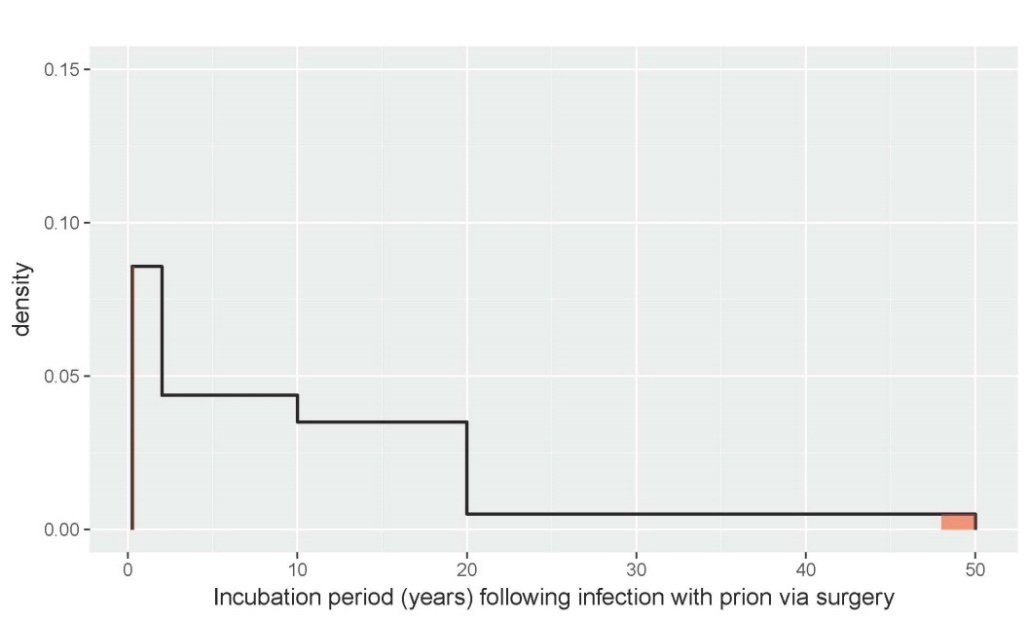
As a central estimate, it was proposed that each interval describes incubation periods for 25% of the population. Incubation periods would be assumed to be uniform in each interval, giving the following estimated distribution.



*Figure 4: an estimate of the distribution of incubation periods for all patients the distribution of incubation period in years, in all patients, following infection with prion via surgery (posterior eye, brain, neuroendoscopy, and intradural spinal surgery), genotype unknown for each patient. The red shaded region indicates that, given this choice of distribution, 98% of incubation periods will lie between 0.32 years and 48.8 years.*

To allow for uncertainty in the estimated distribution, it was proposed to allow the percentages in each interval to vary by up to 15% in intervals 1-3, and up to 10% in interval 4. For example, an alternative distribution would be

|  |  |  |  |
| --- | --- | --- | --- |
| Interval 1 | Interval 2 | Interval 3 | Interval 4 |
| 0.25-2 years | 2-10 years | 10-20 years | 20-50 years |
| 15% | 35% | 35% | 15% |



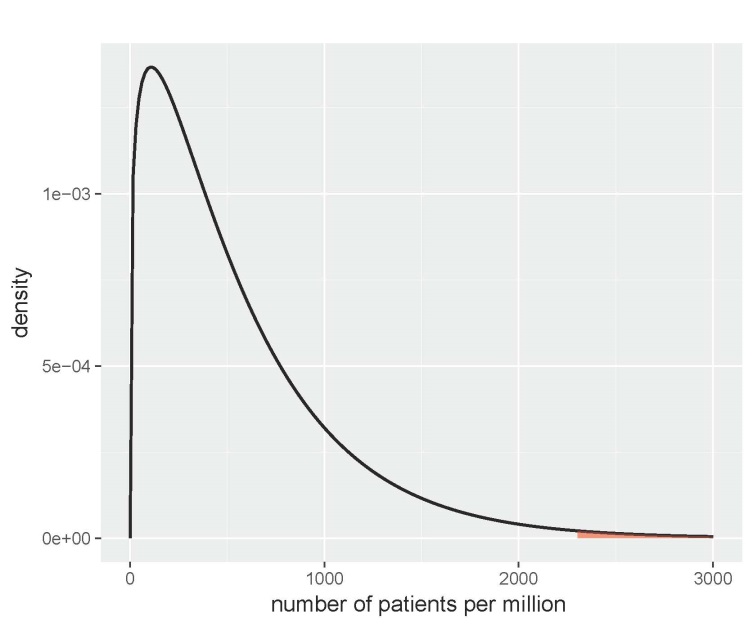
*Figure 5: alternative the distribution of incubation periods, constructed by perturbing the proportions of the population in each interval from the central estimates. The red shaded region indicates that, given this choice of distribution, 98% of incubation periods will lie between 0.37 years and 48 years.*

**4 Susceptibility of patients to CJD-prion infection**

The experts agreed that all patients would be susceptible to infection if a sufficient infectious load was received. This differed from the previous modelling undertaken where it was assumed that proportions of m-v genotype and v-v genotype at codon 129 patients were non-susceptible.

**5 The prevalence of CJD prions in central nervous system tissue**

The experts suggested that there is uncertainty in this parameter, but that using different prevalence distributions for different age bands which resulted in increased prevalence in the 16-39 year old band was not appropriate. It was commented that as sporadic CJD increases with age, but variant CJD incubation could be greatest in younger ages, using the same distribution independent of age would be appropriate. The previous distribution used for 16-39 years old for prevalence per million people was a Beta (1.24, 2225.393). This distribution is shown in Figure 6. The experts commented that this may produce pessimistic numbers as the original elicitation was for all tissue, and not just central nervous system tissue, but thought that the use of the distribution was reasonable, and this was assumed appropriate for all ages. This prevalence was assumed to apply from 2005 onwards.



*Figure 6: the distribution chosen to represent the experts’ consensus judgements for the number of patients per million with CJD-prions in central nervous system tissue. The red shaded region indicates that, given this choice of distribution, a probability of about 0.99 has been assumed that number per million will be less than 2300.*

Percentiles from the fitted Beta distribution

|  |  |  |  |
| --- | --- | --- | --- |
| 1st | 5th | 95th | 99th |
| 12 | 46 | 1547 | 2304 |

# Appendix 5: The operations considered to be at high risk

Brain operations – Patients modelled to die within 12 months

|  |  |
| --- | --- |
| A01.1 | Hemispherectomy |
| A01.2 | Total lobectomy of brain |
| A01.3 | Partial lobectomy of brain |
| A01.8 | Other specified major excision of tissue of brain |
| A01.9 | Unspecified major excision of tissue of brain |
| A02.1 | Excision of lesion of tissue of frontal lobe of brain |
| A02.2 | Excision of lesion of tissue of temporal lobe of brain |
| A02.3 | Excision of lesion of tissue of parietal lobe of brain |
| A02.4 | Excision of lesion of tissue of occipital lobe of brain |
| A02.5 | Excision of lesion of tissue of cerebellum |
| A02.6 | Excision of lesion of tissue of brain stem |
| A02.7 | Excision of transcranial dermoid cyst |
| A02.8 | Other specified excision of lesion of tissue of brain |
| A02.9 | Unspecified excision of lesion of tissue of brain |
| A04.1 | Open biopsy of lesion of tissue of frontal lobe of brain |
| A04.2 | Open biopsy of lesion of tissue of temporal lobe of brain |
| A04.3 | Open biopsy of lesion of tissue of parietal lobe of brain |
| A04.4 | Open biopsy of lesion of tissue of occipital lobe of brain |
| A04.5 | Open biopsy of lesion of tissue of cerebellum |
| A04.6 | Open biopsy of lesion of tissue of brain stem |
| A04.8 | Other specified open biopsy of lesion of tissue of brain |
| A04.9 | Unspecified open biopsy of lesion of tissue of brain |
| A08.1 | Biopsy of lesion of tissue of frontal lobe of brain NEC |
| A08.2 | Biopsy of lesion of tissue of temporal lobe of brain NEC |
| A08.3 | Biopsy of lesion of tissue of parietal lobe of brain NEC |
| A08.4 | Biopsy of lesion of tissue of occipital lobe of brain NEC |
| A08.5 | Biopsy of lesion of tissue of cerebellum NEC |
| A08.6 | Biopsy of lesion of tissue of brain stem NEC |
| A08.8 | Other specified other biopsy of lesion of tissue of brain |
| A08.9 | Unspecified other biopsy of lesion of tissue of brain |

Brain operations – Patients modelled to have a 50% chance of death within 12 months, otherwise normal life expectancy

|  |  |
| --- | --- |
| A03.1 | Stereotactic leucotomy |
| A03.2 | Stereotactic ablation of tissue of thalamus |
| A03.3 | Stereotactic ablation of tissue of globus pallidus |
| A03.8 | Other specified stereotactic ablation of tissue of brain |
| A03.9 | Unspecified stereotactic ablation of tissue of brain |
| A05.1 | Drainage of abscess of tissue of brain |
| A05.2 | Evacuation of haematoma from temporal lobe of brain |
| A05.3 | Evacuation of haematoma from cerebellum |
| A05.4 | Evacuation of intracerebral haematoma NEC |
| A05.8 | Other specified drainage of lesion of tissue of brain |
| A05.9 | Unspecified drainage of lesion of tissue of brain |
| A07.1 | Open division of tissue of brain |
| A07.2 | Removal of foreign body from tissue of brain |
| A07.3 | Exploration of tissue of brain |
| A07.4 | Excision of abscess of tissue of brain |
| A07.6 | Complete callosotomy |
| A07.7 | Partial callosotomy |
| A07.8 | Other specified other open operations on tissue of brain |
| A10.2 | Aspiration of abscess of tissue of brain |
| A10.3 | Aspiration of haematoma of tissue of brain |
| A10.4 | Aspiration of lesion of tissue of brain NEC |
| A10.5 | Puncture of tissue of brain NEC |
| A10.8 | Other specified other operations on tissue of brain |

Brain operations – Patients modelled to have normal life expectancy

|  |  |
| --- | --- |
| A06.1 | Excision of basal encephalocele |
| A06.2 | Excision of occipital encephalocele |
| A06.3 | Excision of syncipital encephalocele |
| A06.4 | Repair of post-traumatic meningoencephalocele |
| A06.8 | Other specified other excision of lesion of tissue of brain |
| A06.9 | Unspecified other excision of lesion of tissue of brain |
| A09.1 | Implantation of neurostimulator into brain |
| A09.2 | Maintenance of neurostimulator in brain |
| A09.3 | Removal of neurostimulator from brain |
| A09.4 | Operation on neurostimulator in brain NEC |
| A09.5 | Insertion of neurostimulator electrodes into the brain |
| A09.8 | Other specified neurostimulation of brain |
| A09.9 | Unspecified neurostimulation of brain |
| A11.1 | Placement of depth electrodes for electroencephalography |
| A11.2 | Placement of surface electrodes for electroencephalography |
| A11.3 | Monitoring of pressure in tissue of brain |
| A11.4 | Cortical mapping |
| A11.8 | Other specified operations on tissue of brain |
| A12.1 | Ventriculocisternostomy |
| A12.2 | Creation of ventriculovascular shunt |
| A12.3 | Creation of ventriculopleural shunt |
| A12.4 | Creation of ventriculoperitoneal shunt |
| A12.5 | Creation of subcutaneous cerebrospinal fluid reservoir |
| A12.8 | Other specified creation of connection from ventricle of brain |
| A13.1 | Maintenance of proximal catheter of cerebroventricular shunt |
| A13.2 | Maintenance of distal catheter of cerebroventricular shunt |
| A13.3 | Insertion of antisyphon device into cerebroventricular shunt |
| A13.4 | Renewal of valve of cerebroventricular shunt |
| A13.8 | Other specified attention to component of connection from ventricle of brain |
| A13.9 | Unspecified attention to component of connection from ventricle of brain |
| A14.1 | Renewal of cerebroventricular shunt |
| A14.2 | Revision of cerebroventricular shunt NEC |
| A14.3 | Removal of cerebroventricular shunt |
| A14.4 | Irrigation of cerebroventricular shunt |
| A14.5 | Attention to cerebroventricular shunt NEC |
| A14.8 | Other specified other operations on connection from ventricle of brain |
| A14.9 | Unspecified other operations on connection from ventricle of brain |
| A16.1 | Open drainage of ventricle of brain NEC |
| A16.8 | Other specified other open operations on ventricle of brain |
| A20.1 | Drainage of ventricle of brain NEC |
| A20.2 | Ventriculography of brain |
| A20.3 | Monitoring of pressure in ventricle of brain |
| A20.8 | Other specified other operations on ventricle of brain |
| A20.9 | Unspecified other operations on ventricle of brain |
| A22.1 | Drainage of subarachnoid space of brain |
| A22.2 | Puncture of cistern of brain |
| A22.3 | Isotopic cisternography |
| A22.8 | Other specified operations on subarachnoid space of brain |
| A25.1 | Intracranial transection of optic nerve (ii) |
| A25.2 | Intracranial transection of oculomotor nerve (iii) |
| A25.3 | Intracranial transection of trigeminal nerve (v) |
| A25.4 | Intracranial transection of facial nerve (vii) |
| A25.5 | Intracranial transection of acoustic nerve (viii) |
| A25.6 | Intracranial transection of glossopharyngeal nerve (ix) |
| A25.7 | Intracranial transection of vagus nerve (x) |
| A25.8 | Intracranial transection of specified cranial nerve NEC |
| A26.1 | Intracranial destruction of optic nerve (ii) |
| A26.2 | Intracranial destruction of oculomotor nerve (iii) |
| A26.3 | Intracranial destruction of trigeminal nerve (v) |
| A26.4 | Intracranial destruction of facial nerve (vii) |
| A26.6 | Intracranial destruction of glossopharyngeal nerve (ix) |
| A26.8 | Intracranial destruction of specified cranial nerve NEC |
| A26.9 | Unspecified other intracranial destruction of cranial nerve |
| A29.1 | Excision of lesion of optic nerve (ii) |
| A29.8 | Excision of lesion of specified cranial nerve NEC |
| A29.9 | Unspecified excision of lesion of cranial nerve |
| A31.3 | Intracranial stereotactic neurolysis of trigeminal nerve (v) |
| A31.5 | Intracranial stereotactic neurolysis of acoustic nerve (viii) |
| A31.8 | Intracranial stereotactic neurolysis of specified cranial nerve NEC |
| A32.1 | Decompression of optic nerve (ii) |
| A33.1 | Introduction of neurostimulator into cranial nerve |
| A33.2 | Maintenance of neurostimulator in cranial nerve |
| A33.3 | Removal of neurostimulator from cranial nerve |
| A33.4 | Insertion of neurostimulator electrodes into the cranial nerve |
| A33.8 | Other specified neurostimulation of cranial nerve |
| A33.9 | Unspecified neurostimulation of cranial nerve |
| A34.1 | Exploration of optic nerve (ii) |
| A34.3 | Exploration of trigeminal nerve (v) |
| A34.4 | Exploration of facial nerve (vii) |
| A34.5 | Exploration of acoustic nerve (viii) |
| A34.7 | Exploration of vagus nerve (x) |
| A34.8 | Exploration of specified cranial nerve NEC |
| A34.9 | Unspecified exploration of cranial nerve |
| A36.8 | Other specified other operations on cranial nerve |
| A38.1 | Extirpation of lesion of meninges of cortex of brain |
| A38.2 | Extirpation of lesion of meninges of sphenoidal ridge of cranium |
| A38.3 | Extirpation of lesion of meninges of subfrontal region of brain |
| A38.4 | Extirpation of lesion of meninges of parasagittal region of brain |
| A38.5 | Extirpation of lesion of falx cerebri |
| A38.6 | Extirpation of lesion of tentorium cerebelli |
| A38.8 | Other specified extirpation of lesion of meninges of brain |
| A38.9 | Unspecified extirpation of lesion of meninges of brain |
| A39.1 | Repair of meningoencephalocele |
| A39.2 | Repair of dura of anterior fossa of cranium |
| A39.3 | Repair of dura of middle fossa of cranium |
| A39.4 | Repair of dura of posterior fossa of cranium |
| A39.5 | Repair of dura of vault of cranium |
| A39.8 | Other specified repair of dura |
| A39.9 | Unspecified repair of dura |
| A41.1 | Evacuation of subdural haematoma |
| A41.2 | Drainage of abscess of subdural space |
| A41.8 | Other specified drainage of subdural space |
| A41.9 | Unspecified drainage of subdural space |
| A42.1 | Creation of anastomosis of dura |
| A42.2 | Biopsy of lesion of meninges of brain |
| A42.8 | Other specified other operations on meninges of brain |
| A43.1 | Extirpation of lesion of meninges of skull base |
| A43.2 | Extirpation of lesion of meninges of skull clivus |
| A43.8 | Other specified other extirpation of lesion of meninges of brain |
| A43.9 | Unspecified other extirpation of lesion of meninges of brain |
| A44.1 | Chordectomy of spinal cord |
| A44.2 | Extirpation of lesion of spinal cord NEC |
| A44.3 | Excision of lesion of intradural intramedullary spinal cord |
| A44.4 | Excision of lesion of extradural spinal cord |
| A44.5 | Excision of lesion of intradural extramedullary spinal cord |
| A44.8 | Other specified partial extirpation of spinal cord |
| A44.9 | Unspecified partial extirpation of spinal cord |
| A45.1 | Stereotactic chordotomy of spinal cord |
| A45.2 | Open chordotomy of spinal cord NEC |
| A45.3 | Myelotomy of spinal cord |
| A45.4 | Open biopsy of lesion of spinal cord |
| A45.5 | Removal of foreign body from spinal cord |
| A45.6 | Open aspiration of lesion of spinal cord |
| A45.8 | Other specified other open operations on spinal cord |
| A47.1 | Needle destruction of substantia gelatinosa of cervical spinal cord |
| A47.2 | Radiofrequency controlled thermal destruction of spinothalamic tract |
| A47.3 | Percutaneous chordotomy of spinal cord |
| A47.8 | Other specified other destruction of spinal cord |
| A48.1 | Biopsy of lesion of spinal cord NEC |
| A48.2 | Aspiration of lesion of spinal cord |
| A48.3 | Insertion of neurostimulator adjacent to spinal cord |
| A48.4 | Attention to neurostimulator adjacent to spinal cord NEC |
| A48.6 | Removal of neurostimulator adjacent to spinal cord |
| A48.7 | Insertion of neurostimulator electrodes into the spinal cord |
| A48.8 | Other specified other operations on spinal cord |
| A49.1 | Freeing of spinal tether NEC |
| A49.2 | Closure of spinal myelomeningocele |
| A49.3 | Closure of spinal meningocele |
| A49.4 | Complex freeing of spinal tether |
| A49.8 | Other specified repair of spina bifida |
| A49.9 | Unspecified repair of spina bifida |
| A51.1 | Extirpation of lesion of meninges of spinal cord |
| A51.2 | Freeing of adhesions of meninges of spinal cord |
| A51.3 | Biopsy of lesion of meninges of spinal cord |
| A51.8 | Other specified other operations on meninges of spinal cord |
| A51.9 | Unspecified other operations on meninges of spinal cord |
| A53.1 | Cerebrospinal syringostomy |
| A53.3 | Creation of syringoperitoneal shunt |
| A57.1 | Extirpation of lesion of spinal nerve root |
| A57.6 | Reimplantation of spinal nerves into spinal cord |
| A57.8 | Other specified operations on spinal nerve root |
| A57.9 | Unspecified operations on spinal nerve root |
| B01.1 | Transethmoidal hypophysectomy |
| B01.2 | Trans-sphenoidal hypophysectomy |
| B01.4 | Transcranial hypophysectomy |
| B01.8 | Other specified excision of pituitary gland |
| B02.2 | Implantation of radioactive substance into pituitary gland |
| B04.1 | Excision of lesion of pituitary gland |
| B04.2 | Biopsy of lesion of pituitary gland |
| B04.3 | Decompression of pituitary gland |
| B04.4 | Exploration of pituitary gland |
| B04.5 | Operations on pituitary stalk |
| B04.8 | Other specified other operations on pituitary gland |
| B06.1 | Excision of pineal gland |
| B06.8 | Other specified operations on pineal gland |
| B06.9 | Unspecified operations on pineal gland |
| L33.1 | Excision of aneurysm of cerebral artery |
| L33.2 | Clipping of aneurysm of cerebral artery |
| L33.3 | Ligation of aneurysm of cerebral artery NEC |
| L33.4 | Obliteration of aneurysm of cerebral artery NEC |
| L33.8 | Other specified operations on aneurysm of cerebral artery |
| L34.1 | Reconstruction of cerebral artery |
| L34.2 | Anastomosis of cerebral artery |
| L34.3 | Open embolectomy of cerebral artery |
| L34.4 | Open embolisation of cerebral artery |
| L34.8 | Other specified other open operations on cerebral artery |

Neuroendoscopy operations

|  |  |
| --- | --- |
| A17.1 | Endoscopic extirpation of lesion of ventricle of brain |
| A17.2 | Endoscopic third ventriculostomy |
| A17.8 | Other specified therapeutic endoscopic operations on ventricle of brain |
| A17.9 | Unspecified therapeutic endoscopic operations on ventricle of brain |
| A18.1 | Diagnostic endoscopic examination of ventricle of brain and biopsy of lesion of ventricle of brain |
| A18.9 | Unspecified diagnostic endoscopic examination of ventricle of brain |

Posterior eye operations

|  |  |
| --- | --- |
| C85.1 | Retinopexy using cryotherapy |
| C84.5 | Drainage of subretinal fluid through retina |
| C84.6 | Retinotomy NEC |
| C89.2 | Injection of steroid into posterior segment of eye |
| C85.5 | Retinopexy NEC |
| C84.1 | Epiretinal dissection |
| C85.2 | Retinopexy using diathermy |
| C89.3 | Injection of therapeutic substance into posterior segment of eye NEC |
| C84.8 | Other specified other operations on retina |
| C82.8 | Other specified destruction of lesion of retina |
| C89.1 | Insertion of sustained release device into posterior segment of eye |
| C85.8 | Other specified fixation of retina |
| C01.1 | Exenteration of orbit |
| C84.3 | Biopsy of lesion of retina |
| C84.2 | Excision of lesion of retina NEC |
| C84.9 | Unspecified other operations on retina |
| C01.2 | Enucleation of eye |
| C01.3 | Evisceration of eye |
| C82.9 | Unspecified destruction of lesion of retina |
| C89.8 | Other specified operations on posterior segment of eye |
| C83.3 | Limited macular translocation |
| C85.4 | Retinopexy using tissue adhesive |
| C85.9 | Unspecified fixation of retina |
| C01.8 | Other specified excision of eye |
| C01.9 | Unspecified excision of eye |
| C85.3 | Retinopexy using mechanical tacks |
| C89.9 | Unspecified operations on posterior segment of eye |
| C88.9 | Unspecified destruction of subretinal lesion |

# Appendix 6: The assumed age profile of patients receiving each operation

Figure 20: The assumed age profile of patients undergoing brain surgery who are assumed to have normal life expectancy

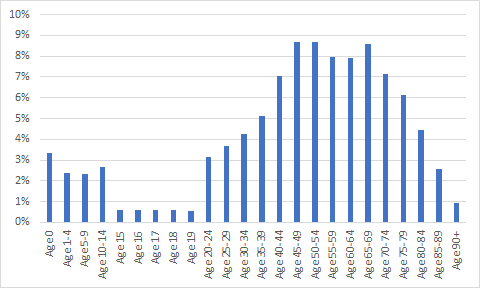


Figure 21: The assumed age profile of patients undergoing brain surgery assumed to die within 12 months

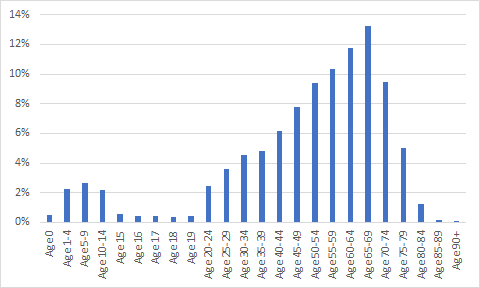


Figure 22: The assumed age profile of patients undergoing brain surgery who are assumed to have a 50% chance of death within 12 months otherwise who are assumed to have normal life expectancy

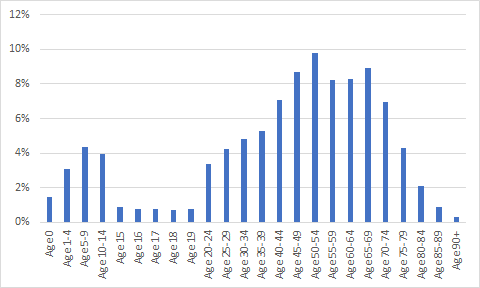


Figure 23: The assumed age profile of patients undergoing neuroendoscopy

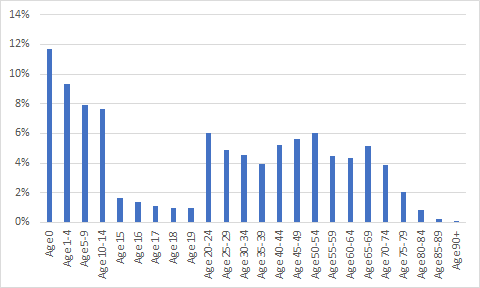
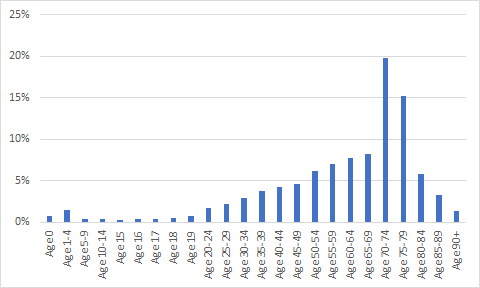


Figure 24: The assumed age profile of patients undergoing posterior eye operations



# Appendix 7: The calibration methodology

**Notation**

We define the following

* : the simulation model inputs. The true values of these inputs are uncertain; following various expert elicitation sessions, we have constructed a prior distribution for .
* - the number of transmissions of CJD via surgery that result in clinical symptoms (CJDcs) in age category , over the period 2005-2018. The age categories are : 59 years and below; : 60-79 years; : 80 years and above. We write .
* - the number of transmissions of CJDcs, in age category , over the period 2005-2018, that resulted in deaths *recorded* as being due to CJD. Note that for each , we have .
* : the data available for calibrating the simulation model. We know that over the period 2005-2018, there were 15 recorded deaths from CJD, where the individuals were known to have had surgery. Hence, any number between 0-15 of these individuals could have acquired CJD from surgery. The age categories for these 15 recorded deaths are unavailable to us, so the calibration data is the observation of the event that
* : the percentage of patients, in age category , whose death was due to CJD, that are misdiagnosed as having died from another neurodegenerative disease, since 2005. These percentages are unknown, and we have elicited probability distributions for them. Note that we treat these as elicited ‘posterior distributions’ .

We suppose that

We collect the parameters into vector and write

* the *maximum* number of transmissions of CJDcs, in age category , over the period 2005-2018, that resulted in deaths *recorded* as being due to CJD. We have

and that

for . Defining

we make the assumption that

i.e. that each of the 15 potential cases was equally likely to be in any age category. This is likely to give too much weight to the oldest age category, but the assumption is conservative in the sense of minimising the risk of underestimating numbers of transmissions of CJDcs: patients in the oldest age category are judged the most likely to be misdiagnosed as having died from another neurodegenerative disease. Allocating a higher number of the 15 cases into the oldest age category will ‘permit’ higher numbers of transmissions of CJDcs, as more can be undetected.

* : a vector of scenario values for each surgical centre. Each is coded as 1:, 2:, 3:. The definitions of surgical centres are provided in Section 3.5.1, with S4-S6 being denoted S1 to S3 when it is assumed that the P96 group are not infectious from birth.
* : the number of discounted QALYs that would be lost, as a result of transmission of CJDcs, due to surgery that took place between the period 2019-2023.

**Estimating the number of QALYs lost due to a stCJD caused by an operation between 2019 and 2023**

The aim is to draw a sample of values from the probability distribution of , from which we can provide an estimate of the expected value . This distribution can be expressed as

Hence, we can obtain a sample by obtaining a sample from , and then sampling from . In essence, we are

1. calibrating the simulation model by updating the model inputs from to : we update what we know about the model inputs in light of the calibration data ;
2. running the simulation model forward to predict , at input values sampled from : input values identified to be consistent with the calibration data .

**Sampling from**

The method we use to sample from is known as Approximate Bayesian Computation (ABC). This is a standard technique when we have a simulation model that can generate a random value of given an input , but no *formula* can be obtained for the likelihood function . The basic ABC algorithm is as follows.

1. Generate one random value from the elicited prior
2. Given the model input , run the model, and observe whether the event has occured within the model simulation.
3. If the event has occurred within the model simulation, accept as a valid draw from . Otherwise, reject, and return to step 1. Repeat until a candidate value is accepted.

The process is repeated as many times as required to produce a sample from . For each accepted value, the model can be run forward to produce the desired sample . We refer to this as the “simple rejection ABC algorithm”.

**Implementing the simple rejection ABC algorithm**

The output quantities produced by the simulation model are . To determine from these whether the event has occurred, we additionally sample and , so that we are in effect sampling from the joint distribution . We write

and we assume

We have the multinomial distribution for , and the elicited distribution for , from which we can simulate values easily.

Note that

since given , we already know : the total of .

The ABC algorithm is then, in effect, used to sample from , where the ‘prior’ distribution is , and we assume independence between and :

1. Sample from .
2. Sample from .
3. Run the simulation model to generate outputs
4. Given the outputs , sample , where
5. Observe whether, within the simulation model, the event

for has occurred. If it has, we accept as a sample from . Otherwise, we reject and return to step 1.

**Estimation of**

Applying the ABC algorithm would give a sample . Running the simulation model forward at these inputs only, we obtain an independent sample , from the distribution of , from which we can estimate via

and an approximate 95% confidence interval for can be calculated as , with

We actually use a slightly different estimator for which has a lower variance, but we retain the confidence interval given above. Note also that there is a computational bottleneck in step 3 of this algorithm: running the model to observe whether has occurred can be computationally expensive.

**Speeding up the computation**

We can speed up the computation by noting that, in some cases, it will not be necessary to simulate outcomes for all 27 surgical centres. Based on the number of simulated transmissions of CJDcs for a single surgical centre, an upper bound can be placed on the probability that the parameter value will ultimately be accepted. For example, if there were simulated transmissions of CJDcs in the age under 60 category, no more than 50 of these could result in undetected CJD cases, and the probability of this occuring would be of the order of ; the final probability of acceptance could be no more than this, regardless of what other events are simulated. (Under such a scenario, almost certainly, there would be transmissions of CJDcs in the other age groups, which would reduce the probability of acceptance by further orders of magnitude.)

Based on an understanding of the model’s behaviour, and some preliminary analysis of the model outputs we can determine parameter combinations that are guaranteed to be rejected. Specifically, we consider the term

where is the mean infectious titre (in log terms) log reduction in infectivity associated with the first autoclaving cycle log reduction associated with detergent on the first cycle; is the residual mass on an instrument the proportion of residual mass transferred to the patient); is the proportion of asymptomatic individuals with CJD prions in their tissue.

2000 parameter sets were drawn from the appropriate distributions, was calculated in each case, and twelve random number streams (corresponding to twelve surgical centres) were simulated for each of the following scenarios: S1, S2 and S3. We identified that for , the final probability of acceptance would be negligible (too many transmissions of CJDcs would be simulated), and so the corresponding parameter set could be rejected, without running the full simulation to produce .

For , it would still be possible for the candidate to be rejected. In other cases, we can be certain that a candidate value will be rejected, based on a ‘partial’ simulation run: we do not have to simulate the full calibration output . We used the following approach.

1. Generate a candidate value , for which .
2. Under scenario S3, first simulate the number of transmissions of CJDcs for 6 random number streams (6 surgical centres)
3. If the total number of transmissions of CJDcs for the first 6 random number streams for the age category below 60 years exceeds 36, reject and return to step 1.
4. Continue simulating random number streams in batches: reject if in streams 7 to 13 the rejection threshold was increased to 40; to 45 for random number streams 14 to 17; to 55 for random number streams 18 to 23; and 66 for random number streams 24 to 27.

**A weighted ABC scheme**

Instead of using the estimator , we can instead calculate a weight : the *probability* that the model will simulate the event to have occurred. The estimate for will then be of the form

with

This approach instead generates (weighted) samples directly from the marginal distribution , rather than joint samples from . Each weight is estimated using the following Monte Carlo procedure. For each candidate value , we the model simulates numbers of transmissions of CJDcs in each age band, under *all* scenarios for each surgical centre. The transmissions of CJDcs corresponding to the scenarios in can then be selected.

For :

1. Randomly sample from its prior distribution, and denote this value by . Given the model simulation run for input value and scenario set , extract the number of transmissions of CJDcs in each age band. Denote these by for .
2. Randomly sample from its multinomial distribution. Denote the sampled values by
3. Randomly sample from the three elicited prior distributions. Denote these values by
4. Given the sampled values in step 2, we now have
5. Compute, from the corresponding binomial distributions in step 3,
6. The weight is estimated as

**Implementation**

We started with a sample of 2000 parameter values. Applying the screening based on the calculated values, we obtained a set that were not rejected. The weighted ABC algorithm was used to estimate , and the (conservative) confidence interval using the simple rejection ABC algorithm was calculated for this estimate. Applying the simple rejection ABC algorithm reduces the sample size from 509 candidate parameter values to 119 when it was assumed that the P96 group could be infectious from birth and 134 when it was assumed that the P96 group were not infectious from birth; the estimator would be based on 119 and 134 model runs respectively.

1. National CJD Research & Surveillance Unit (2016), available at https://www.cjd.ed.ac.uk/sites/default/files/report25.pdf [↑](#footnote-ref-1)