Systematic review of Creutzfeldt-Jakob disease (CJD) risk via surgical interventional procedures and economic evaluation of management policies to reduce this risk

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	16th March 2018

Word Count 42,193

Abstract

Background

Creutzfeldt-Jakob disease (CJD) is a fatal neurological disease caused by abnormal infectious proteins called prions. Prions on surgical instruments cannot be completely deactivated and patients subsequently operated on may become infected resulting in surgically transmitted CJD (stCJD).

Objective

To update literature reviews, consultation with experts and economic modelling published in 2006, and to provide the cost-effectiveness of strategies to reduce the risk of stCJD.

Methods

Eight systematic reviews were undertaken for clinical parameters. One review of cost-effectiveness was undertaken. Electronic databases including MEDLINE and EMBASE were searched from 2005 to 2017. Expert elicitation sessions were undertaken. An advisory committee, convened by the National Institute for Health and Care Excellence (NICE) to produce guidance, provided an additional source of information.

A mathematical model was updated focussing on brain and posterior eye surgery and neuroendoscopy. The model simulated both patients and instrument sets. Assuming potentially 15 stCJD cases between 2005 and 2018 Approximate Bayesian Computation was used to obtain samples from the posterior distribution of the model parameters to generate results. Heuristics were used to improve computational efficiency. The modelling conformed to the NICE reference case. Strategies evaluated included: neither keeping instruments moist nor prohibiting set migration; ensuring that instruments were kept moist; prohibiting instrument migration between sets; and employing single-use instruments. Threshold analyses were undertaken to establish prices at which single-use sets or completely effective decontamination solutions would be cost-effective.

Results

One hundred and sixty-nine papers were identified for the clinical review. The evidence from published literature was not deemed sufficiently strong to take precedence over the distributions obtained from expert elicitation. Forty-eight papers were identified in the review of cost-effectiveness. The previous modelling structure was revised to add the possibility of misclassifying stCJD as another neurodegenerative disease, and assuming that all patients were susceptible to infection.

Keeping instruments moist was estimated to reduce the risk of stCJD cases and associated costs. Based on probabilistic sensitivity analyses, keeping instruments moist was estimated to produce on average 2.36 (range 0-47) stCJDs cases (across England) caused by infection between 2019 and 2023.

Prohibiting set migration or employing single-use instruments reduced the estimated risk of stCJD cases further but at considerable cost. The estimated costs per quality-adjusted life-year gained of these strategies in addition to keeping instruments moist were in excess of £1 million. It was estimated that single-use instrument sets (currently £350 - £500) or completely effective cleaning solutions would need to cost approximately £12 per patient to be cost-effective using a £30,000 per quality-adjusted life-year gained value.

Limitations

As no direct published evidence to implicate surgery as a cause of CJD has been found since 2005, the estimations of potential cases from elicitation are still speculative. A particular source of uncertainty was in the number of potential stCJD cases that may have occurred between 2005 and 2018.

Conclusions

Keeping instruments moist is estimated reduce the risk of stCJD cases and associated costs. Further surgical management strategies can reduce the risks of stCJD but have considerable associated costs.

Keywords

Creutzfeldt-Jakob Disease; iatrogenic transmission; surgical instruments; decontamination; systematic review; economic model.

Table of Contents

TABLES

FIGURES

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
CJDAS	Creutzfeldt-Jakob disease Advisory Sub-Committee
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
H_2O_2	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
PrP^{res}	protease-resistant prion protein
PrP^{Sc}	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) and to explore the value for money of strategies to reduce the chance of any future stCJD cases. Current recommendations include keeping sets of surgical instruments together for 'high-risk' operations and using separate instruments for people born after 1996. The project involved reviewing published papers, speaking with experts, and building a computer model.

The literature reviews found that CJD occurs in around one to two per million people and that no definite cases of stCJD have been observed since the 1970s. The reviews also looked for information on the possibility of patients being infected with CJD after having surgery on 'high-risk' tissues, such as the brain and the back of the eye. They found that there was a great deal of uncertainty regarding who might have CJD, but not yet have symptoms, as well as the risk of transmission and the ability of strategies to reduce this risk.

The computer model aimed to estimate value for money of different strategies to reduce the risks of stCJD. However, the reviews found that some of the numbers needed for the model were not known, so experts were asked to estimate this information instead along with the range of possible values. This information included the effectiveness of different cleaning practices and the chances of infected tissue being transmitted between patients undergoing 'high risk' surgery.

The model found that keeping surgical instruments moist prior to cleaning was likely to save money and reduce the chance of future stCJD cases. However, additional measures, such as only using sets of single-use instruments, ensuring that instruments were kept together in their sets, 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. Surgical instruments can become contaminated with prions when a person who has CJD, but does not exhibit clinical symptoms, undergoes surgery on 'high-risk' tissues. Such surgery is: 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. These prions are unlikely to be completely deactivated by conventional hospital cleansing and sterilisation techniques, therefore, subsequent patients may be infected iatrogenically with CJD by surgical instruments, resulting in surgically transmitted CJD (stCJD). Previous work involving authors of this report had assessed the cost-effectiveness of sets 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 (NICE) in establishing Interventional Procedures Guideline 196 (IPG196). IPG196 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 be either single-use or to remain with the set to which they were introduced. An age split was also recommended with separate instruments used for people born before 1997 (and at risk of variant CJD [vCJD] due to dietary exposure to bovine spongiform encephalopathy (BSE)) and those born after 1996 (who were believed at the time of writing IPG196 to be at zero risk of dietary exposure to BSE).

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 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 to identify cost and utility data and in order that methods used in previous potentially-relevant papers could be incorporated. Titles and abstracts were examined by one reviewer, and 10% were checked by another reviewer. Where appropriate, full papers were reviewed for pertinent information.

Elicitation methods

In order to provide plausible distributions on key parameters where there were no direct published data, elicitation was undertaken. This process used four experts and asked the group to answer eight questions relating to the decision problem. The elicitation was conducted using the Sheffield Elicitation Framework (SHELF). A face-to-face meeting between the experts and the facilitator was convened. For each uncertainty quantity, the experts were asked to independently make their probability judgements, without conferring. These individual judgements were then presented to all the experts. Following discussion between the experts and facilitator, a single set of probability judgements was proposed, from which a probability distribution could be constructed. The probability distribution was presented to the experts at the meeting for comment and, if necessary, revision. Following the meeting, a report with all the elicited distributions was sent to the experts, with the experts given a further opportunity to suggest modifications.

Evaluation of cost-effectiveness

The mathematical model used previously to assess the cost-effectiveness of strategies to reduce stCJD was updated in this report. This model simulated a surgical centre assuming that there were 27 such centres in England. All assumptions were agreed with a NICE committee convened to provide national guidance, and conformed to the NICE reference case, using an NHS and personal social services perspective. Key changes between the earlier modelling work and this work include: re-eliciting key parameters; assuming that all patients, irrespective of genotype, were susceptible to stCJD infection; taking into account the possibility that patients with stCJD could be misdiagnosed with an alternative neurodegenerative disease; and setting a calibration target of the number of possible stCJD cases observed between 2005 and 2018. To reduce the impact of sampling error, 27 random number streams were used for each Probabilistic Sensitivity Analysis (PSA) configuration. Calibrating the model was complex and required the use of heuristics to initially rule out parameter configurations that were incompatible with observed data, and then estimating likelihoods for the remaining parameter configurations. These were used to calculate the cost-effectiveness of each strategy considering infections estimated to occur between 2019 and 2023.

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

1) Do nothing, assuming that the current situation is maintained with respect to surgical centres' adherence to IPG196

2) Full adherence to IPG196, and guidance on keeping instruments moist for those units where this is not followed, with the exception of single-use neuroendoscopes.

3) Full adherence to guidance on keeping instruments moist for those units where this is not followed.

4) Removal of the requirements to have separate instrument sets for patients born after 1996.

5) Modelling interventions which prohibit the possibility of stCJD. These are likely to take the form of the introduction of sets of single-use instruments or a completely effective decontamination product.

Threshold analyses were undertaken to see at what price per operation sets of single-use instruments, or a completely effective cleaning solution, would need to be to reach cost per QALY gained values of £30,000 (a typical threshold for cost-effectiveness used by NICE) and £300,000 (the maximum value used by NICE for highly-specialised technologies). Further threshold analyses were undertaken to look at the maximum costs associated with following IPG196 to be at, or below, thresholds of £30,000 and £300,000 per QALY gained. 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.

Based on advice provided by the NICE committee, modelling of decontamination products was not conducted other than that contained in strategy five. The reasons for this include: the heterogeneity of the studies of decontamination products for CJD prions across several domains, which precluded accurate estimates of effectiveness; problems of commercial availability; and additional steps potentially required in the decontamination process.

Results

Literature searches for the clinical reviews yielded 8549 citations from which 169 papers were relevant to the eight review questions. The incidence of any type of CJD case is reported to be between 1 to 2 per million worldwide, but the 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 there have been no stCJD cases since the 1970s and that the risk of iatrogenic CJD is presently very low, with no cases reported between 2005 and 2017. However, there remains a possibility that undetected cases have been mistaken for alternative neurodegenerative diseases. 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. Some agents appear to be

completely effective in deactivating certain prions, but there are major issues with the agents and the evidence base, though the reduction of residual mass to ≤5µg residual protein per instrument and keeping instruments in moist conditions prior to autoclaving and sterilisation enhances the efficacy of decontamination strategies. A paucity of direct evidence exists on whether surgical instruments for high-risk procedures stay in their original sets, and on the risks and benefits of reusable versus single-use instruments. Evidence on the risk of future surgery for patients undergoing high-risk procedures is limited.

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 reduce the estimated number of stCJD cases. However, there was still a risk of CJD transmission. Based on probabilistic sensitivity analyses, keeping instruments moist was estimated to produce on average 2.36 stCJDs cases infected between 2019 and 2023, with a maximum value of 47 stCJD cases across the 27 assumed surgical centres combined. From a position of keeping instruments moist, the cost per quality-adjusted life year (QALY) of introducing single-use instruments was in excess of £1.0 million in all scenarios. From a position of implementing IPG196 and keeping instruments moist, the cost per QALY of introducing 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 with a cost-effectiveness threshold of £300,000 per QALY a single-use set (or completely effective detergent) would need to be £50 or less per operation 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 implementing 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 indicated that there would not be a large change in the numbers of QALYs lost due to stCJD (below 0.20) if guidance that patients born after 1996 should have different instrument sets was removed.

Discussion

Direct evidence to answer 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 and animal data. 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' studies raise the possibility of either a low background prevalence of abnormal prion proteins or an extended period of BSE-related infection. The possibility of under-diagnosis of vCJD also exists. 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 highly heterogeneous, with limited external validity to the clinical setting. As published data on instrument set-keeping and single-use instruments were not identified, 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 was limited and lacked 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 committee and amended accordingly: it is thus believed that key facets of the decision problem have been incorporated although it is possible that some relevant aspects were omitted. 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 gained. 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.

It is possible that a completely effective cleaning solution may be cost-effective. Further research would be required to prove the efficacy and the commercial viability of such agents.

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 identified indicates that there have been no observed cases of stCJD since the 1970s. Evidence implicating surgery as a risk factor for CJD is restricted to case-control designs, and the evidence on decontamination agents and processes has limited applicability. 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 answer the review questions was limited.

The modelling undertaken indicates that keeping surgical instruments moist is a dominant strategy. 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.

The modelling indicates that it is still possible that there are a number of stCJD cases that could occur despite keeping instruments moist. In the event of multiple stCJD cases being identified, performing an urgent update of this review, with an amended calibration target is likely to be informative.

This study is registered as PROSPERO CRD42017071807.

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 appearing.

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 (PrP^{Sc}). 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 techniques[4] 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 instruments[11, 12] The outputs from the model and a separate risk assessment conducted by the Department of Health Economics, Statistics and Operational Research (ESOR) Division[13] 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 IPG196[11] 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 techniques for instruments infected 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 address these research questions. These reviews adhered to best practice systematic review methodology according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2009[18] standards.

2.1.1 *Eligibility criteria*

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

Table **1**.

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 techniques for instruments infected 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 involving 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:

i.   Incidence, prevalence and incubation
ii.   Risk via surgery, infectivity and decontamination
iii. Set-keeping of instruments
iv.   Complication rates of single-use instruments
v.   The risk of future surgery in patients who have had high-risk procedures

i.   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) were 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]

ii.   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) were combined with 'CJD' population terms in humans or non-human mammals (18-25).

iii.   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) were combined with 'high-risk surgical procedures' (42-56). A list of high-risk surgical procedures were taken from Appendix C of NICE IPG196.[14]

iv.   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 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), were combined with 'high-risk surgical procedures' (65-79) or 'complications' (81-84).

v.   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' were combined (88-90) with 'high-risk surgical procedures' (92-106). As the review question was re-conceptualised to be more sensitive to potentially relevant studies than the previous review undertaken in 2006, 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

Formal quality assessment using standard checklists such as Cochrane Risk of Bias tool was considered for these systematic reviews. 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. There are a range of different quality assessment tools available depending on the study type included, and quality assessment is not only amenable to a review of RCTs. However, 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. Furthermore, 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. As these included studies were mainly observational in nature, the data of interest were less vulnerable to author conflicts of interest or systematic bias. Assessment of study heterogeneity is most important when performing formal synthesis to estimate treatment effects, which is not the objective of this review. Indeed, limitations to review 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 was 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 to be explored using meta-regression where comparable data were available. However, 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 were 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 was that the evidence generated from the reviews was less amenable to replication. However, the purpose the clinical reviews was 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 (see Appendix 3 for the table of excluded studies). A PRISMA flow diagram illustrating the process of identifying citations through to final study selection for each review question is shown in Figure 1.
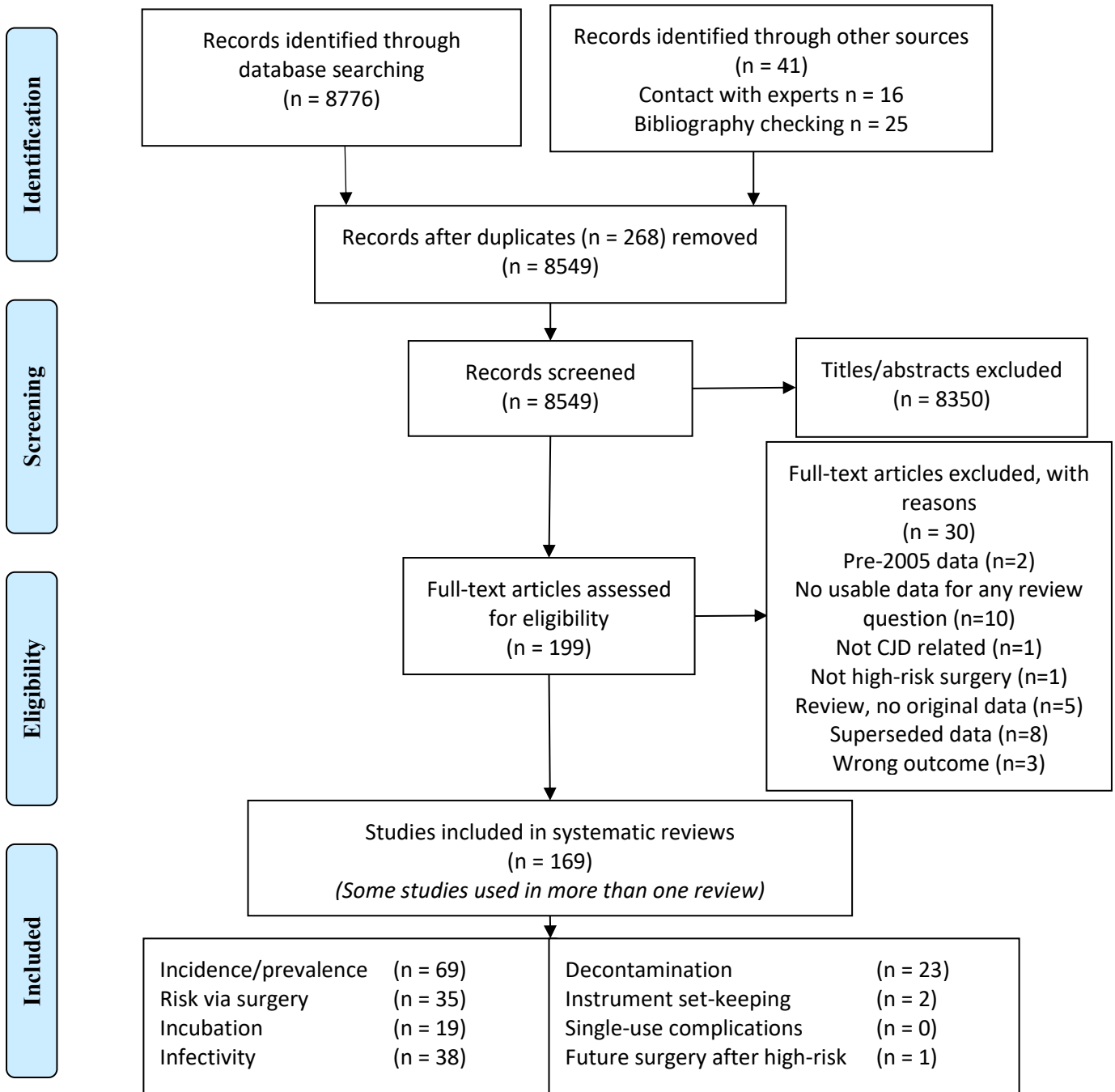
Figure 1: **PRISMA flow diagram of studies included in systematic reviews**

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:

a)   the incidence of CJD (sporadic, genetic, variant and iatrogenic) and

b)   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	EuroCJD[19]
Australia	1993-2016	1.20	Sporadic	EuroCJD[19]
Belgium	1997-2017	1.19	Sporadic	EuroCJD[19]
Canada	1994-2017	1.03	Sporadic	EuroCJD[19]
Czech Republic	2000-2017	1.16	Sporadic	EuroCJD[19]
Denmark	1993-2017	1.45	Sporadic	EuroCJD[19]
Estonia	2004-2017	0.32	Sporadic	EuroCJD[19]
France	1993-2017	1.53	Sporadic	EuroCJD[19]
Germany	1993-2017	1.36	Sporadic	EuroCJD[19]
Hungary	1997-2017	1.07	Sporadic	EuroCJD[19]
Italy	1993-2017	1.44	Sporadic	EuroCJD[19]
Netherlands	1993-2017	1.21	Sporadic	EuroCJD[19]
Norway	1995-2017	0.96	Sporadic	EuroCJD[19]
Slovakia	1993-2017	0.85	Sporadic	EuroCJD[19]
Slovenia	1993-2017	1.38	Sporadic	EuroCJD[19]
Spain	1993-2017	1.30	Sporadic	EuroCJD[19]
UK	1993-2017	1.19	Sporadic	NCJDRSU 2016[1]
USA	2016	1.22	Excludes vCJD	US Government[21]
Japan	1999-2015	1.3	All types	Yamada *et al.* 2016[22]
Australia	1993-2014	1.2	All types	Klug *et al.* 2016[23]
Finland	1997-2013	1.45	Sporadic	EuroCJD[19]
Cyprus	1995-2013	0.70	Sporadic	EuroCJD[19]
Germany	1993-2013	1.33	Excludes vCJD	EuroCJD[19]
Holland	1993-2013	1.21	Excludes vCJD	EuroCJD[19]
Hungary	1997-2013	1.65	Excludes vCJD	EuroCJD[19]
Sweden	1997-2013	1.44	Excludes vCJD	EuroCJD[19]
Switzerland	1993-2013	1.72	Sporadic	EuroCJD[19]
Argentina	2008	0.85	All types	Begue *et al.* 2011[24]
Greece	1997-2008	0.62	Sporadic	EuroCJD[19]
Taiwan	1998-2007	0.55	Sporadic	Lu *et al.* 2010[25]

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 out of a group of 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.
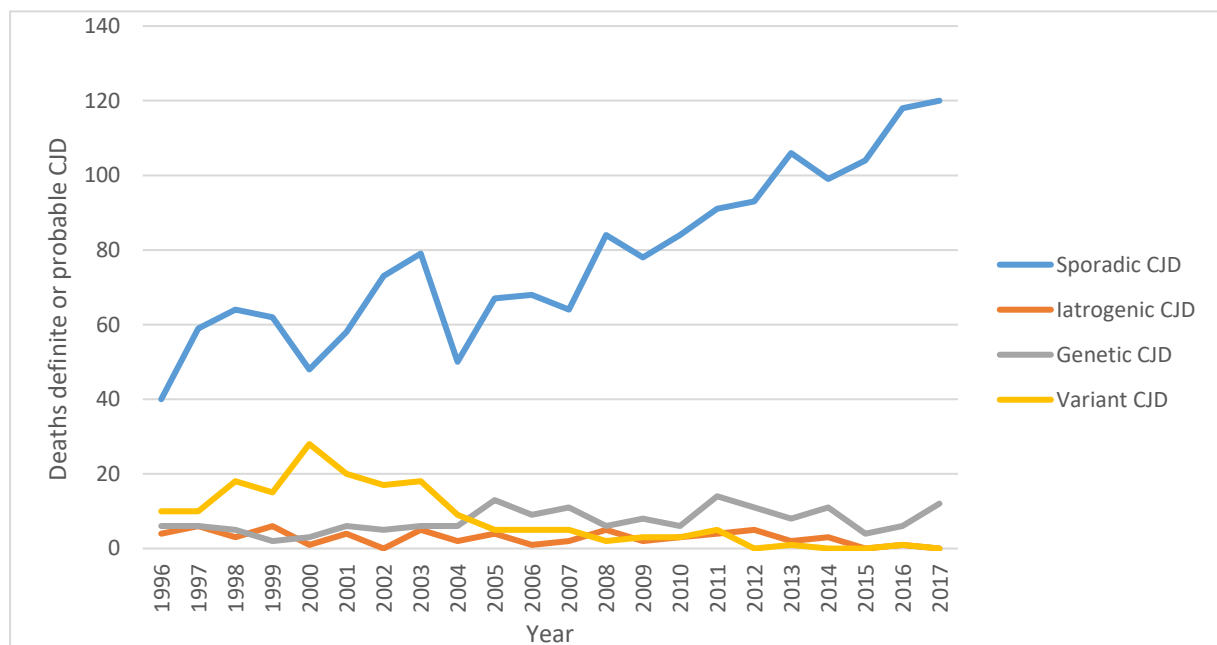
Figure 2: **Deaths from probable or definite CJD in the UK using data from the NCJDRSU between 1996-2017**

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

i.) improved case-ascertainment due to clinician awareness and/or improvements in diagnostic testing;

ii.) population increases;

iii.) an ageing population;

iv.) 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.* (2016[35]) 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.* 2013[36] 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]

Geographical differences in CJD incidence are likely to be influenced by ascertainment bias in countries where access to healthcare is free and moreover when active national CJD surveillance is in place.

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 UK[2], 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.
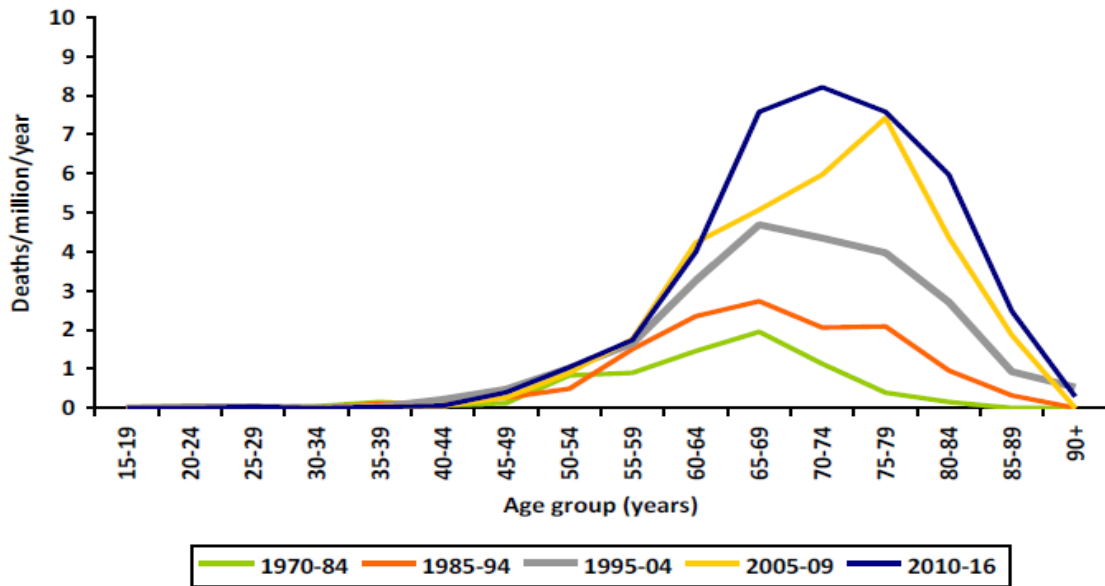
Figure 3: Age-specific mortality rates from sporadic CJD in the UK 1979-2016: replicated from NCJDRSU Annual Report 2016

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 decompensation[46] 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 heterozygous[33] 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 (PrP[res]) 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 CJD[73] 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 UK[64] 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
i. Appendices removed between 1970-1979 and before the BSE epidemic	2 positive samples from 14,692 appendices	1 in 7,000
ii. 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 strain characteristics of both individuals are similar to the UK cases, implying BSE as the source of infection and supporting the hypothesis of risk via ingestion of high titre bovine material.

The Appendix III study[84] 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 could suggest that there is low background prevalence of abnormal prion protein staining in human lymphoid tissue that may not represent subclinical vCJD or be related to the BSE outbreak, and may be unlikely to progress to vCJD. 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 of human exposure to the BSE epidemic (between the years 1980-1996). 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).[69].
. These two possible explanations 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).[88] 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.* 2013[69]	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.* 2010[89]	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.* 2009[90]	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.[91] 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.[92] 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 adhered to dryinstruments), 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)[93-95]	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)[96]	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)[97]	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)[98]	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)[99]	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)[100] Mahillo-Fernandez *et al.* (2008)[101]	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)[102, 103]	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,	Two published papers (included in de

	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.	Pedro *et al.* (2012))
Ruegger *et al.* (2009)[104]	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)[105]	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)[106]	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)[107] 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 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. Therefore, use of community controls and ascertainment of surgical exposures through use of medical records in case-control designs is currently the most feasible approach for identifying the potential association between surgery and CJD at a population level.

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.[108] As a result, Alcade-Cabero *et al.* (2012)[108] 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). From a range of occupations, only people working at physicians' offices were found to be at a statistically significant risk of sCJD (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 overall there is no evidence of an increased occupational risk for health professionals. The authors do 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.[109] From a study of 167 probable or definite CJD cases and 835 matched controls 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.[107] 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.[110] 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 et al. (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.[111]

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.[112] 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.[113] 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.[114, 115]

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 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,[105,106] 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 Orrú *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.[116, 117] 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 PrP^res in the brain, lymphoreticular system, pituitary and adrenal glands, and gastrointestinal tract, PrP^res was also detected in the dura mater, liver, pancreas, kidney, ovary, uterus, and skin.[118] 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.[119]

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.[120] 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)[121] 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.[122]

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.[123] 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.[124] 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.[125]

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.

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 et al (2016)[31]	Epidemiological surveillance	iCJD	Dura mater graft	Japan	149
Brown et al. (2012)[3]	Epidemiological surveillance	iCJD	All	International	469
Brown et al. (2015)[6]	Review	iCJD	Neurosurgery	International	6
Chohan et al. (2010)[78]	Case study	iCJD	Blood products	UK	1
Collinge et al. (2008a)[126]	Epidemiological surveillance, cohort	Kuru	Ingestion	Papua New Guinea	11
Collinge et al. (2008b)[127]	Review	Kuru	Ingestion	Papua New Guinea	NA
Collinge et al. (2006a)[128]	Epidemiological surveillance, cohort	Kuru	Ingestion	Papua New Guinea	11
Collinge et al. (2006b)[129]	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)[130]	Review	CJD	All	International	N/A
Hamaguchi et al. (2013)[131]	Epidemiological surveillance	iCJD	Dura mater graft	Japan and international	195
Heath et al. (2006)[132]	Epidemiological surveillance	iCJD	Dura mater graft	UK	8
Hirst et al. (2005)[133]	Epidemiological surveillance	iCJD	Human Growth Hormone	UK	1
Peden et al. (2010)[72]	Case study	iCJD	Blood products	UK	3
Meissner et al. (2009)[134]	Retrospective cohort	iCJD	Dura mater graft	Germany	10
Ritchie et al. (2017)[135]	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)[136]	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 in Table 7, 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	175[a]	12	(-)	Haik (2014)[130], NCJDRSU (2017)[112]
Kuru	-	0	12*	(4 to >40)	Haik 2014[130], Collinge (2006)[128], Ritchie (2017)[135]
Secondary transmission					
Dura mater graft	228	8	12	(1.3 to 30)	Brown (2012)[3], Haik (2014)[130]
Neurosurgical instruments	4†	3	1.4	(1 to 2.3)	Brown (2015)[6], Brown (2012)[3], Haik (2014)[130]
EEG needles	2	0	-	(1.3, 1.7)	Brown (2015)[6], Brown (2012)[3], Haik (2014)[130]
Corneal transplant	2	0	-	(1.5, 27)	Brown (2012)[3], Haik (2014)[130]
Growth hormone	226	78 21	17 20	(5 to 42) § (8-31)	Ritchie (2017)[135] 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)[130] Wroe (2006)[136], Peden (2004)[73], Ironside (2010)[137]; 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 *et al.* 2015; Kobayashi *et al.* 2015, Xiao *et al.* 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 *et al.* 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)[132], Ritchie (2017)[135]**
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)[135] Brown (2012)[3] Ritchie [135] 2017**
Gonadotropin	0	NA	NA	-
Packed red blood cells	3	-	(6.5-8.3)	Brown (2012)[3], Haik (2014)[130]

*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 2016[31]). Frequency data and mean incubation periods by genotype, extracted from Brown *et al.* (2012)[3], are also presented in Table 9 for a subset of the worldwide affected population. Hamaguchi *et al.* (2013)[138] 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.[139]

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, 131]	54†	65%	12 years	20%	16 years	15%	12 years
Japan* [3, 131]	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.

Meissner et al. (2009)[134] reported on a sample of 10 cases (nine from Germany, one 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 et al. (2015)[64], Brown et al. (2012)[3]). As reported in

Table 7, 78 cases had been reported in the literature for the UK as of 2017 (Ritchie et al.2017), an increase from the 65 cases reported by Rudge et al. (2015)[64] previously. Ritchie et al. (2017)[135] 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 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 et al. (2015).[64] Rudge et al. (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 et al. (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 et al. (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 et al. (2015),[64] while seven of the eight MM homozygotes occurred after 2004 Rudge et al. (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 equally distinct, in terms of genotype, from individuals with sCJD (Ritchie *et al.* (2017)[135]).

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 et al.2017**[13][5]
	37	10%		68%		22%		32%			Ritchie et al. (2017)[135]
	56/65	14% (n=8)	30.8 years	59% (n=33)	23.4 years	27% (n=15)	14.3 years	41%		23 years	Rudge et al. (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 et al. (2015)[64]
	28	4% (n=1)	21 years	50% (n=13)	23 years	46% (n=14)	18 years	54%	20 years	23 years	Brown et al. (2012)[3]
France	111/119	54%	12 years			15%	9 years	69%	11 years	17 years	Brown et al. (2012)[3], Haik et al. (2014)[130]
USA	11/29	55%	21 years			18%	18 years	73%	20 years	23 years	Brown et al. (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 *et al.* (2006a)[128], Collinge *et al.* (2008b)[127]) 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 *et al.* (2008a)[126], Collinge *et al.* (2006b)[129]). 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,[130] Ritchie *et al.* 2017).[135] For example, most cases of hGH-iCJD in France were of the MM genotype, whilst in the UK the VV and MV genotypes predominate. Infections that appear to affect certain genotypes in a particular location may reflect an absence of genotypic resistance to a particular strain, and thus shorter incubation times. Hence, it is believed that the MM genotype in the UK hGH-iCJD cohort had the longest incubation times because the infectious strain was of the VV or MV genotype. Other possible factors include higher infectious doses and/or differences in the actual data, for example where the precise date of likely contamination is known, incubation times appear to be shorter (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 *et al.* (2017)[135]and Kobayashi *et al.* (2015)[140] 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 *et al.* (2017).[135] 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 ID_{50s}. One ID_{50} 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	$10^8\,ID_{50s}$ / g
Medium	Spinal cord Tonsils Spleen Lymphoid tissue anterior eye peripheral nerves	$10^6\,ID_{50s}$ / g $10^{5.5}\,ID_{50s}$ / g $10^{5.5}\,ID_{50s}$ / g $10^{4.5}\,ID_{50s}$ / g $10^{3.5}\,ID_{50s}$ / 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 PrP^{Sc} in Syrian hamsters.[141] Using this method they were able to detect infectious titres ranging from $10^{8.6}$ 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.[142] 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.[143] 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.[144] 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.[142]

Subtype or phenotype of CJD

In sCJD, an interaction between host genotype at codon 129 and the causative agent identified as either PrP^{Sc} 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 PrP^{Sc} conversion.[145] 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.[146] All subtypes have been found to be transmissible to at least one genotype in mice studies (Bishop *et al.* 2010).[147] 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 PrP^{res} biochemical glycotype 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),[93] for example, propose the distinctive combination of 129M/M genotype, kuru plaques, and intermediate type PrP^{Sc}, 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 PrP[Sc] types 1 and 2 in sCJD in different areas, or the same area, of the brain from a single sCJD patient.[148] This finding complicates the diagnosis and the current classification of sCJD[145] 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.[146] 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.[149] 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.[150] 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.[151] 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.[152] 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.[153]

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.[154] Cali *et al.* (2015) demonstrated that novel phenotypes may arise potentially due to adaptation of heterologous prion strains of sCJD through contaminated growth hormone.[155] 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.[156] 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.[157] 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.[158] 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.[159] For example, the identified heterozygous clinical vCJD patient, aged 36 years in 2016[33] tested negative for 14-3-3 protein, RT-QuIC and the vCJD-focussed direct detection assay but immunoblotting of brain homogenate at autopsy confirmed the presence of vCJD prions. Moreover, immunostaining performed in this patient for abnormal prion protein labelled amyloid plaques highlighted a relative lack of peripheral tissue involvement with only minute amounts detected in the spleen and no detection in the appendix or mesenteric lymph nodes. However, Douet *et al.* (2017) used a highly sensitive protein misfolding cyclic amplification (PMCA) assay to assess abnormal prion

accumulation in the identified heterozygous subclinical vCJD patient, aged 82 years in 2017.[160] 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, 144] 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 tissues[14], 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.[144, 161] 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.[162] 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.[142]

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.[163] 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.[164] 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: PrP^{Sc} 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)[165] found from an analysis of four heterozygous cases of sCJD, that the PrP^{Sc} allotype ratio is highly variable, with PrP^{Sc} (-M129 and –V129) differing markedly between different regions within the same sCJD brain.[165] However, an analysis of six heterozygous cases of iCJD found the composition of PrP^{Sc} iCJD was more homogenous and tended to contain a higher proportion of PrP^{Sc}-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 PrP^{Sc} formation and increased disease incubation. However, the study authors report that in both types of CJD, the PrP^{Sc} allotype ratio had no correlation with CJD type, age at clinical onset, or disease duration. This evidence suggests therefore that factors other than PrP^{Sc} 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 10^8 ID$_{50s}$ 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).[166] 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),[167] Lemmer *et al.* (2008),[168] Rogez-Kreuz *et al.*, 2009[169]); two used vCJD ((Belondrade *et al.* (2016),[170] Rogez-Kreuz *et al.*, 2009[169]); and the following prion strains were investigated in only a single study: 127S (Belondrade *et al.* (2016)[170]), M1000 (Lawson *et al.* 2007[171]) and BSE 6PB1 (Rogez-Kreuz *et al.*, 2009[169]). All studies used steel wires contaminated with the prion (one study also used steel sheets: Rogez-Kreuz *et al.* 2009[169]); 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 (H_2O_2) 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)[167] to >5-6 (Rogez-Kreuz *et al.*, 2009),[169] 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).[169] 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)[168]).

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.* 2007[171]).

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.*, 2016[170]	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.*, 2007[171]	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,[167]	263K scrapie	BH (10%)	Wires	134°C - 18 mins	H$_2$O$_2$ (30 mins) AF (10 mins) Np-Np- H$_2$O$_2$/Cu (10 mins – 5 mins – 15 mins) Dp-Dp- H$_2$O$_2$/Cu (10 mins – 5 mins – 15 mins) Np-Dp- H$_2$O$_2$/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,[168]	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.*, 2009[169]	263K scrapie, vCJD†, BSE 6PB1†	BH (10% or 20%)	Wires, sheets†	134°C - 18 mins	NaOH 1N (60mins) H$_2$O$_2$ (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; NaOCl: 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); H$_2$O$_2$: 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. 2016[170]	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. 2007[171]	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,[167]	263K	134˚C - 18 mins		4.11	57%	140
Lemmer et al. 2008,[168]*	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. 2009[169]	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; NaOCl: 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); H_2O_2: Hydrogen peroxide; $TICU_w$: 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 <u>other than</u> 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,[172] Bellon *et al.* 2014,[173] Fichet *et al.* 2007,[174] Herve *et al.* 2010a,[175] Lehmann *et al.* 2009,[167] Lemmer *et al.* 2008,[168] Rogez-Kreuz *et al.* 2009[169]); three used vCJD (Beekes *et al.* 2010,[172], Bellon *et al.* 2014,[173], Belondrade *et al.* 2016[170]); two used ME7 (Herve *et al.* 2010b,[176] Howlin *et al.* [177]); and the following prion strains were investigated in only a single study: RML (Edgeworth *et al.* 2011[178]); BSE 6PB1 and TGB1 (Fichet *et al.* 2007,[174]); M1000 (Lawson *et al.* 2007[171]); and 127S (Belondrade *et al.* 2016[170]). Nine studies used steel wires contaminated with the prion; one study used steel tokens (Herve *et al.* 2010b,[176]) and one, steel sheets (Rogez-Kreuz *et al.* 2009[169]).

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)[178] 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 was 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,[172]); 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,[173]); 2mg/L gaseous H_2O_2 at 30°C for 3 or 6 pulses (Fichet *et al.* 2007,[174]); H_2O_2 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,[167]); the alkaline detergent B 1% for 10 minutes at 55°C; the Sterrad NX1 advanced cycle and Sterrad NX2 continuous advanced cycles (H_2O_2 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)[169]); and Cold Atmospheric Plasma (Herve *et al.* 2010a,[175]). According to Rogez-Kreuz *et al.* (2009),[169] 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 H_2O_2 at 30°C for 3 pulses (Fichet *et al.* 2007,[174]). 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,[175] Howlin *et al.*[177] Belondrade *et al.* 2016,[170] Lawson *et al.* 2007[171]).

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,[172]	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,[173]	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. 2016[170]	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. 2011[178]	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,[174]	263K scrapie, 6PB1 BSE, TGB1 BSE	BH (10%)	Wires	6% liquid H_2O_2, 20°C (60 mins) 2mg/L gaseous H_2O_2, 30°C (3 pulses) 2mg/L gaseous H_2O_2, 30°C (6 pulses)	Animal, WB
* Herve et al, 2010a,[175]	263K scrapie	NR	Wires	Cold Atmospheric Plasma (CAP)	Animal
Herve et al. 2010b,[176]	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. [177]	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. 2007[171]	M1000	BH (10%)	Wires	RMEC A (Enzymatic detergent) RMEC B (Enzymatic detergent) NaOH 1M - 60mins	Tga20 mice WB
Lehmann et al. 2009,[167]	263K scrapie	BH (10%)	Wires	H_2O_2 (30 mins) AF (10 mins) Np-Np- H_2O_2/Cu (10 mins – 5 mins – 15 mins)	Hamsters

				Dp-Dp- H_2O_2/Cu (10 mins – 5 mins – 15 mins) Np-Dp- H_2O_2/Cu (10 mins – 5 mins – 15 mins) Nmp-Nmp- PAA/Cu (10 mins – 5 mins – 15 mins, 40°C)	
Lemmer et al. 2008,[168]	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. 2009[169]	263K scrapie, vCJD†, BSE 6PB1†	BH (10% or 20%)	Wires, sheets†	NaOH 1N (60mins) H_2O_2 (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); H_2O_2: 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. TICU$_w$)
Beekes *et al.* 2010,[172]	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,[173]	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.* 2016[170]	127S	NaOH 0.1N - 15 mins	> 3	12/12	NR	
	vCJD	NaOH 0.1N - 15 mins	3	6/8	NR	
Edgeworth *et al.* 2011[178]	RML	Rely-On PI‡	5.5	0/19	>250	
		Rely-On PI§	8	NR	NR	<0.003TICU$_w$
		Prionzyme+2 M NaOH§	8	NR	NR	<0.003TICU$_w$
		2 M NaOH§	8	NR	NR	<0.003TICU$_w$
		HAMO 100 0.8%§	NR	NR	NR	0.3†
		HAMO 100 1.6%§	NR	NR	NR	0.07†
Fichet *et al.* 2007,[174]	263K	6% liquid H$_2$O$_2$, 20°C (60 mins)	1	11/11 (100%)	114 (13)	
		2mg/L gaseous H$_2$O$_2$, 30°C (3 pulses)	>5.5	0/8	>540	
		2mg/L gaseous H$_2$O$_2$, 30°C (6 pulses)	>5.5	0/8	>540	
	6PB1 BSE	2mg/L gaseous H$_2$O$_2$, 30°C (3 pulses)	>5.5	0/9	>540	
	TGB1 BSE	2mg/L gaseous H$_2$O$_2$, 30°C (3 pulses)	>5.3	0/9	>540	
* Herve *et al*, 2010a,[175]	263K	Cold Atmospheric Plasma (CAP)	>6	NR	NR	

Study	Prion strain	Decontamination methods	Log reduction	Transmission rate	Incubation period days (SD)	Other (e.g. TICU$_w$)
Herve *et al.* 2010b,[176]	ME7	Cleaner 4 (most efficient): 50°C for 5 mins	3	NR	NR	99.21% of initial prion amyloid load removed
Howlin *et al.* [177]	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/mm^2, wet or dry			
Lawson *et al.* 2007[171]	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,[167]	263K	H$_2$O$_2$ (30 mins)	≥5.25	0%	≥370	
		AF (10 mins)	≥5.25	0%	≥370	
		Np-Np- H$_2$O$_2$/Cu (10 mins – 5 mins – 15 mins)	4.55	43%	133	
		Dp-Dp- H$_2$O$_2$/Cu (10 mins – 5 mins – 15 mins)	≥5.25	20%	159	
		Np-Dp- H$_2$O$_2$/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,[168]	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.* 2009[169]	263K	H$_2$O$_2$ (10 mins)	>5 to 6	50%	443 ±140	
		H$_2$O$_2$ (20 mins)	>5 to 6	50%	428 ±142	
		Enzymatic detergent 2% (10 mins, 37°C)	1.1	100%	95 ±0	

Study	Prion strain	Decontamination methods	Log reduction	Transmission rate	Incubation period days (SD)	Other (e.g. TICU$_w$)
		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 (Table 16). In terms of prion strain, two studies used 10% or 20% brain homogenate of RML (Jackson *et al.* (2005)[179], Edgeworth *et al.* (2011)[178]), and two studies investigated sc237 and sCJD (Peretz *et al.* (2006)[180] and Giles *et al.* (2007)[181]), with the following prion strains investigated in only a single study: 263K scrapie (Baxter *et al.* (2005)[182]), and 301V BSE and cattle BSE (Giles *et al.* (2007)[181]). Five studies used steel wires contaminated with the prions, and one study used steel spheres (Baxter *et al.* (2005)[182]); 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)[181]).

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' ($TICU_w$) (Edgeworth *et al.* (2011)[178]). This study recorded that autoclaving at 134°C for 18 minutes reduced the $TICU_w$ 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).

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)[183]). 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)[179]). 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)[179]). 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)[180]and Giles *et al.* (2007)[181]). 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)[180]).

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)[182]	263K	BH (20%)	Spheres	137°C - 18 mins	Trigene disinfectant Radio-frequency (RF) gas plasma	Hamsters
Edgeworth *et al.* (2011)[178]	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)[181]	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)[183]	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)[179], McKintosh *et al.* (2005)[184]	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)[180]	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)[183]), Sc237 and sCJD prions strains (Peretz *et al.* (2006)[180]); 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)[183]); and autoclaving at 65°C for 18 hours plus 2% SDS + 1% AcOH for the Sc237 and sCJD prions strains (Giles *et al.* (2007)[181]). 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)[179]).

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)[182], Jackson *et al.* (2005)[179]).

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)[182]	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)[178]	RML	134°C - 18 mins	NR	5%	NR
Giles et al. (2007)[181]§	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)[183]	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

Study	Prion strain	Decontamination methods		Transmission rate	Incubation period days (SD)
		Autoclaving	**Other**		
		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)[179], McKintosh *et al.* (2005)[184]	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)[180]	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

Study	Prion strain	Decontamination methods		Transmission rate	Incubation period days (SD)
		Autoclaving	**Other**		
		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

Nine studies reported this outcome after autoclaving with and without other decontamination processes (Table 18): seven studies for surgical instruments and two studies for endoscopes (Herve *et al.* 2013[176], 2016[185]). 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, *et al.* 2006[186]; Herve *et al.* 2016[185]). All studies reported that cleaning essentially involved conventional procedures for the equipment concerned. With the exception of two studies (Baxter R, *et al.* 2006[186]; Murdoch, *et al.* 2006[187]), 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 *et al.* (2006[187]) reported a mean protein per instrument of 71.67µg (range, 8-91 µg); R Baxter *et al.* (2006[186]) reported a median range of 163-756µg per instrument; Lipscomb *et al.* (2006a[188] & b[189]) 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/mm^2 and 4 is >4.4µg/mm^2. The most recent study, Smith *et al.* (2018[190]), 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 *et al.* 2006[191] & 2009[192]). The studies assessing endoscopes reported either <10ng/mm^2 after processing (Herve *et al.* 2013[176]) 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 *et al.* 2016[185]).

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, *et al.* 2006[186]	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 *et al.* 2006a[188]*	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 Unclear[b]	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/mm^2 and class 4 is >4.4µg/mm^2.*	
Lipscomb *et al.* 2006b[189]*	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*	*Levels of soiling (scores averaged for each instrument): severe (66%: CI score, >3 to 4); moderate (17%: CI score, >2 to 3); low-level (7%: CI score, 0 to 2). Across the nine trays, the mean CI per instrument set ranged from 2.4 to 3.6; overall mean CI value for all the instruments: 3.2. Contamination index (CI): class 3 is 0.42-4.2 µg of protein/mm^2 and class 4 is >4.4µg/mm^2.* 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 *et al.* 2006[187]	UK	Five Department of Health hospitals	A range of instruments (n=43)	'autoclaved'	'protein extraction and quantification methods', i.e. levels of protein	71.67 µg ‡ 8-91 µg (range)†	NR

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)
					removed from instruments and identified in the 'buffer' or ''wash'		
Baxter H, et al. 2006[191]	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 Unclear[b]	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, et al. 2009[192]	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, et al. 2018[190]	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	SDS extraction and OPA, ProReveal Unclear[b]	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): <5 µg per instrument side; 96% (179/187): <10 µg per instrument side	NR

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)
				agents (Steris pre-klenz and sterile water)			
Herve *et al.* 2013[176]	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/mm^2 after standard cleaning (see Figure 3 in the paper for details)	
Herve *et al.* 2016[185]	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) [a]Smith 2018[190], Supplemental table XV.
[b]Unclear: 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 (Table 19). 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 *et al.* 2015[193]) to 24 hours (Secker *et al.* 2011[194], Secker *et al.* 2015[193]).

The process to keep steel tokens or wires 'wet' was different in each study: Secker *et al.* (2015[193]) used a 'wet bag' (Humibag), i.e. a sealed bag containing 35ml distilled water for set time periods; Secker *et al.* (2011[194]) used an air-tight container lined with moist tissue for 17 hours; Howlin *et al.* (2010[177]) treated steel wires immediately, rather than allowing them to dry; and Lipscomb *et al.* (2007[195]) 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 *et al.* 2015[193]); air dry for 24 hours (Secker *et al.* 2011[194]); air dry for 16 hours (Howlin *et al.* 2010[177]) and air dry for 17 hours (Lipscomb *et al.* 2007[195]). 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 *et al.* studies (2011[194], 2015[193]) reported on protein residue after 24 hours at room temperature before cleaning: 324.7 ± 15.0 ng/mm^2 for the air dry conditions compared with 6.0 ± 3.5 ng/mm^2 for the wet conditions (98.2% reduction compared to air dry, $p\leq0.001$) (Secker *et al.* 2011[194]) and 1000 ± 205.0 ng/mm^2 for the air dry conditions compared with 31.9 ± 5.3 ng/mm^2 for wet conditions (Secker *et al.* 2015[193]). After the application of pre-soaks or cleaners, Lipscomb *et al.* (2007[195]) reported a reduction in protein between 64% and 96% on the pre-soaked or treated tokens compared to the dry, untreated controls; and Howlin *et al.* (2010[177]) 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 *et al.* (2015[193]) and Lipscomb *et al.* (2007[195]) 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 et al. 2007[195]	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 22°C*: Control = 100%	Percentage of final residual protein contamination compared with control at 22°C*: Klenzyme = 19% Endozyme AW=36% Enzol=4% Liquid 52= 17%
Howlin et al. 2010[177]	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 et al. 2011[194]*	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 (4°C-8°C)	DT=24h Moist: Air-tight container lined with moist tissue RT or F (4°C-8°C)	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)	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)

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**
								Endozime applied after 2h: RT=194.3±7.9 ng/mm²	
Secker *et al.* 2015[193]	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†

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**
						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 *et al.*2010[196], abstract too *Data for 30°C too but 'efficacy changes little between the ambient temperatures' †Level of difference is $p \leq 0.05$ 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 *et al.* (2010[177]): 'A concentration of 0.03 ng/mm² prion-associated amyloid was detected in situ on the wires'; Secker *et al.* (2015[193]): '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, 2016[197]). However, these published data are based on different assays and detection methods and the most recent data (Smith *et al.* 2018[190]) 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 *et al.* 2011[194], 2015[193]) 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 *et al.* 2011[194]). 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 *et al.* 2013[176]).

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),[198] Belay *et al.* (2013),[114] Rutala *et al.* (2010),[199] Dickinson *et al.* (2009),[200] Fichet *et al.* (2004)[201]). 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)),[169] SDS 0.2%/NaOH 0.3% (Lemmer *et al.* 2008)[168], Rapid Multi Enzyme Cleaner trial formulation (RMEC) B (Lawson *et al.* 2007)[171], 4% SDS + 1% AcOH (Giles *et al.* 2008)[183], Peretz *et al.* 2006)[180], H_2O_2 and gas plasma (Sterrad NX1 and 2 cycles) (Rogez-Kreuz *et al.* 2009). [169] 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)[199]).

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)[178]); sodium chloride (NaOH) (Edgeworth *et al.* (2011),[178] Bellon *et al.* (2014)[173]); trigene disinfectant and RF gas plasma (Baxter *et al.* (2005)[182]); SDS-PK-Pronase (Jackson *et al.* (2005)[179]); H_2O_2 and gas plasma (Rogez-Kreuz *et al.* 2009,[169] Lehmann *et al.* 2009[167]); and combinations of enzymatic detergents and disinfectants (Lehmann *et al.* (2009)[167]). 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),[167] Rutala *et al.* (2010)[199]), although sodium hydroxide is reported to be less corrosive than sodium hypochlorite (Belay *et al.* (2013)[114]). A combination of immersion in sodium hydroxide or sodium hypochlorite, followed by autoclaving, is recommended by the WHO (Belay *et al.* (2013)[114]; 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),[114] Rutala *et al.* (2010),[199] Rochefort *et al.* (2010),[202] Jackson *et al.* (2005),[179] Rogez-Kreuz *et al.* (2009)[169] and Bonda *et al.* (2016)[198]). Such differences also make direct comparison between findings difficult for human prions and other TSE prions (Belondrade *et al.* (2016)[170]). 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),[182] Murdoch *et al.* (2006),[187] Herve *et al.* (2010)[203]), 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),[203] Dickinson *et al.* (2009)[200]).

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).[112] 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 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)[114]	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 2016[204]	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)[114], NICE 2016).[204] In 2013, an article was published by Belay *et al.* (2013)[114] 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 index 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 used on the CJD index case. 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 (

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 IPG196[14] 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)[114]	*By the time of a CJD diagnosis, the identification of contaminated instruments had become almost impossible in some hospitals, in part because12/19 (63%) hospitals were known to have multiple neurosurgical sets.* *The number of neurosurgical sets per hospital ranged from 1 to 12 (data permitting).* *It was not possible to identify the CJD-contaminated sets in 11 (58%) of the 19 hospitals; it was therefore also not possible to determine the exact number of patients exposed to the instruments used on the index patient in these hospitals.*
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 reusables 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)[114]). 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 guidance[14] 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.* 2015[112]) 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),[199] and Department of Health[205]) or which are now single-use (NICE 2016).[204] 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 IPG196[14] 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).[206] 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),[207] 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)[207]	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)[207]). Two additional procedures from this paper have also been included here as potentially relevant: unspecified excision of brain, and excision of brain lesion(s). This is due to their low five-year 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 *et al.* (2009)[207] report, the future procedures are always the same as the index procedure (i.e. if the index procedure was concerned with 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 (Table 23).

Table 23: **Findings of Bird *et al.* (2009)[207] 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 (Table 23). This ranged from 10.7% for individuals having one or more additional procedures for the drainage of extra- and sub-dural haematoma to 49.5% for individuals having one or 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)[207] 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)[207] 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 CJD Advisory Sub-Committee (CJDAS) who produced interventional procedures guidance (IPG) 196.[208] 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. However, with the agreement of NICE, the current work focuses solely on 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.

3.1.1   Elicitation

Many model parameters are subject to considerable uncertainty and were populated following two elicitation sessions undertaken in 2005, one with epidemiological experts and one with decontamination experts. These elicitations were reported in Stevenson *et al.*[11] and the results are repeated in this report. At a meeting of the NICE interventional procedures 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.

3.1.1.1 Elicitation methods

The 2018 elicitation session was conducted using the Sheffield Elicitation Framework (SHELF). Four experts participated in a face-to-face facilitated workshop. The experts first completed a training exercise (using a quantity known to the facilitator, but unknown to them), to familiarise themselves with the elicitation methodology. For each parameter, the experts first recorded their probability judgements individually, without conferring. Experts were asked to separately consider lower and upper plausible limits; different scenarios that might lead to 'high' values or 'low' values of the parameter. Probabilities were not attached to these plausible limits; the purpose of eliciting the limits is to mitigate the effects of anchoring and overconfidence, which may occur if a 'best guess' is first provided, followed by some assessment of uncertainty around such a guess.

The experts were then asked to provide median values by dividing their plausible ranges into two intervals judged to be equally likely. They were then asked to divide each interval into two further equally likely intervals, hence providing their lower and upper quartiles.

Each expert then declared his/her judgements to the facilitator, who then presented a graphical comparison of all the experts' individual judgments. Disagreements between the experts' judgements were highlighted, and the experts were invited to justify their own opinions and question each other. Following the discussion, the experts were asked to imagine a "Rational Impartial Observer" (RIO): an independent observer who has heard and understood the discussion, and on that basis form his/her own probability judgements. It was for the experts to decide how much weight RIO would give to the different opinions/arguments that had been stated; if the experts disagreed, with no convincing experts to favour one side over the other, RIO's uncertainty would be expected to reflect the disagreement.

The experts agreed on a median and quartiles for RIO's distribution. The facilitator then fitted a probability distribution to these judgements, by choosing a parametric family of distributions, and selecting parameter values using a least-squares fit to the cumulative distribution function. The selected distribution was presented to the experts, with feedback in the form of 5th and 95th percentiles (which had not been directly elicited). The experts were asked to comment on whether the fitted distribution was an acceptable representation of RIO's uncertainty; whether the level of uncertainty would be justified based on the proceeding discussion. The distribution would be modified as necessary, before being adopted within the ensuing calibration and probabilistic sensitivity analysis.

Experts were recruited from within the NICE advisory committee. We believed the workshop format to be important to allow for sufficient training of and discussion between the experts. However, owing to the timescale of the project, it was only possible to convene one workshop with four experts.

3.1.2   Cost-effectiveness literature review

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

Previously, authors of this report had undertaken work for the CJDAS to assess the cost-effectiveness of single-use instruments to reduce the risk of vCJD through surgical procedures.[11] The paper by Stevenson *et al.*[12] provided further information having utilised a Bayesian approach to take into account data observed since the generation of the results for NICE and submission of the manuscript. As this model was used by the research team in the initial appraisal in 2005 there was a preference to use, or adapt, this model unless it was shown to be not fit for purpose.

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. Bennet *et al.* had three broad aims: to clarify the possible scale of vCJD infection via surgical instruments; to identify the most important factors contributing to this risk and to help prioritise scientific research. 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*.' As the paper by Bennett *et al.* was published earlier than that of Stevenson *et al.* (2005 compared with 2009) this was not preferred to the previous modelling structure.

A further paper by Garske *et al.*[209] was identified that 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. The former was noted to be a key parameter in Stevenson *et al.*[12] which also explored uncertainty in the mass transferred, and was published later than the Garske *et al.* paper (which was published in 2006) and thus this model was not deemed preferable to that of Stevenson *et al.*

Based on the authors' critique of Bennett *et al.*[13, 209] and Garske *et al.*[209] there appeared no strong reason to diverge from a model foundation as described by Stevenson et al.[12]. This model was amended in consultation with 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 in Stevenson *et al.*[12] is shown in Figure 4; this model works on an individual patient level for those with CJD infection. 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. Population of the model is detailed in Section 3.3. Figure 4 depicts the flows of patients, instrument sets and supplementary instruments (SI) that have the potential to transmit CJD surgically. Patients have been categorised into three discrete groups: patients who are not infected with CJD; patients who are infected with CJD that are not infectious; and patients who are infected with CJD and are infectious, but asymptomatic. Patients who have clinical CJD would not be operated on with reusable instruments and are assumed outside of the modelling process. Across time, patients can move from the non-infected state to the infectious but asymptomatic state following an operation with a contaminated instrument, patients can move to the infected and infectious state when the incubation period of the disease for that patient has been reached and patients can be removed from the model when the CJD infection becomes symptomatic. In all states patients can die in accordance with background mortality rates applicable to the age of the hypothetical patient. 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. The rate of instrument migration is important in circumstances where there are multiple contaminated instruments in one set. Therefore, maintaining set fidelity can limit the spread of infection compared to a situation where the contaminated instruments are spread across a number of sets which can result in a greater number of subsequent transmissions. In order to model this, dynamic SIs were modelled at an individual level whilst sets were modelled with the possibility of instrument migration.

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 initial work undertaken by ScHARR 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 five-year period was agreed with the NICE advisory committee to be an appropriate time period that would be sufficiently long to allow potential cases of stCJD to become apparent, but short enough that the computational time required to generate the results was not excessive and that did not limit the committee to a decision that could not be changed in the longer term if required. The five-year period matched the value used in Stevenson *et al.*[12] The measure of benefit was reported in terms of life-years gained and quality-adjusted life years (QALYs). A lifetime perspective was undertaken for the patients simulated to have high-risk surgery within the five-year period.

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.[210]
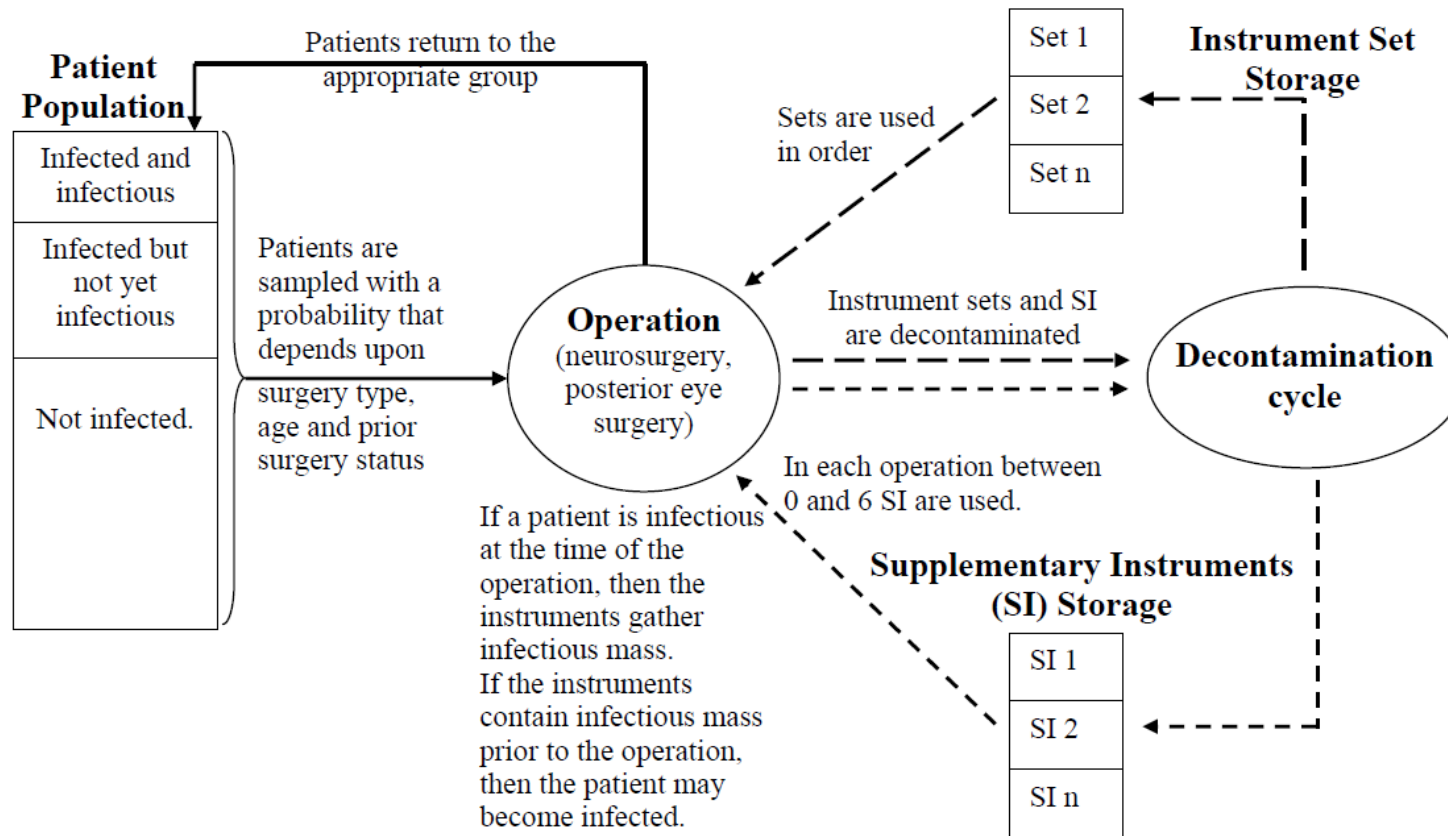
Figure 4: **The conceptual model relating to the infection process**
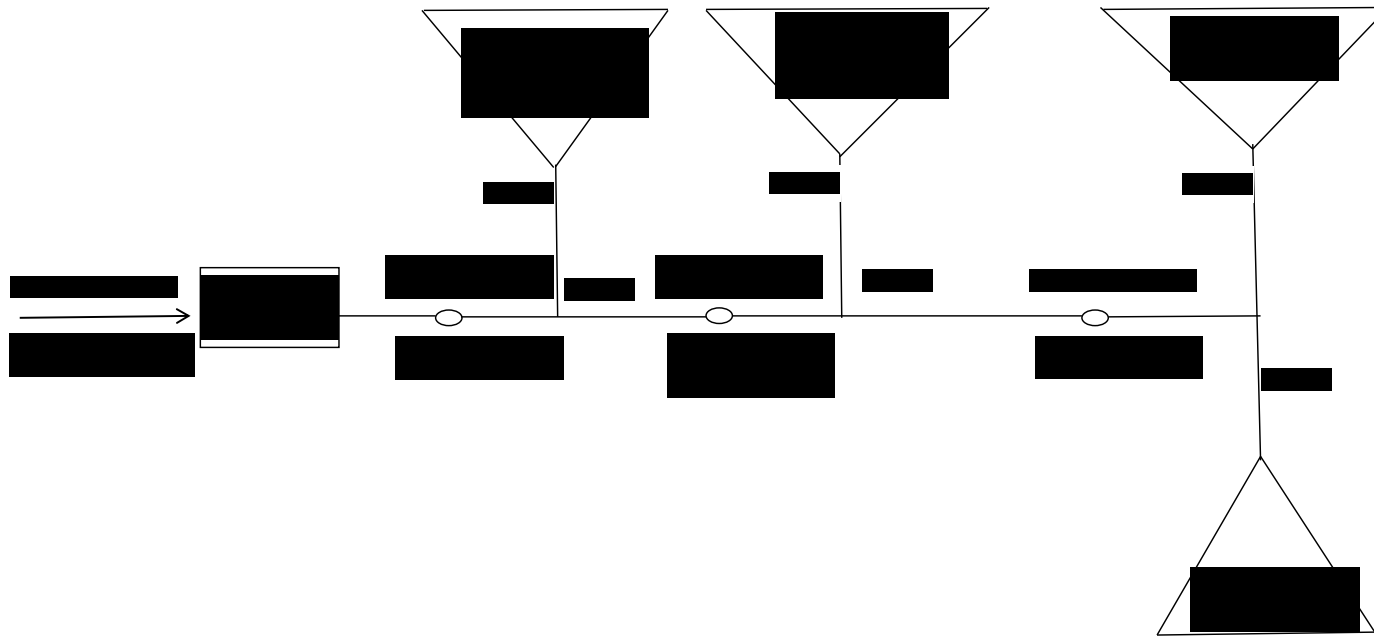
Figure 5: **The conceptual model relating to patient outcome post infection**

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 as the probability in all tissue will be greater than that confined to just the central nervous system. 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.
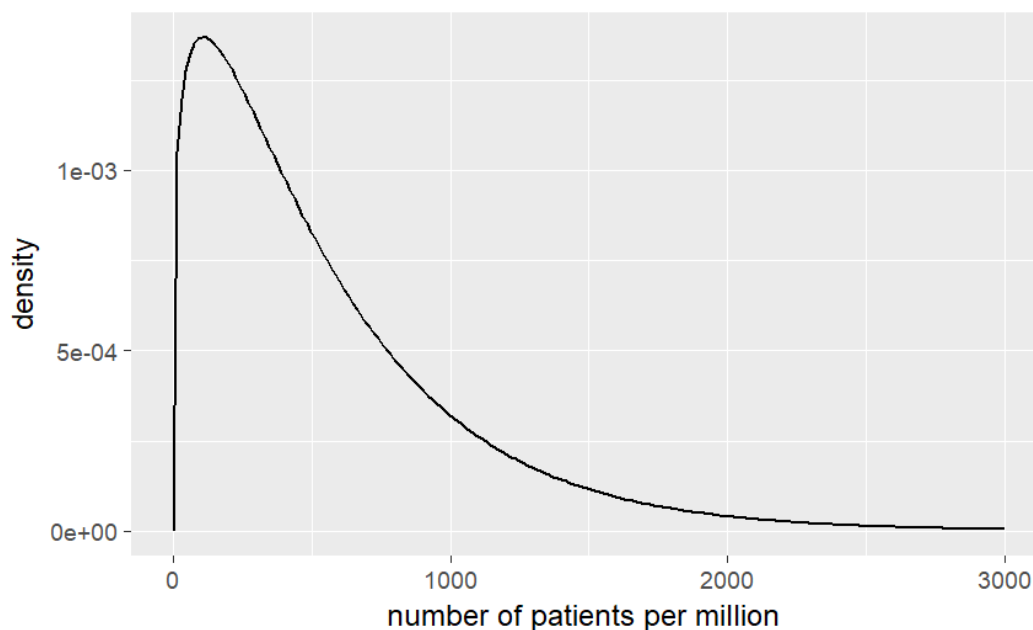
Figure 6: **The prevalence of CJD prions within central nervous tissue**

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 report[11] 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.*[211] 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.*[190] 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.*[186] and between 8-91µg (mean 71.67 µg; 43 instruments) in Murdoch *et al.*[187] Lipscomb *et al.*[189] 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.*[190] 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. It was assumed that the reduction in protein residue on instruments will translate into a reduction in the possibility of transmission of stCJD.

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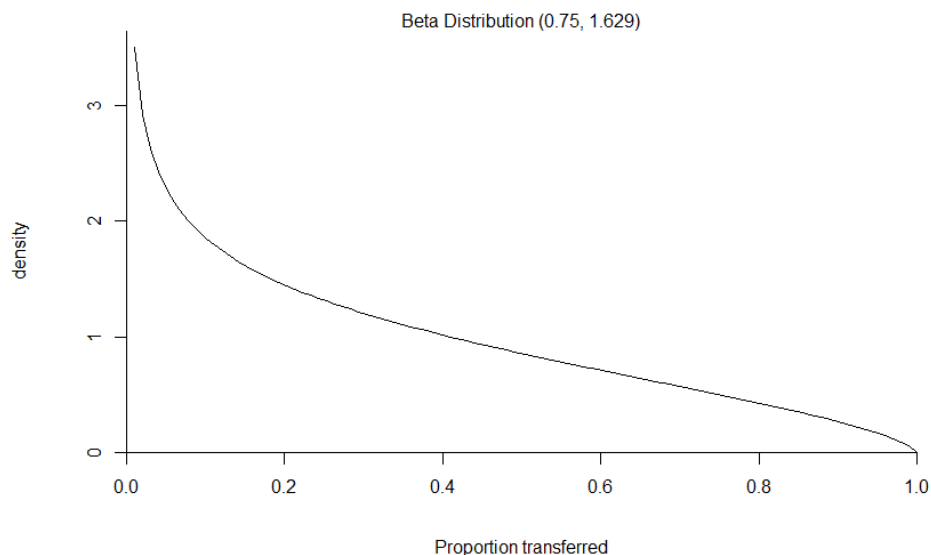
Figure 7:   The proportion of residual mass transferred to a patient

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%.

Beta Distribution (0.675, 70.451)

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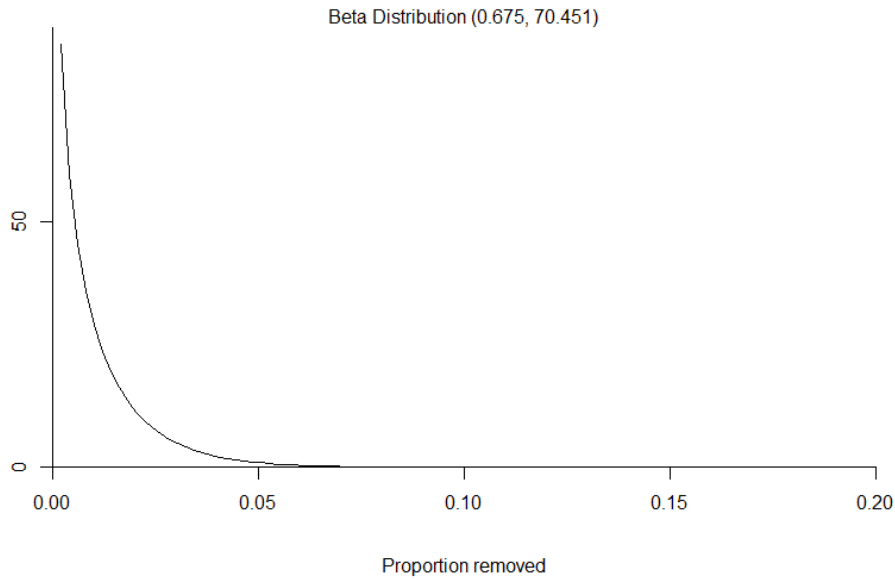
Figure 8:   **The proportion of residual mass removed in a subsequent decontamination cycle**

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 work[11] 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 the previous modelling undertaken,[11] brain and posterior eye tissue were assumed to have 10^8 ID_{50s} per gram with this value assumed fixed and applied from the moment the patient became infectious to the moment when clinical symptoms of CJD were observed, in which instance reusable instruments would not be used on the patient.

The NICE committee requested, based on the collective experience of its members, that the previous assumptions were amended to allow more heterogeneity in patients who have CJD prions in high-risk tissue. Firstly, the mean infectious titre was varied between 10^7 and 10^9 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 10^6 to 10^{10} ID_{50s} 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 report[11] 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.
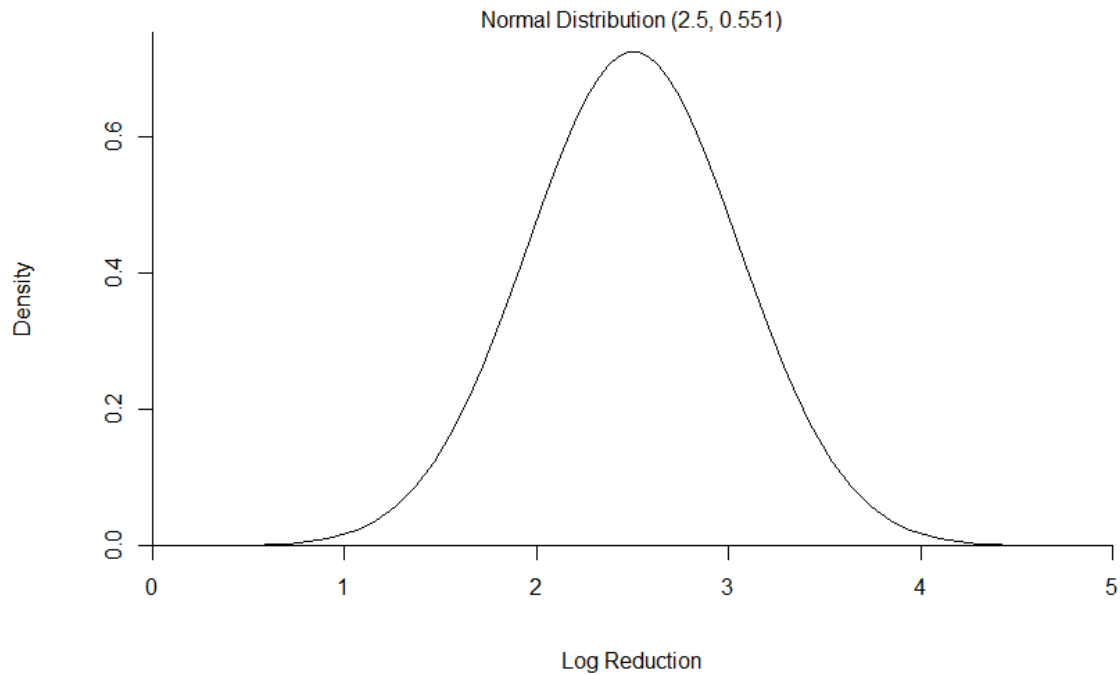
Figure 9: **The reduction in infectivity in the first autoclaving cycle**

The distribution assumed for the infectivity reduction associated with the first cycle of detergents y 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.
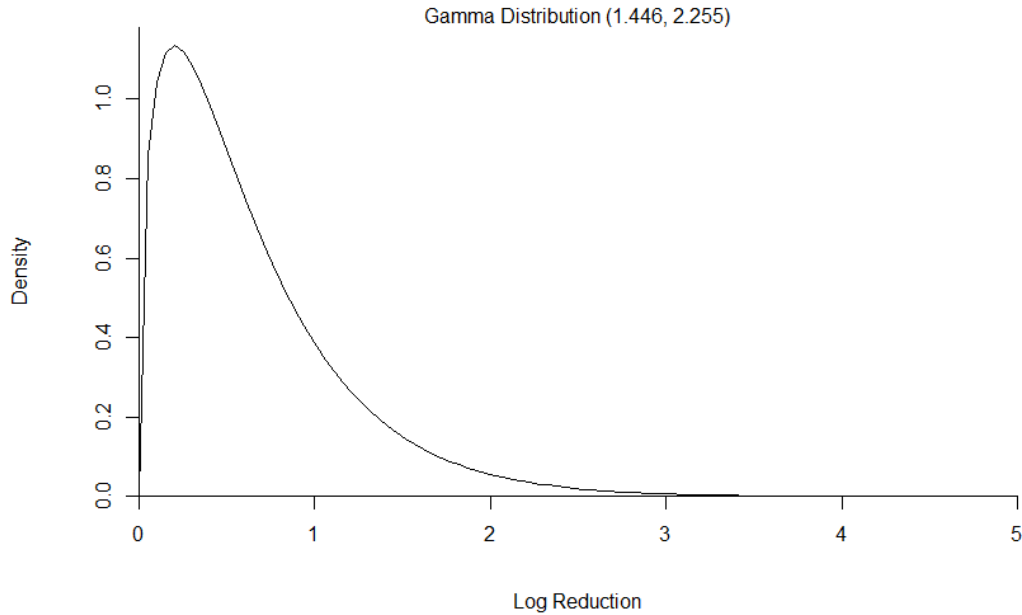
Figure 10: **The reduction in infectivity in the first detergent cycle**

3.3.2.2.2 The effectiveness of infectivity reduction in subsequent decontamination cycles

It was assumed in the ScHARR report[11] that the second and third autoclaving cycles would reduce prion infectivity, although this would be to a lesser extent than the initial autoclaving cycle. These subsequent autoclaving cycles would occur following a subsequent operation. 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.
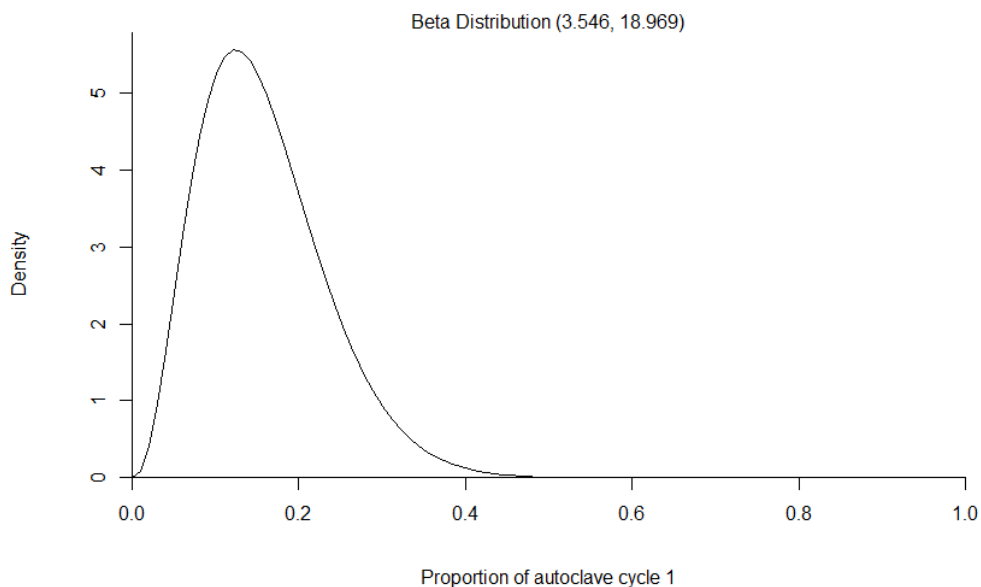
Figure 11: **The proportion of autoclave cycle 1 log reduction achieved by cycles 2 and 3**

116

It was assumed in the ScHARR report[11] 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.
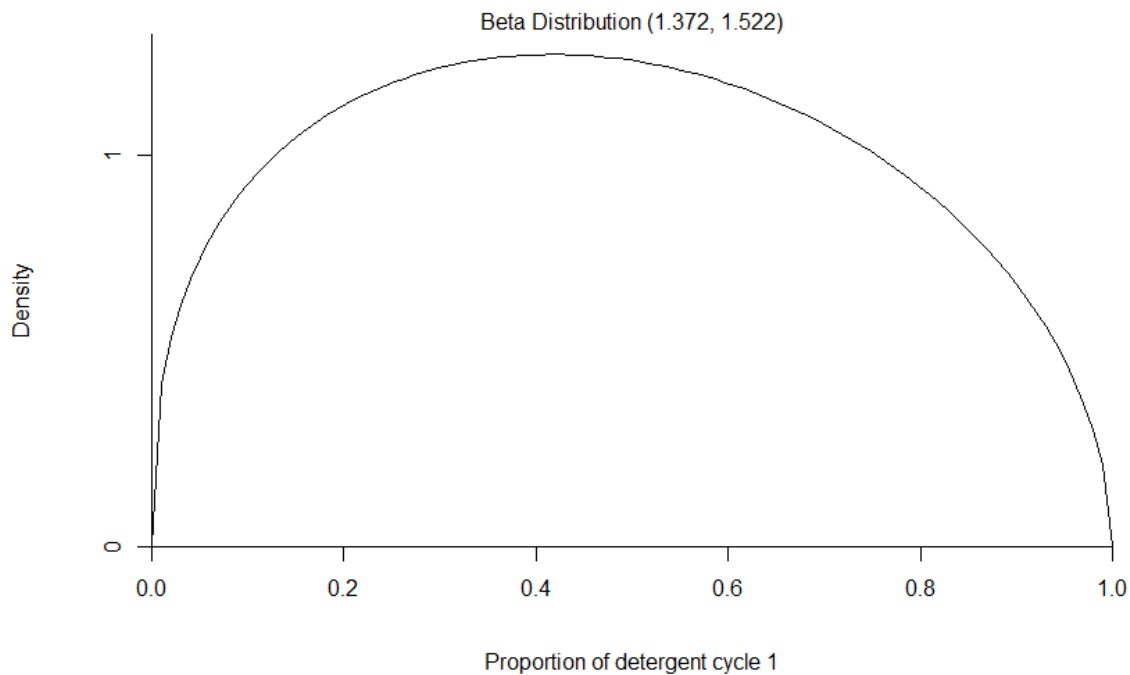
Figure 12:   The proportion of detergent cycle 1 log reduction achieved by cycle 2

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 reusable 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. In discussions with the committee, it was believed that the serviceable life of a reusable instrument was longer than that previously assumed and the probability of an instrument being disposed of was reduced to 1/2500 with a range of 1/2000 to 1/3000.

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 eye surgery set, it was assumed that between 0% and 25% (sampled from a uniform distribution) of infectious load was removed from the set. The midpoints of these distributions (6% and 12.5%) were chosen such that it was close to the proportion of the set that one instrument comprised. This is (as detailed in Section 3.3.3) 1/14 (7%) for an instrument in a neurosurgery set and 1/9 (11%) for an instrument in a posterior eye surgery set. Uncertainty was incorporated by allowing a range between 0% and approximately twice the midpoint value.

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, IPG196[208] 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 report[11] 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. These values were chosen as there were approximately 10 instruments in a surgical set, which would be expected to contain 10% of all mass (infectious or not) and that there would be expected to be uncertainty around the proportion of mass contained on individual instruments.

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 distribution used to model infectious mass transference due to SI migration is associated with smaller mass levels than non-SI instruments.

The model has the facility to alter the levels of set migration following the publication of IPG196,[208] 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,[208] 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.

Confidential until published

3.3.3.4 The costs associated with reusable 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 reusable instrument is likely to be in the region of £100 - £200.

The ScHARR report assumed that a reusable rigid neuroendoscope costs £397 and a reusable flexible neuroendoscope costs £9300. More recent prices estimate that a reusable rigid endoscope set including instruments would cost approximately £8850 with a flexible endoscope costing approximately £21,000. Whilst there will have been inflation during the period the increase in prices for rigid neuroendoscopes in particular, look high. Clinical advice suggests that in 2005 these were very cheap disposal rigid neuroendoscopes, but that these have since been withdrawn. This puts downward pressure on the costs of the reusable rigid neuroendoscopes and furthermore, it is likely that the volume of sales of neuroendoscopes has decreased resulting in an increase in the price. Whatever the reasons underlying the increase, the NICE committee were comfortable that the prices used in this report was appropriate.

3.3.3.5 The costs associated with decontaminating reusable instruments

Data provided by a committee member indicated that the costs of decontaminating a reusable 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.*[190] 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 reusable 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 ID_{50s} per gram, where an ID_{50s} is the dose required to infect 50% of the susceptible population,). It was assumed that the relationship between the number of ID_{50s} and probability of infection was:

Probability of infection = MIN (No of ID_{50s} transferred * 50%, 100%)

Such that $2ID_{50s}$ or more would result in a certain infection. In the earlier ScHARR model the use of a geometric sequence was used, such that $2ID_{50s}$ would result in only 75% of patients being infected ($1-0.5^2$) but the committee did not want to use this assumption as the dose to infection was not robustly known, and high levels of ID_{50s} transferred could be associated with definite, rather than a high probability of infection, and the committee wished to err on the side of caution. The linear assumption was upheld by the NICE appraisal committee.

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 Statistics[212]), 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.[212] 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 13. 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.

Beta Distribution (50.126, 199.646)

Density

Proportion of incubation time infectious at CNS
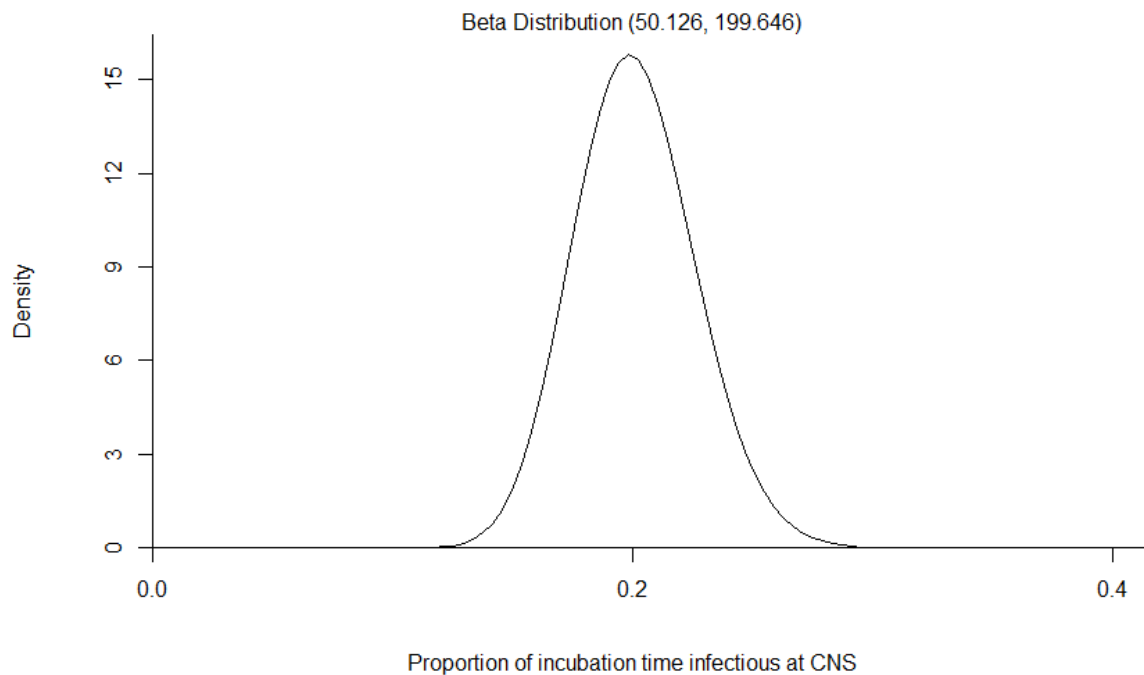
Figure 13: **The proportion of the incubation period during which the patient is infectious**

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 report[11] 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 report[11] 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,[213] and Curtis[214] 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.[215] 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 14.

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 15. 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 16. 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 3[216])) 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.
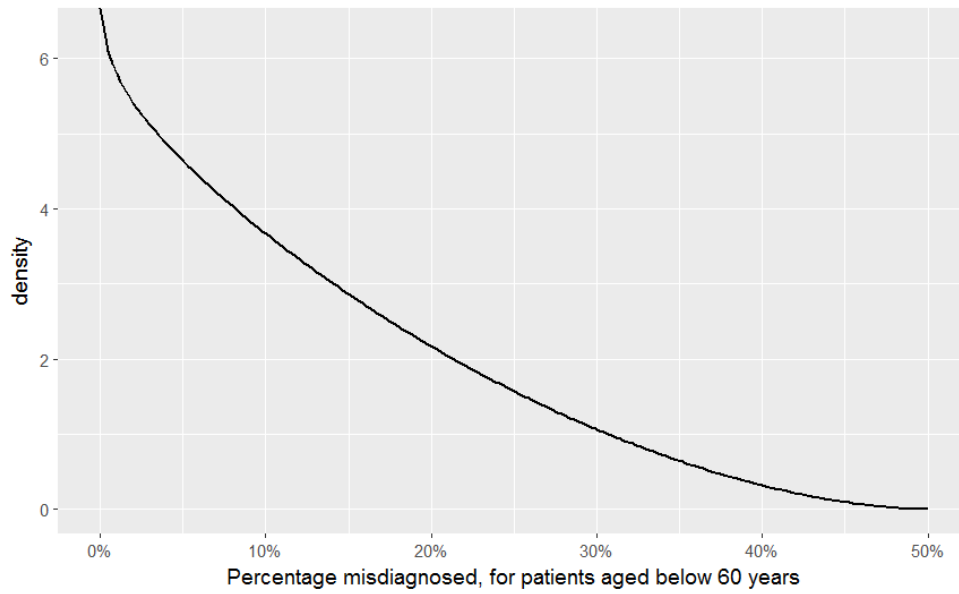
Figure 14: **The proportion of patients under 60 years with clinical CJD symptoms that are diagnosed with another neurodegenerative disease**
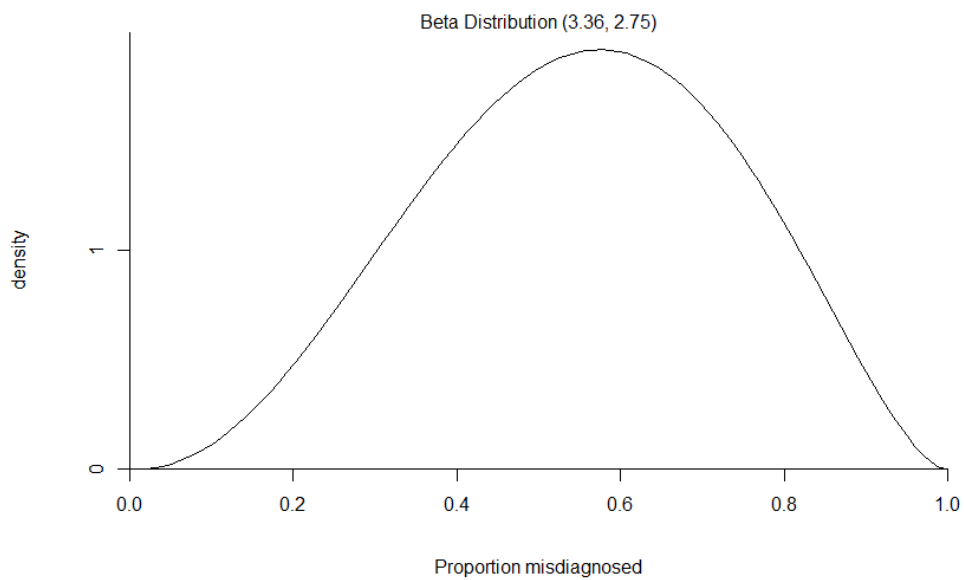
Figure 15: **The proportion of patients over 80 years with clinical CJD symptoms that are diagnosed with another neurodegenerative disease**
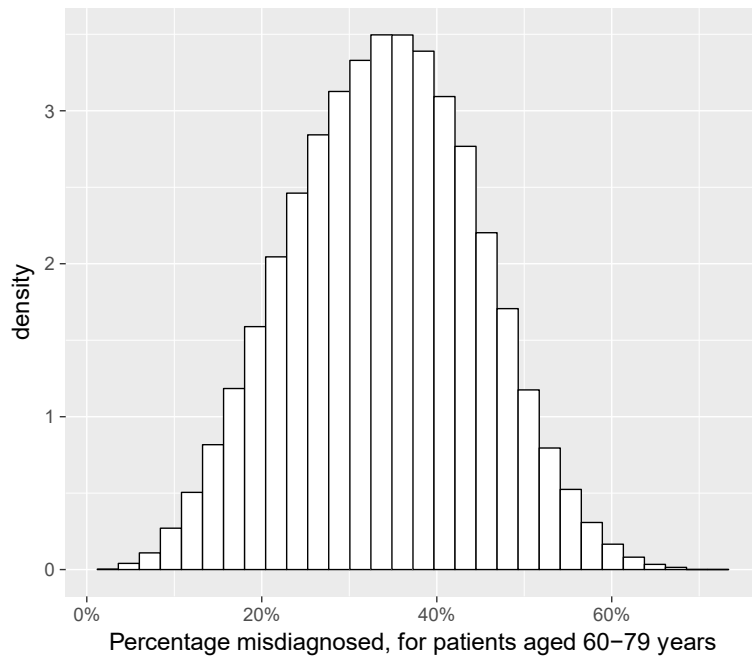
Figure 16: **The simulated proportion of patients aged between 60 and 80 years inclusive with clinical CJD symptoms that are diagnosed with another neurodegenerative disease**

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 report[11] 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 6.

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 as a previous operation may not be recalled. 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. The committee member erred on the side of caution, stating whether operation could have the potential to transmit CJD prions to the patient. However, it is possible that some of the cases reviewed occurred in other parts of the UK than England, to which this guidance in limited, which would result in an over-estimated calibration target.

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 (rounding to the nearest integer). 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.

Based on the opinion of members of the NICE committee 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. These probabilities were altered in a scenario analysis

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 = 10^A 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 $> e^{12}$ would effectively have zero weight and could be discarded without affecting the results. Any draw with a value $\leq e^{12}$ 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 $\leq e^{12}$ 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 $\leq$ e^{12}, 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 7. 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 17. 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.
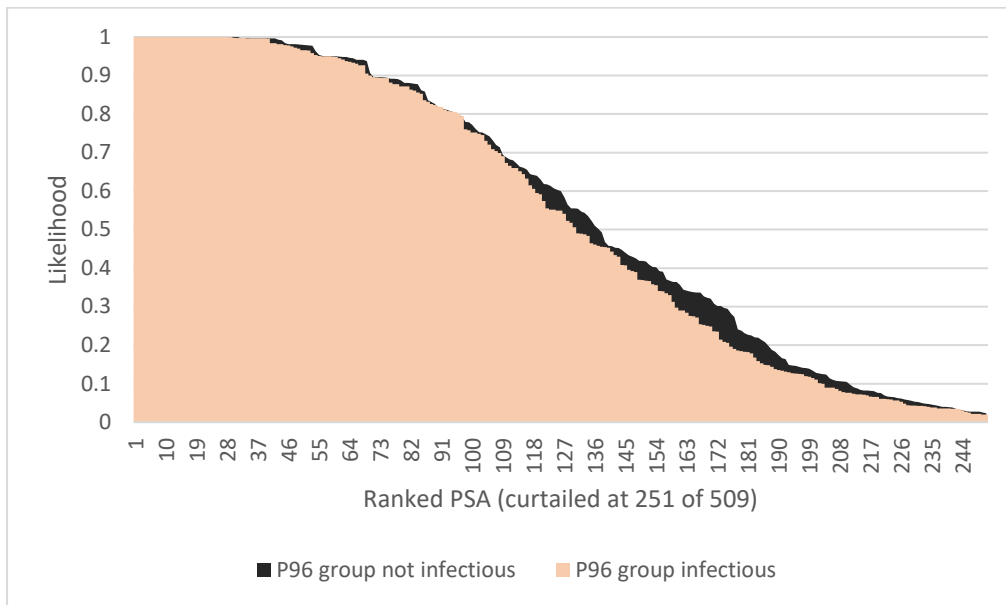
Figure 17: **The likelihoods of the PSA configurations being compatible with the observed data (curves are drawn on top of each other)**

3.5.5   Generating estimates of the expected numbers of future stCJD deaths, life years lost, and 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 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 with respect to surgical centres' adherence to IPG196

2) Full adherence to IPG196, and guidance on keeping instruments moist for those units where this is not followed.

3) Full 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 completely 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 reusable instruments were equivalent.

Based on advice provided by the NICE committee, no modelling of decontamination products was conducted other than that contained in strategy five. The reasons for this were multiple. Firstly, there was a lack of homogeneity in the identified studies of decontamination products in terms of: prion

strains; drying times; infectious titre of the material used; time and temperature of the exposure to the decontaminant; dose of the decontaminant; observation period; substrate used; assay; infectivity detection method used. Secondly, the findings for some agents also inevitably differed both within and between studies, due to the described heterogeneity (see results for Rely+On depending on assay or NaOH depending on prion strain). Identifying the most 'efficacious' decontaminant – requiring comparison across agents – was therefore not possible. Thirdly. as far as we could tell, the majority of the decontaminants (and combinations thereof) were also not commercially available, but had been developed for the laboratory tests while others that did exist as distinct products were few and, in some cases, are no longer on the market, e.g. Rely+On. Fourthly, uptake of an additional decontaminant solutions might be very low in practice due to requiring an extra step in the sterilisation process. Major concerns therefore affected the certainty and generalisability of the evidence on decontaminants for reducing the risk of prions in surgery. The authors wanted to provide an indication of the potential prices that could be cost-effective if a completely effective decontamination product was commercially available and so explored this in strategy five.

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. The values are per surgical unit, and need to be multiplied by 27 to represent values for England.

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. †The values need to be multiplied by 27 to provide numbers for England rather than surgical units

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 from the 509 PSA configurations were not believed by the authors of this report to be large enough to endanger the conclusions of the analyses are endangered. Given this it was believed that further reductions in the width of the CIs, through running further PSAs were not required.

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. The results are presented in terms of surgical centres, these values would be needed to be multiplied by 27 in order to form estimates for England.

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 18. 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.
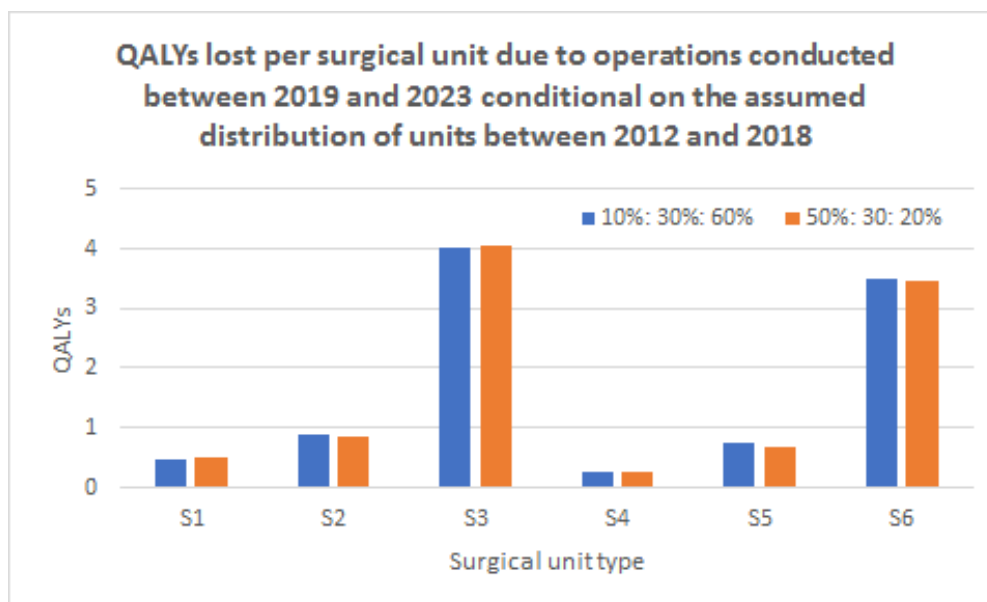
S1 and S4 are assumed to both follow IPG196 and guidance on keeping instruments moist

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.

Figure 18:   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

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 reusable instruments; the costs of autoclaving reusable 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,[210] and between £100,000 and £300,000 for highly specialised technologies.[217]

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 reusable 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	£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 £1,814,139 which would produce an expected 0.459 QALYs, thereby resulting in a cost per QALY gained of £4.0 million. For an S4 unit, the net costs were similar (£1,814,545) with fewer QALYs gained (0.275) resulting in a cost per QALY gained of £6.7 million. 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 gained 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 gained 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 gained of adhering to IPG196 would be in the region of £1.6 million.

3.8.2.4 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 19 when it is assumed that the P96 group are infectious, and in Figure 20 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.
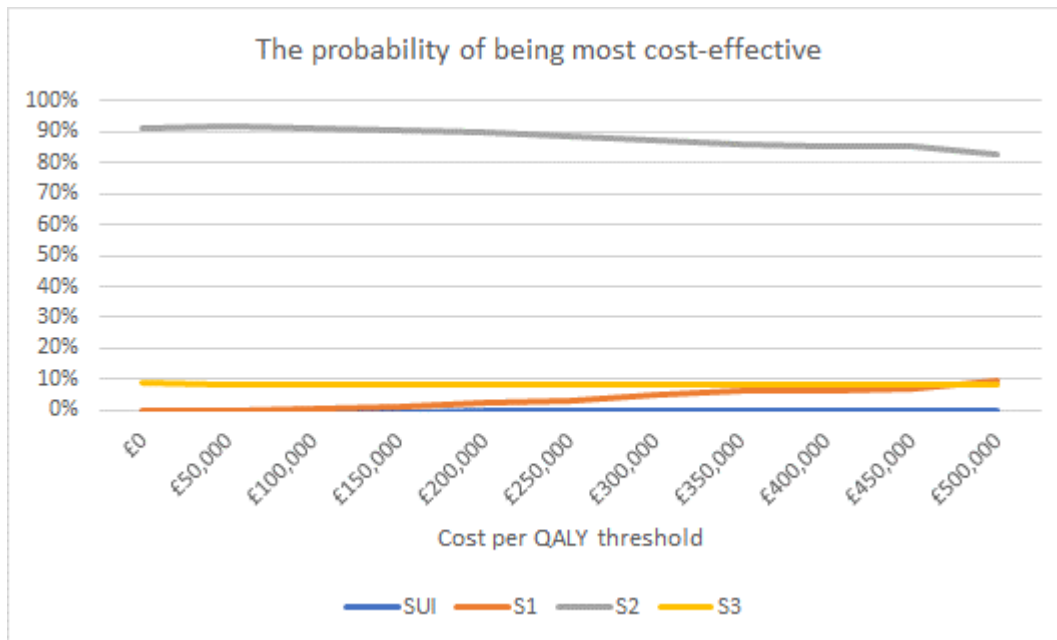
SUI: single-use instruments.

Figure 19: **The probabilities that S1, S2, S3 and single-use instruments are most cost-effective at a range of cost per QALY thresholds**
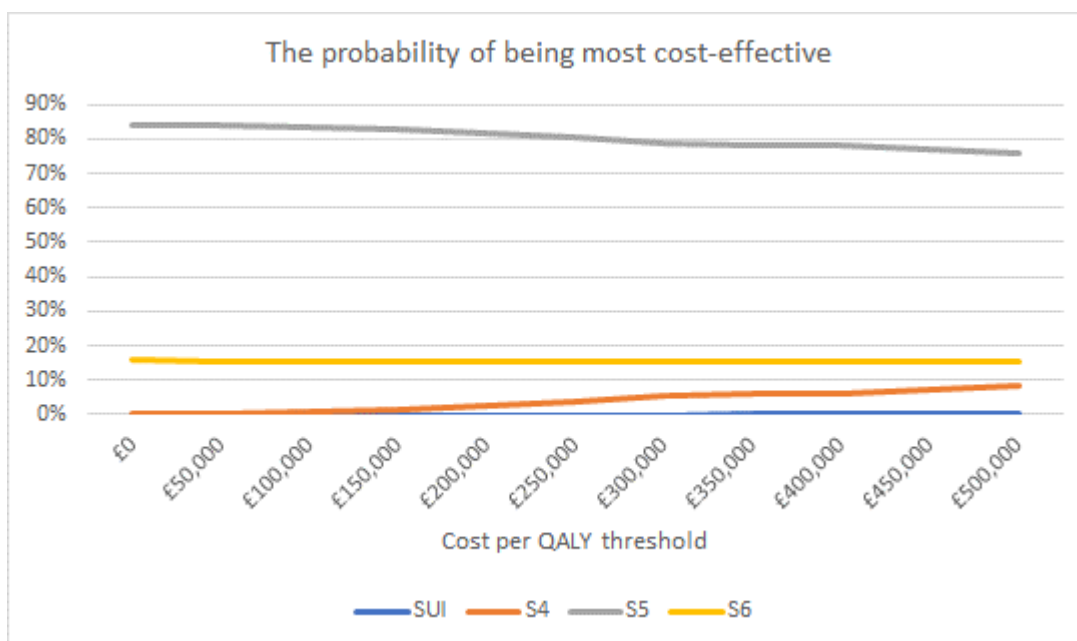
SUI: single-use instruments.

Figure 20: **The probabilities that S4, S5, S6 and single-use instruments are most cost-effective at a range of cost per QALY thresholds**

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

143

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 reusable 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 £2.9 million, whilst the ICER for an S4 unit became £4.9 million. 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 £2.4 million, whilst the ICER for an S5 unit became £2.9 million. 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) would be at cost-effective at cost per QALY thresholds of £30,000, £50,000, £100,000 and £300,000. These results are identical to the threshold cost of a cleaning solution which was 100% effective at removing CJD prions as both approaches (single-use instruments and cleaning solutions) are assumed to prohibit CJD infection via surgery.

The 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 reusable 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**

Unit Type	Assumptions	Cost per QALY threshold			
		£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 reusable instruments and completely effective cleaning solutions. The results are presented in

Table 30. The estimated costs of implementing IPG196 is estimated to be £750,000 which is greater than the threshold values provided in

Table 30.

Table 30:   Threshold analyses on the cost of implementing IPG196

Unit Type	Assumptions	Cost per QALY threshold			
		£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

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 marginally more QALYs lost when the recommendation that the P96 group are operated on using different instrument sets is removed and the P96 group is considered infectious on model entry. 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. Conversely, where the requirement for different instrument sets are removed given the assumption that the P96 group are not infectious on model entry, there are an additional 0.18 QALYs lost although marginally fewer deaths.

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 answer 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 with few recent clinical cases observed, CJD remains an iatrogenic risk in surgery, mainly from sporadic and genetic forms. Abnormal prion protein, using vCJD specific immunostaining, has also been detected in stored anonymised appendix tissue in cohorts of people considered not to have had significant exposure to the BSE epidemic, as reported in the recent Appendix III study. Studies using advanced detection assays also highlight wide vCJD accumulation 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 central nervous system (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 reports of observed cases of stCJD 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 were identified, but some animal studies using advanced detection methods indicate that infectious doses greater than 10^8 ID_{50s} 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 these 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 are limited in their potential to inform the model as these did not focus solely on high-risk procedures and do not compare the risk of additional procedures with control data for those who had not undergone an index high-risk procedure.

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. Based on the analyses run to inform this report the maximum number of cases of stCJD simulated that were infected between 2019 and 2023 was 47 across England, although the mean estimate was 2.36. Not adhering to keeping instruments moist had a higher mean number of cases (approximately 11), and a maximum amongst the simulations undertaken of 115. As such, keeping instruments moist should be undertaken wherever possible.

Whilst simplifications were made in the modelling process all decisions were made in consultation with the NICE advisory committee meaning that it is likely that most key aspects were included, but there remains the possibility that some were not identified by the committee and were therefore omitted. The use of a distribution for prevalence data based on prions in lymphoid tissue rather than just the central nervous system will overestimate the potential numbers used as prior distributions in the model runs used for calibration. However, this will not restrict the posterior distribution formed in the PSA that are consistent with observed information.

Given the large ICERs produced for the strategies modelled, the additional QALYs that would need to be gained through improved public perception of infection control would have to be very large to bring the ICERs for strategies below the thresholds commonly used by NICE. Similarly, the cost implications related to a potential future public inquiry, would need to be very large to alter the conclusions. Both the impact of public perception of infection control and any future inquiry would need to be weighted by the probability of a large number of cases being observed, which is expected to be small given the

expected number of potential stCJD deaths per unit (less than 0.08 (Table 27)) having kept instruments moist, noting that these cases would appear in the future and may be misdiagnosed.

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. However, 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 compared with not, and that all other ICERs are in excess of £1 million per QALY gained; these values are greater than the cost-effectiveness thresholds reported by NICE. Keeping instruments moist is also aligned with guidance from Department of Health and Social Care (2016).[197]

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. The current estimated cost of a single-use set is £425 thus it does not appear likely that costs can be reduced to the threshold levels. The additional cost per set of using a completely effective novel decontamination method is unknown and thus it is possible that standard NICE threshold levels can be achieved, for a commercially available agent that is proven to be completely effective at removing CJD prions.

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. Given that the estimated costs of installing a system to track surgical instruments is estimated to be £750,000 per unit, it is not expected that the prices would fall to the estimated threshold levels.

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.

Within this report the authors have presented ICERs on a number of strategies. Using a cost per QALY gained threshold of either £30,000 or £300,000 it would appear that the following strategy would be cost-effective: implementing measures to ensure that instruments are kept moist, which is estimated to increase health and save money. Strategies to prevent instrument migration, to use different instrument sets for the P96 group and the non-P96 group, or to use single-use instruments (at current prices) do not appear cost-effective. These results appear robust to assumptions regarding the current standard of

decontamination amongst surgical units. If a decontamination solution became commercially available that was proven to be perfectly effective at removing CJD prions it is possible that it could be cost-effective dependent on the acquisition price. The ultimate decision in terms of any strategy recommended is, however, the responsibility of NICE.

Strengths and limitations of the work

There has been a comprehensive review of published literature of factors associated with stCJD. The modelling work considered all aspects deemed important by the NICE advisory committee and was calibrated to the potential number of stCJD cases that have been observed between 2005-2018. Limitations with the work are primarily due to the lack of evidence on key parameters, in particular the number of stCJD cases that have actually occurred in England and which was used as the calibration target. Elicitation sessions were conducted to provide an estimation of possible values where there was little published evidence. Owing to the timescale of the project, it was only possible to elicit opinion from four experts, which may be a limitation. It is highlighted that the model focussed only on brain surgery, posterior eye surgery and neuroendoscopy based on the results of previous work

The approach was also selective on what to include in the model; these decisions were made in conjunction with the NICE advisory committee, but it is possible that pertinent costs or changes in utility have been omitted. It is acknowledged that gains that may be achieved in surgical procedures unrelated to CJD have not been included within the model.

A further limitation is that novel decontaminant cleaning solutions could not be included, although exploratory analyses were performed to estimate the maximum price that a completely effective decontaminant could command to be cost-effective.

Whilst the work undertaken in this report suggests that ensuring instruments are kept moist is the most cost-effective option, there remains a possibility of future stCJD cases given this strategy due to the uncertainty in the calibration targets and the estimated posterior distributions for each parameter. If there are multiple suspected or definite stCJD cases observed in the near future, then re-assessing the decision problem promptly would be required.

Recommendations for future work

Clinical trials in this rare disease are not a feasible recommendation for research, however, future investigations could take advantage of data from national surveillance programmes such as NCJDRSU and national Hospital Episode Statistics to conduct and publish well-designed studies to provide an indication of the number of CJD cases that could potentially be attributed to surgical transmission. Case-

control studies using appropriately-matched controls and ascertaining surgical exposures through use of medical records are likely to be the best feasible approach for identifying an association between surgery and CJD at a population level. Considering the methodological limitations and potential for bias in these studies it is important that the conduct of each individual case-control study is well-planned, pre-registered and rigorously executed.

The accuracy of the results produced within the model can be improved through better knowledge relating to the number of stCJD that have been observed in England. Historic data are unlikely to provide further insight, however, prospectively assessing whether patients diagnosed with alternative neurodegenerative diseases have a history of high-risk surgery could improve the ascertainment rates of stCJD; further autopsy studies of patients dying with dementia could also help to assess the extent of underdiagnoses of CJD.

It is acknowledged that surgical history data are gathered and assessed for patients with confirmed CJD by the NCJDRSU. Where family consent is given following the death of suspected, or confirmed, CJD cases, routine post-mortem analysis and publication of clinicopathological data may provide further understanding on the transmissibility and infectivity of CJD. Additionally, seeking in-life permission from those identified as being at risk of exposure to vCJD to perform an autopsy may also improve the rate of CJD confirmation. Furthermore, increasing the number of future and stored appendices tested for prions may allow an improved estimate of the prevalence of asymptomatic CJD within the UK population.

Further studies of the effectiveness of the wetting of surgical instruments in producing log reductions in prion load, and on reductions in transmission, would be informative to further validate understanding of the efficacy of current decontamination procedures. Currently, the information used in the model is indirect as it assumes that reductions associated with protein residue translate to reductions in the potential for transmission of vCJD.

The analyses undertaken did not exclude the possibility that a cleaning solution could be cost-effective providing it was sufficiently efficacious at removing CJD prions, priced appropriately, and was commercially available. Further research into proving the efficacy of such products may be worthwhile. It is noted that should a policy to prevent surgical instruments migrating between sets be put in place, then the threshold costs for a completely effective cleaning solution would be approximately half that contained in

Table 29, as the QALYs likely to be gained are approximately halved (

Table 27).

In the event of identification of multiple stCJD cases performing an urgent update of this review, with an amended calibration target is likely to be informative. .

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.

Data sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted following review..

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.
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.
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.
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.
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.
16. Advisory Committee on Dangerous Pathogens TSE Subgroup. Updated position statement on occurrence of vCJD and prevalence of infection in the UK; 2016.

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. *International Journal of Experimental Pathology* 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. *British Medical Journal* 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. *British Medical Journal* 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. 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.

89. 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.

90. 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. *British Medical Journal* 2009;338:b1442.

91. 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.

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

93. 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.

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

95. 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.

96. 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.

97. 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.

98. 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.

99. 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.

100. 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.

101. 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.

102. 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.

103. 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.

104. 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.

105. 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.

106. 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.

107. 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.

108. 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.

109. 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.

110. 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.

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

112. 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.

113. 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.

114. 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.

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

116. 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.

117. Zou W, Orru CD, Yuan J, Appleby BS, Li Y, Rarick J, *et al.* PrP[Sc] in the skin of CJD patients. *Prion* 2016;10:S29.

118. 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.

119. 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.

120. 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.

121. 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.

122. 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.

123. 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.

124. 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.

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

126. 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.

127. 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.

128. 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.

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

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

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

132. 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.

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

134. 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.

135. 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.

136. 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.

137. Ironside JW. Variant Creutzfeldt-Jakob disease. *Haemophilia* 2010;16 Suppl 5:175-80.
138. 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.
139. 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.
140. 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.
141. Makarava N, Savtchenko R, Alexeeva I, Rohwer RG, Baskakov IV. Fast and ultrasensitive method for quantitating prion infectivity titre. *Nature communications* 2012;3:741.
142. 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.
143. Ironside JW. Variant Creutzfeldt-Jakob disease: an update. *Folia Neuropathologica* 2012;50:50-6.
144. 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.
145. 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.
146. 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.
147. 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.
148. 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.
149. 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.
150. 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.
151. 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.
152. 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. *British Medical Journal open* 2013;3:e003400.

153. 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.

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

155. 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.

156. 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.

157. 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.

158. 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.

159. 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.

160. 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.

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

162. 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.

163. 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.

164. 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. 10188, p. S98-S.

165. 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.

166. 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#a 7 (Accessed 15.03.2018).

167. 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.

168.   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.

169.   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.

170.   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* 2016;11:e0146833.

171.   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.

172.   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.

173.   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.

174.   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.

175.   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.

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

177.   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.

178.   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.

179.   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.

180.   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.

181.   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.

182.   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.

183. 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.

184. 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* 2005:923-7.

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

186. 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.

187. 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.

188. 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.

189. 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.

190. 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.

191. 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.

192. 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.

193. 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.

194. 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.

195. 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.

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

197. 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.

198. 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.

199. 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.

200. 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.

201. 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.

202. 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.

203. 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.

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

205. 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).

206. 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.

207. 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.

208. National Institute for Health and Care Excellence. Patient safety and reduction of risk of transmission of Creutzfeldt-Jakob (CJD) via interventional procedures. 2006.

209. 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.

210. 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).

211. 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.

212. Office for National Statistics. National life tables: United Kingdom. 2017.

213. Curtis LA, Burns A. Unit Costs of Health and Social Care 2017. University of Kent; 2017.

214. Curtis L. Unit Costs of Health & Social Care 2014. University of Kent.; 2014.

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

216. 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.

217. National Institute for Health and Care Excellence. Interim Process and Methods of the Highly Specialised Technologies Programme Updated to reflect 2017 changes. 2017.

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 from 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 from 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 probability judgements for Parameter 1 as shown in Table 31.

Table 31: The probability judgements for each expert 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. Agreed percentiles for Parameter 1 are provided in Table 32.

Table 32: Consensus percentiles for Parameter 1

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. This is shown in Figure 21. 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 distribution for Parameter 1 are shown in Table 33.

Figure 21:   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

Table 33:   Percentiles from the fitted distribution for Parameter 1

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 probability judgements for Parameter 2 as shown in Table 34.

Table 34:   The probability judgements for each expert 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.[2] 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.

Table 35:   Consensus percentiles for Parameter 1

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 as is shown in Figure 22. 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 distribution fitted to Parameter 2 are provided in Table 36.

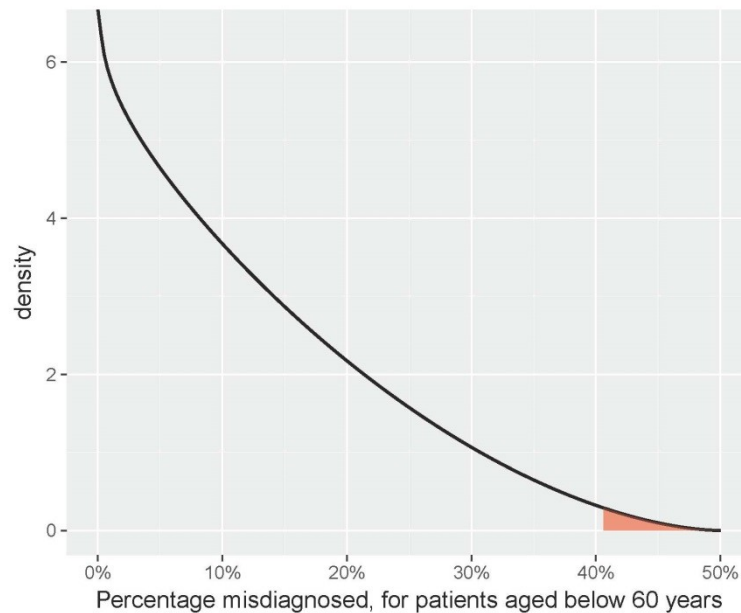**Figure 22:** **The distribution chosen to represent the experts' consensus judgements for Parameter 2: the percentage of patients, aged 80 and above, whose death was due to CJD, that are misdiagnosed as having died from another neurodegenerative disease, since 2005**

Table 36: **Percentiles from the fitted distribution for Parameter 2**

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 2 (the percentages for the two age groups: below 60, and 80 and above). Its implied distribution can be obtained by simulation and is shown in Figure 23. Percentiles of this distribution are estimated by simulation and are provided in Table 37.
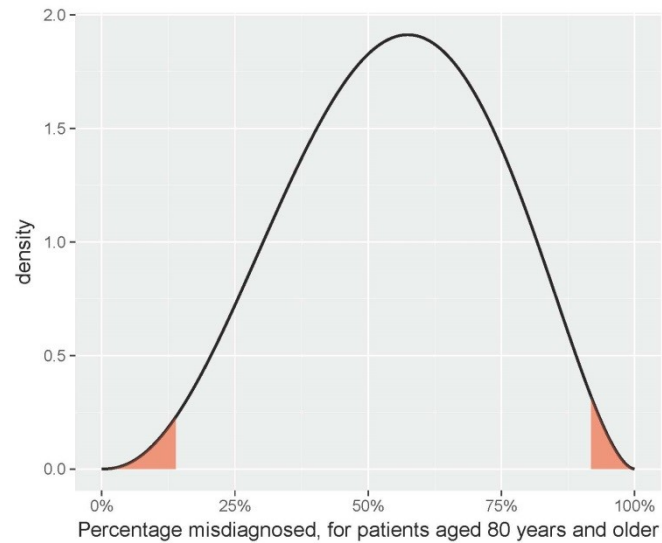
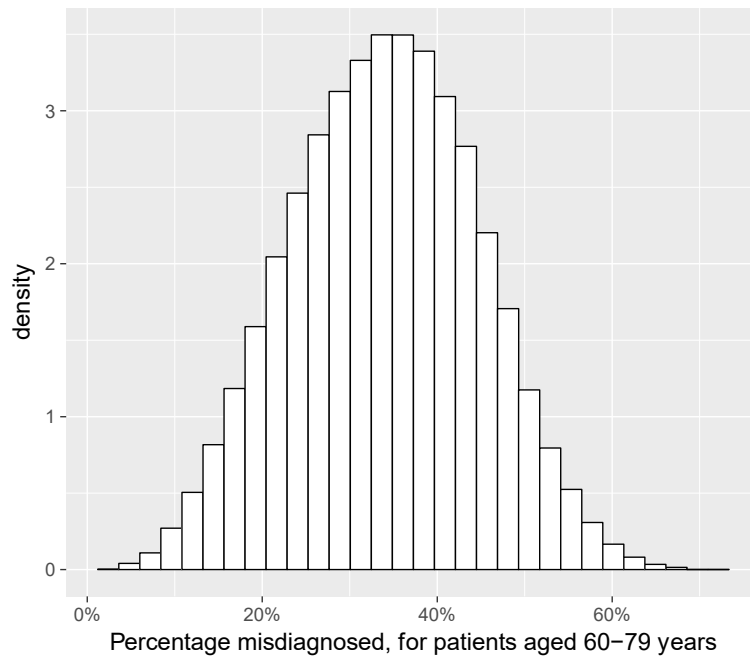**Figure 23:** **The distribution chosen to represent the experts' consensus judgements for Parameter 3: the percentage of patients, aged between 60 and 79 years, whose death was due to CJD, that are misdiagnosed as having died from another neurodegenerative disease, since 2005**

Table 37: **Simulated percentiles from Parameter 3**

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. These values are provided in Table 38.

Table 38: The probability judgements for each expert related to incubation periods

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. These intervals are provided in Table 39.

Table 39: Consensus quartile intervals related to incubation periods

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 estimated

distribution shown in Figure 24. 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.
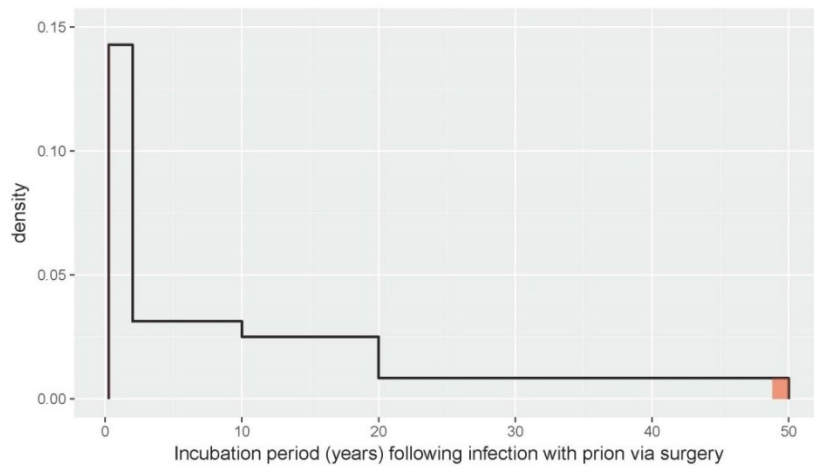
Figure 24: **An estimate of the distribution of incubation periods for all patients the distribution of incubation period in years, in all patients, following infection with prion via surgery (posterior eye, brain, neuroendoscopy, and intradural spinal surgery), genotype unknown for each patient**

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 as shown in Table 40 and in Figure 25. The red shaded region indicates that, given this choice of distribution, 98% of incubation periods will lie between 0.37 years and 48 years.

**Table 40:** **An illustrative alternative distribution of patients between incubation intervals**

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%
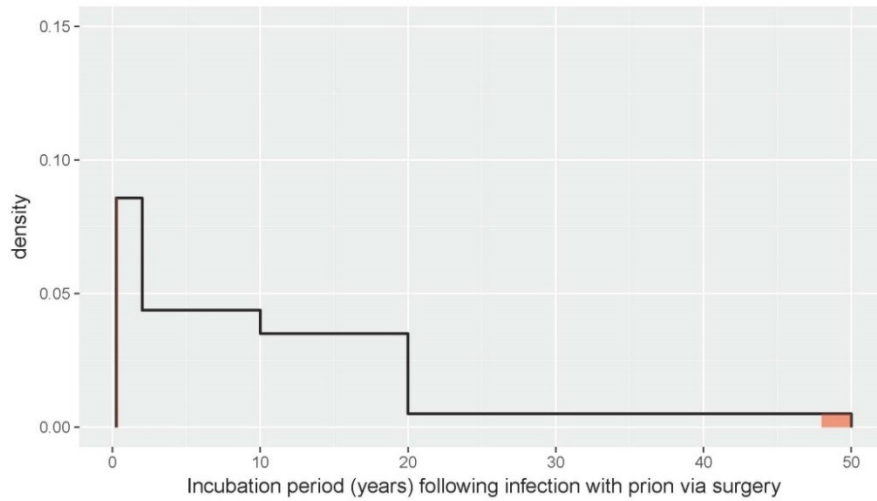
Figure 25: **Alternative the distribution of incubation periods, constructed by perturbing the proportions of the population in each interval from the central estimates.**

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 26. 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 distribution are shown in Table 41. 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.
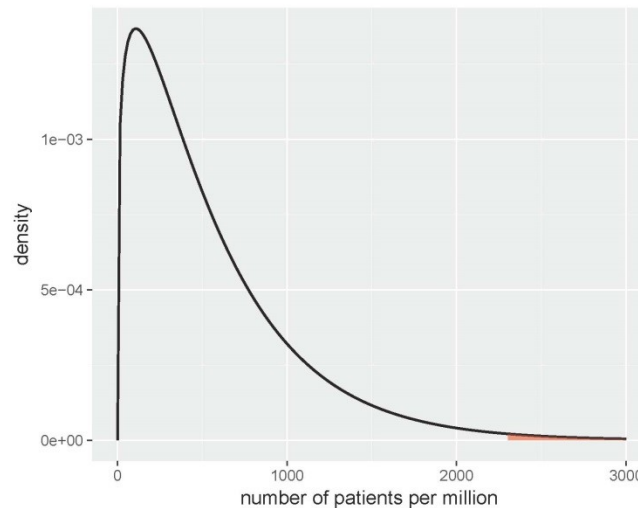

Figure 26:   **The distribution chosen to represent the experts' consensus judgements for the number of patients per million with CJD-prions in central nervous system tissue**

Table 41:   **Percentiles from the fitted distribution for the prevalence of CJD in the central nervous system**

1st	5th	95th	99th
12	46	1547	2304

Appendix 5:   The operations considered to be at high risk

The operations considered to be high-risk are contained in Table 42 to Table 46, conditional on the type of operation and expected prognosis.

Table 42:   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

Table 43: **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

Table 44:   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

Table 45:   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

Table 46: **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

The assumed age profiles for patients undergoing brain surgery (conditional on survival category), posterior eye surgery and neuroendoscopy are contained in Figure 27 to Figure 31.
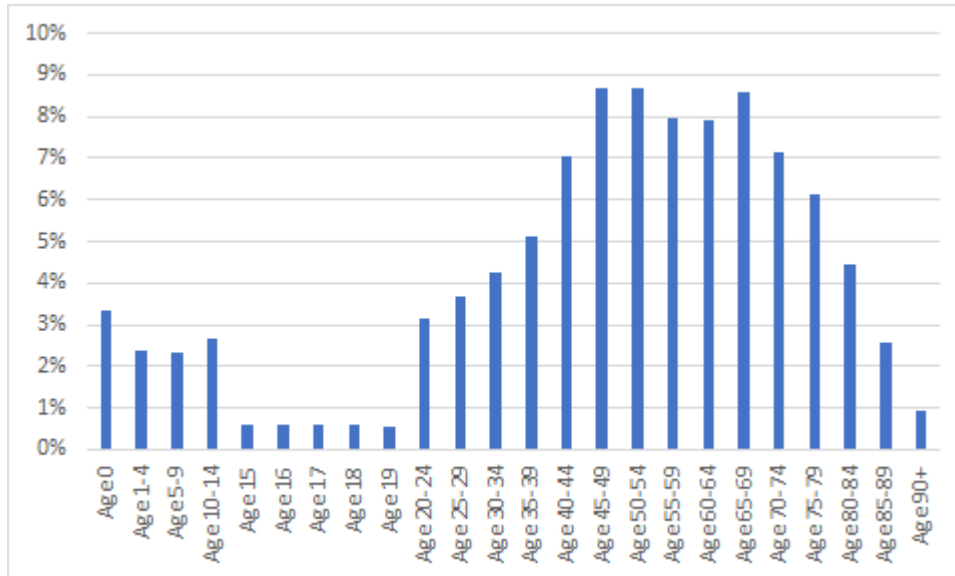

Figure 27:   The assumed age profile of patients undergoing brain surgery who are assumed to have normal life expectancy
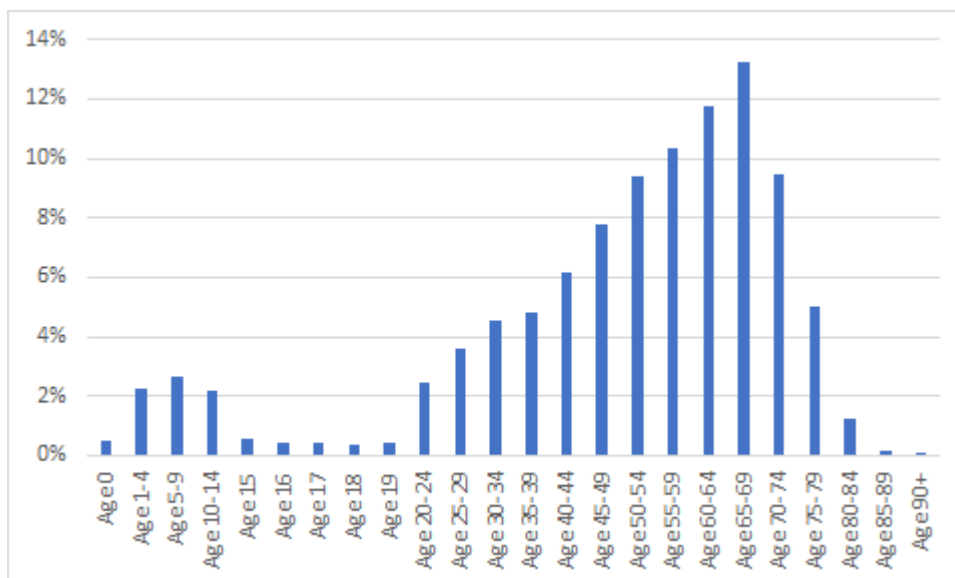

Figure 28:   The assumed age profile of patients undergoing brain surgery assumed to die at 18 months
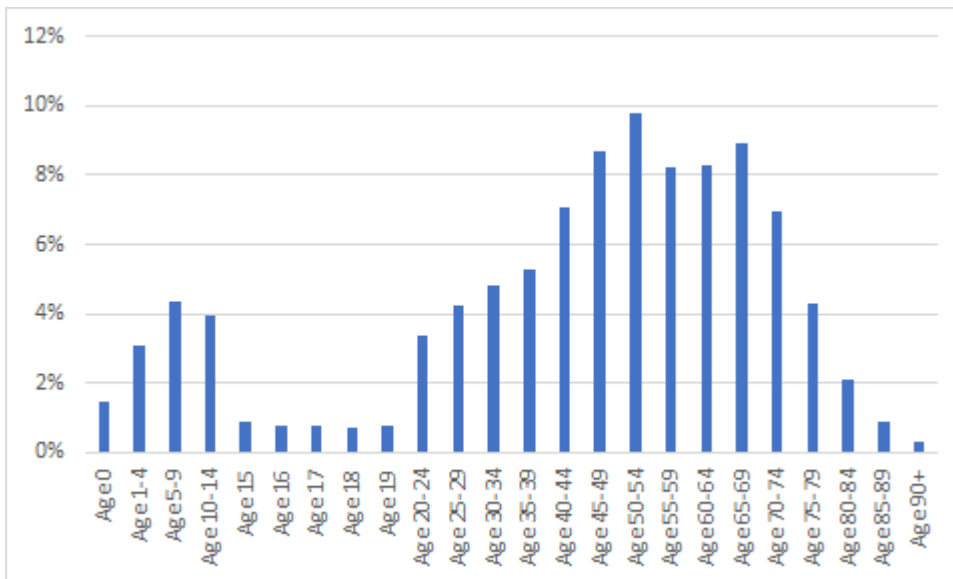
Figure 29: The assumed age profile of patients undergoing brain surgery who are assumed to have a 50% chance of death at 18 months otherwise who are assumed to have normal life expectancy
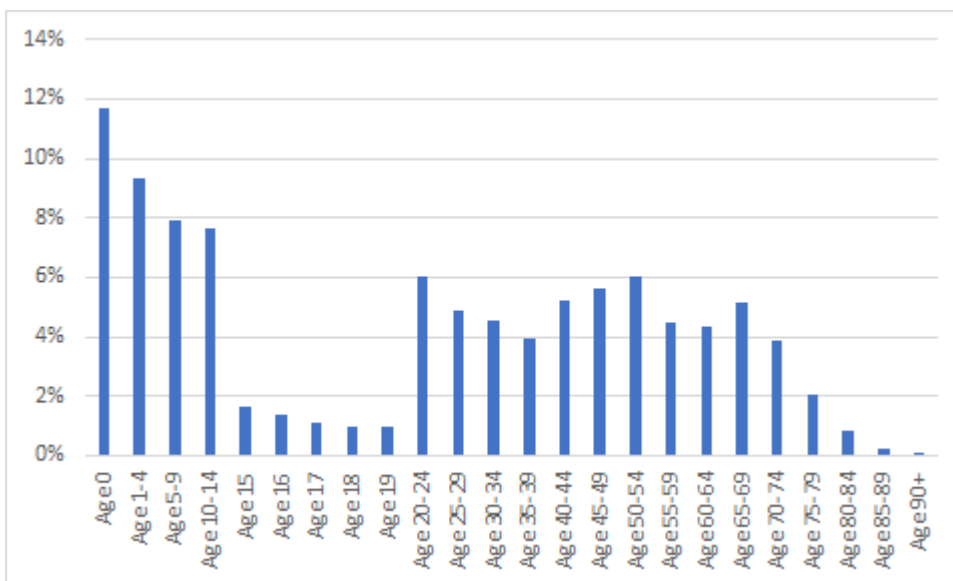

Figure 30: The assumed age profile of patients undergoing neuroendoscopy
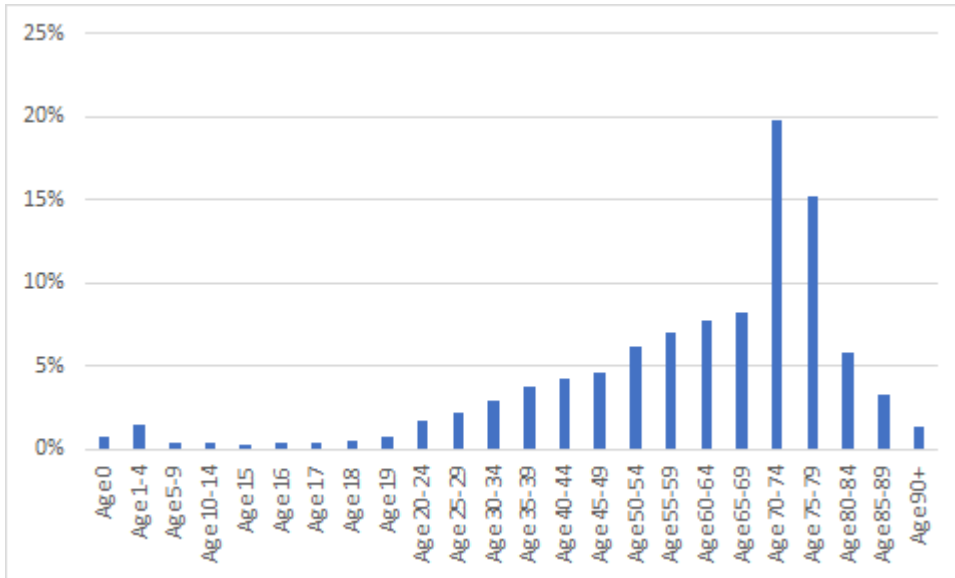
Figure 31: **The assumed age profile of patients undergoing posterior eye operations**

Appendix 7: The calibration methodology

Notation

We define the following

- θ: the simulation model inputs. The true values of these inputs are uncertain; following various expert elicitation sessions, we have constructed a prior distribution $p(\theta)$ for θ.

- $T^{(i)}$ - the number of transmissions of CJD via surgery that result in clinical symptoms (CJDcs) in age category i, over the period 2005-2018. The age categories are $i = 1$: 59 years and below; $i = 2$: 60-79 years; $i = 3$: 80 years and above. We write $T = (T^{(1)}, T^{(2)}, T^{(3)})$.

- $R^{(i)}$ - the number of transmissions of CJDcs, in age category i, over the period 2005-2018, that resulted in deaths *recorded* as being due to CJD. Note that for each i, we have $R^{(i)} \leq T^{(i)}$.

- C: 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 C is the observation of the event that

$$0 \leq R^{(1)} + R^{(2)} + R^{(3)} \leq 15.$$

- $\phi^{(i)}$: the percentage of patients, in age category i, 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' $p(\phi^{(i)}|C)$.

We suppose that

$$R^{(i)}|T^{(i)}, \phi^{(i)} \sim Binomial(T^{(i)}, 1 - \phi^{(i)}).$$

We collect the $\phi^{(i)}$ parameters into vector ϕ and write

$$\phi = (\phi^{(1)}, \phi^{(2)}, \phi^{(3)}).$$

- $M^{(i)}$ the *maximum* number of transmissions of CJDcs, in age category i, over the period 2005-2018, that resulted in deaths *recorded* as being due to CJD. We have

$$M^{(1)} + M^{(2)} + M^{(3)} = 15,$$

and that

$$R^{(i)} \leq M^{(i)},$$

for $i = 1,2,3$. Defining

$$M = (M^{(1)}, M^{(2)}, M^{(3)}),$$

we make the assumption that

$$M|C \sim Multinomial\left(15; \frac{1}{3}, \frac{1}{3}, \frac{1}{3}\right),$$

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.

- $S = (s_1, \dots, s_{27})$: a vector of scenario values for each surgical centre. Two separate analyses are performed. In the first, each s_i is coded as an integer from 1-3 inclusive, and in the second, each s_i is coded as an integer from 4-6 inclusive. These correspond to the 6 scenarios S1-S6 defined in Section 3.5.1. (The P96 group are infectious from birth in scenarios S1-S3 only).

-

- Y: 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 $Y_1, \dots, Y_N$ from the probability distribution of $p(Y|C)$, from which we can provide an estimate of the expected value $E(Y|C)$. This distribution can be expressed as

$$p(Y|C) = \int p(Y|C, \theta) p(\theta|C) d\theta.$$

Hence, we can obtain a sample $Y_1, \dots, Y_N$ by obtaining a sample $\theta_1, \dots, \theta_N$ from $p(\theta|C)$, and then sampling Y_i from $p(Y|\theta_i, C)$. In essence, we are

1. calibrating the simulation model by updating the model inputs from $p(\theta)$ to $p(\theta|C)$: we update what we know about the model inputs in light of the calibration data C;

2. running the simulation model forward to predict Y, at input values θ sampled from $p(\theta|C)$: input values identified to be consistent with the calibration data C.

Sampling from $p(\theta|C)$

The method we use to sample from $p(\theta|C)$ 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 C given an input θ, but no *formula* can be obtained for the likelihood function $p(C|\theta)$. The basic ABC algorithm is as follows.

1. Generate one random value θ^* from the elicited prior $p(\theta)$

2. Given the model input θ^*, run the model, and observe whether the event C has occured within the model simulation.

3. If the event C has occurred within the model simulation, accept θ^* as a valid draw from $p(\theta|C)$. Otherwise, reject, and return to step 1. Repeat until a candidate value θ^* is accepted.

The process is repeated as many times as required to produce a sample $\theta_1, \dots, \theta_N$ from $p(\theta|C)$. For each accepted θ value, the model can be run forward to produce the desired sample $Y_1, \dots, Y_N$. 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 $T^{(1)}, T^{(2)}, T^{(3)}$. To determine from these whether the event C has occurred, we additionally sample M, S and ϕ, so that we are in effect sampling from the joint distribution $p(\theta, M, S, \phi|C)$. We write

$$p(\theta, M, S, \phi|C) = p(M, \phi|C)p(\theta, S|M, \phi, C).$$

and we assume

$$p(M, \phi|C) = p(M|C)p(\phi|C).$$

We have the multinomial distribution for $M|C$, and the elicited distribution for $\phi|C$, from which we can simulate values easily.

Note that

$$p(\theta, S|M, \phi, C) = p(\theta, S|M, \phi),$$

since given $M = (M^{(1)}, M^{(2)}, M^{(3)})$, we already know C: the total of $M^{(1)}, M^{(2)}, M^{(3)}$.

The ABC algorithm is then, in effect, used to sample from $p(\theta, S|M, \phi)$, where the 'prior' distribution is $p(\theta, S|\phi)$, and we assume independence between θ, S and ϕ:

$$p(\theta, S|\phi) = p(\theta|\phi)p(S|\phi) = p(\theta)P(S)$$

1. Sample θ^* from $p(\theta|\phi) = p(\theta)$.

2. Sample S^* from $p(S|\phi) = p(S)$.

3. Run the simulation model to generate outputs T

4. Given the outputs T, sample R, where

$$R^{(i)}|T^{(i)}, \phi^{(i)} \sim Binomial(T^{(i)}, 1 - \phi^{(i)}).$$

5. Observe whether, within the simulation model, the event

$$R^{(i)} \le M^{(i)},$$

for $i = 1,2,3$ has occurred. If it has, we accept θ^*, S^* as a sample from $p(\theta, S|M, \phi)$. Otherwise, we reject and return to step 1.

Estimation of $E(Y|C)$

Applying the ABC algorithm would give a sample $\theta^{(1)}, \dots, \theta^{(M)}$. Running the simulation model forward at these inputs only, we obtain an independent sample $Y^{(1)}, \dots, Y^{(M)}$, from the distribution of $p(Y|C)$, from which we can estimate $E(Y|C)$ via

$$\overline{Y} = \frac{1}{M}\sum_{i=1}^{M} Y^{(i)},$$

and an approximate 95% confidence interval for $E(Y|C)$ can be calculated as $\overline{Y} \pm 2\sqrt{S_Y^2/M}$, with

$$S_Y^2 = \frac{1}{M-1}\sum_{i=1}^{M}(Y^{(i)} - \overline{Y})^2.$$

We actually use a slightly different estimator for $E(Y|C)$ 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 C 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 $T^{(1)} = 65$ 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 occurring would be of the order of $1/(10^9)$; 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

$$\gamma = 10^{\theta_M} \times \theta_R \times \theta_P,$$

where θ_M 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; θ_R is the residual mass on an instrument × (1 − the proportion of residual mass transferred to the patient); θ_P is the proportion of asymptomatic individuals with CJD prions in their tissue.

2000 parameter sets $\theta_1, \dots, \theta_{2000}$ were drawn from the appropriate distributions, $\gamma_1, \dots, \gamma_{2000}$ 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 $\gamma > e^{12}$, 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 R.

For $\gamma < e^{12}$, it would still be possible for the candidate θ to be rejected. In other cases, we can be certain that a candidate value θ^* will be rejected, based on a 'partial' simulation run: we do not have to simulate the full calibration output R. We used the following approach.

1. Generate a candidate value θ^*, for which $\gamma < e^{12}$.

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 θ^* and return to step 1.

4. Continue simulating random number streams in batches: reject θ^* 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 $\overline{Y}$, we can instead calculate a weight w_i: the *probability* that the model will simulate the event T to have occurred. The estimate for $E(Y|C)$ will then be of the form

$$\hat{E}(Y|C) = \sum_{i=1}^{509} \widetilde{w}_i \, Y_i,$$

with

$$\widetilde{w}_i = \frac{w_i}{\sum_{i=1}^{509} w_i}.$$

This approach instead generates (weighted) samples directly from the marginal distribution $p(\theta|T)$, rather than joint samples from $p(\theta, M, S, \phi|T)$. Each weight w_i is estimated using the following Monte Carlo procedure. For each candidate value θ_i, 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 S can then be selected.

For $k = 1, \dots, 100000$:

1. Randomly sample S from its prior distribution, and denote this value by S_k. Given the model simulation run for input value θ_j and scenario set S_k, extract the number of transmissions of CJDcs in each age band. Denote these by $T_{j,k}^{(i)}$ for $i = 1,2,3$.

2. Randomly sample M from its multinomial distribution. Denote the sampled values by
$$M_k^{(1)}, M_k^{(2)}, M_k^{(3)}$$

3. Randomly sample $\phi^{(1)}, \phi^{(2)}, \phi^{(3)}$ from the three elicited prior distributions. Denote these values by $\phi_k^{(1)}, \phi_k^{(2)}, \phi_k^{(3)}$

4. Given the sampled values in step 2, we now have
$$R^{(i)}|T_{j,k}^{(i)}, \phi_k^{(i)} \sim Binomial(T_{j,k}^{(i)}, 1 - \phi_k^{(i)}).$$

5. Compute, from the corresponding binomial distributions in step 3,
$$w_{j,k} = \prod_{i=1}^{3} Pr(R^{(i)} \leq M_k^{(i)})$$

6. The weight w_i is estimated as
$$\hat{w}_j = \frac{1}{100000} \sum_{k=1}^{100000} w_{j,k}$$

Implementation

We started with a sample of 2000 parameter values. Applying the screening based on the calculated $\gamma_1, \dots \gamma_{2000}$ values, we obtained a set $\theta_1, \dots, \theta_{509}$ that were not rejected. The weighted ABC algorithm was used to estimate $E(Y|C)$, 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 $\overline{Y}$ would be based on 119 and 134 model runs respectively.