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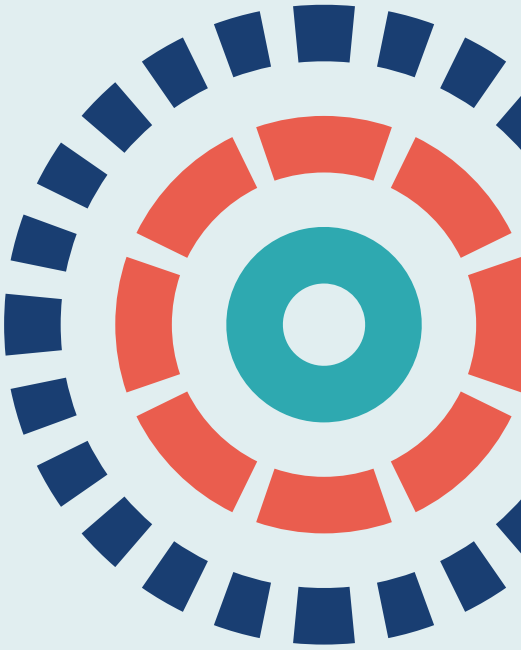
Matt Stevenson, Lesley Uttley, Jeremy E Oakley, Christopher Carroll, Stephen E Chick and Ruth Wong



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Interventions to reduce the risk of surgically transmitted Creutzfeldt–Jakob disease: a cost-effective modelling review

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This report

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Abstract

Interventions to reduce the risk of surgically transmitted Creutzfeldt–Jakob disease: a cost-effective modelling review

Matt Stevenson,[1*] Lesley Uttley,[1] Jeremy E Oakley,[2] Christopher Carroll,[1] Stephen E Chick[3] and Ruth Wong[1]

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Background: Creutzfeldt–Jakob disease is a fatal neurological disease caused by abnormal infectious proteins called prions. Prions that are present on surgical instruments cannot be completely deactivated; therefore, patients who are subsequently operated on using these instruments may become infected. This can result in surgically transmitted Creutzfeldt–Jakob disease.

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 surgically transmitted Creutzfeldt–Jakob disease.

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 to produce guidance, provided an additional source of information. A mathematical model was updated focusing on brain and posterior eye surgery and neuroendoscopy. The model simulated both patients and instrument sets. Assuming that there were potentially 15 cases of surgically transmitted Creutzfeldt–Jakob disease 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 National Institute for Health and Care Excellence reference case. The 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: A total of 169 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 surgically transmitted Creutzfeldt–Jakob disease as another neurodegenerative disease, and assuming that all patients were susceptible to infection. Keeping instruments moist was estimated to reduce the risk of surgically transmitted Creutzfeldt–Jakob disease cases and associated costs. Based on probabilistic sensitivity analyses, keeping instruments moist was estimated to on average result in 2.36 (range 0–47) surgically transmitted Creutzfeldt–Jakob disease cases (across England) caused by infection occurring between 2019 and 2023. Prohibiting set migration or employing single-use instruments reduced the estimated risk of surgically transmitted Creutzfeldt–Jakob disease 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 £1M. 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 Creutzfeldt–Jakob disease 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 surgically transmitted Creutzfeldt–Jakob disease cases that may have occurred between 2005 and 2018.

Conclusions: Keeping instruments moist is estimated to reduce the risk of surgically transmitted Creutzfeldt–Jakob disease cases and associated costs. Further surgical management strategies can reduce the risks of surgically transmitted Creutzfeldt–Jakob disease but have considerable associated costs.

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Contents

List of tables xi

List of figures xv

Glossary xvii

List of abbreviations xix

Plain English summary xxi

Scientific summary xxiii

Chapter 1 Introduction 1
Purpose of the research 2
Research objectives 3

Chapter 2 Clinical evidence 5
Methods for systematic reviews 5
Eligibility criteria 5
Search strategy 6
Literature search results 9
The incidence of Creutzfeldt–Jakob disease and the prevalence of Creutzfeldt–Jakob disease-related prions in humans in the UK 9
The incidence of Creutzfeldt–Jakob disease 10
The estimated prevalence of subclinical variant Creutzfeldt–Jakob disease in the UK 17
Discussion of the incidence and prevalence of Creutzfeldt–Jakob disease 19
The risk of Creutzfeldt–Jakob disease transmission via surgery 20
Observational studies implicating surgery in Creutzfeldt–Jakob disease 20
Discussion/summary of risk of Creutzfeldt–Jakob disease transmission via surgery 24
Incubation periods of acquired transmissible spongiform encephalopathys 25
Studies of incubation periods 25
Discussion/summary of incubation data 29
The infectivity of Creutzfeldt–Jakob disease 29
Studies discussing the infectivity of Creutzfeldt–Jakob disease 30
Discussion/summary of infectivity of Creutzfeldt–Jakob disease 33
The evidence on the efficacy of prion decontamination procedures for surgical instruments 34
Decontamination studies 34
Residual mass/protein studies 47
Discussion/summary of studies on residual mass and decontamination 55
The evidence that instruments used for high-risk procedures remain in their original sets after decontamination 56
Studies relating to evidence that instruments used for high-risk procedures remain in their original sets after decontamination 56
Discussion/summary of evidence on set-keeping for high-risk procedures 58

The evidence for complication rates of single-use compared with reusable instruments for high-risk procedures 58
Studies relating to evidence for complication rates of single-use compared with reusable instruments for high-risk procedures 58
Discussion/summary of complication rates for single-use versus reusable instruments 58
The evidence for the likelihood of future surgery for a patient undergoing high-risk procedures 58
Studies relating to evidence for the likelihood of future surgery for a patient undergoing high-risk procedures 59
Discussion/summary of risk of future surgery in high-risk procedures 60

Chapter 3 Cost-effectiveness **61**
Background 61
Elicitation 61
Cost-effectiveness literature review 62
The conceptual model 62
Key model parameters 65
Parameters relating to the probability and the mass of prions being transferred to surgical instruments 65
Parameters relating to the decontamination of surgical instruments 68
Parameters relating to instrument migration, costs and safety 71
Parameters relating to the probability of infection, the incubation time and consequences if clinical symptoms appear 73
Parameters relating to the numbers of operations that are considered to be high-risk and the characteristics of patients undergoing these operations 76
Calibration targets 77
The observed number of surgically transmitted Creutzfeldt–Jakob disease cases between 2005 and 2018 and the potentially unobserved number of surgically transmitted Creutzfeldt–Jakob disease cases 77
Categorisation of surgical units, establishing probabilistic sensitivity analysis configurations that are plausible and generating likelihood functions for plausible probabilistic sensitivity analysis configurations 79
Categorisation of surgical units 79
Employing a heuristic to rule out probabilistic sensitivity analysis configurations that would produce implausible results 79
Running further analyses to remove probabilistic sensitivity analysis configurations that are potentially consistent with the observed data but generate an implausible number of transmissions when run through the model 80
Calculating the likelihood of each plausible probabilistic sensitivity analysis configuration being consistent with the observed data 80
Generating estimates of the expected numbers of future surgically transmitted Creutzfeldt–Jakob disease, life-years lost and quality-adjusted life-years lost 81
Exploring the uncertainty in the results produced within the base-case analyses 81
Exploring the probability that each type of surgical unit was the most cost-effective 81
Exploring the changes in the results produced with alternative assumptions relating to the assumed distribution of surgical units between the assumed decontamination levels 82
Strategies modelled 82
Epidemiological results 82
Base-case results 83
Interpretation of the base-case results 83
Scenario analyses using the base case as the foundation 84
Scenario analyses using an alternative distribution of surgical unit compliance with following IPG196 and keeping instruments moist 85

Cost-effectiveness results 86
Parameter values within the base-case cost-effectiveness results 86
The base-case cost-effectiveness of strategies for reducing the likelihood of surgically transmitted Creutzfeldt–Jakob disease 87
Sensitivity analyses performed on the base-case results 88
Threshold analyses on the costs of single-use sets or a completely effective cleaning solution 89
Threshold analyses on the costs of adhering to IPG196 89
Estimating the cost-effectiveness of removing the need for the P96 group to be operated on with separate instrument sets 90

Chapter 4 Discussion and conclusions **91**
Strengths and limitations of the work 93
Recommendations for future work 93

Acknowledgements **95**

References **97**

Appendix 1 Clinical effectiveness search strategies **113**

Appendix 2 Cost-effectiveness search strategies **121**

Appendix 3 Excluded studies from the clinical reviews with reasons for exclusion **123**

Appendix 4 Elicitation exercise relating to epidemiological parameters (conducted 18 January 2018) **125**

Appendix 5 The assumed age profile of patients receiving each operation **133**

Appendix 6 The operations considered to be at high risk **137**

Appendix 7 The calibration methodology **145**

List of tables

TABLE 1 Eligibility criteria for each review question 5

TABLE 2 Global estimations of CJD incidence from studies published in 2005 or after (ordered by date, then alphabetically) 11

TABLE 3 Results of the Appendix III study 18

TABLE 4 Studies estimating the prevalence of CJD from peripheral tissue samples, published after 2005 19

TABLE 5 Studies reporting links between CJD and surgery published between 2005 and 2017 20

TABLE 6 Characteristics of included studies for incubation periods, ordered alphabetically 25

TABLE 7 Reported number of cases of iCJD (worldwide and UK) and incubation periods (mean and range) 26

TABLE 8 UK-only data for iCJD incubation periods (reported or calculated by the reviewer in years) 27

TABLE 9 Mean incubation periods by genotype for iCJD because of dura mater grafts 28

TABLE 10 Mean incubation periods reported from included studies by genotype for iCJD caused by human growth hormone 28

TABLE 11 Estimated infectious titre of human tissue by surgical procedure in NICE IPG196 30

TABLE 12 Characteristics of studies reporting log-reductions in prion contamination on steel surfaces after autoclaving with and without other processes 35

TABLE 13 Results of studies reporting log-reductions in prion contamination on steel surfaces after autoclaving with and without other processes 36

TABLE 14 Studies reporting log-reductions in prion contamination on steel surfaces after decontamination processes other than autoclaving 37

TABLE 15 Results of studies reporting log-reductions in prion contamination on steel surfaces by processes other than autoclaving 39

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 42

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 43

TABLE 18 Study characteristics and results 48

TABLE 19 Study characteristics and results 51

TABLE 20 Characteristics of included studies 56

TABLE 21 Findings of included studies 57

TABLE 22 Characteristics of included studies 59

TABLE 23 Findings of Bird *et al.* on subsequent event rates for selected neurosurgical procedures for any patient within the time period 1993–2001 60

TABLE 24 Information relating to the mass transferred to a patient, mass washed off in subsequent decontamination cycles and mass harvested from a patient 68

TABLE 25 The number of operations classified as high-risk by the NICE committee (HES data) 78

TABLE 26 Base-case results per surgical unit 83

TABLE 27 Results of the scenario analyses per surgical unit using the base case as the foundation 85

TABLE 28 Parameter values used within the cost-effectiveness analyses 86

TABLE 29 Threshold analyses on the cost of single-use sets (including disposal costs) and a completely effective cleaning solution 90

TABLE 30 Threshold analyses on the cost of implementing IPG196 90

TABLE 31 The probability judgements for each expert for parameter 1 126

TABLE 32 Consensus percentiles for parameter 1 126

TABLE 33 Percentiles from the fitted distribution for parameter 1 127

TABLE 34 The probability judgements for each expert for parameter 2 127

TABLE 35 Consensus percentiles for parameter 1 127

TABLE 36 Percentiles from the fitted distribution for parameter 2 128

TABLE 37 Simulated percentiles from parameter 3 129

TABLE 38 The probability judgements for each expert related to incubation periods 129

TABLE 39 Consensus quartile intervals related to incubation periods 129

TABLE 40 An illustrative alternative distribution of patients between incubation intervals 130

TABLE 41 Percentiles from the fitted distribution for the prevalence of CJD in the central nervous system **131**

TABLE 42 Brain operations: patients modelled to die within 12 months **137**

TABLE 43 Brain operations: patients modelled to have a 50% chance of death within 12 months, otherwise normal life expectancy **138**

TABLE 44 Brain operations: patients modelled to have normal life expectancy **138**

TABLE 45 Neuroendoscopy operations **143**

TABLE 46 Posterior eye operations **143**

List of figures

FIGURE 1 The PRISMA flow diagram of studies included in systematic reviews 10

FIGURE 2 Deaths attributed to definite or probable CJD in the UK, using data from the NCJDRSU, between 1996 and 2017 12

FIGURE 3 Age-specific mortality rates from sCJD in the UK 1979–2016: reproduced from NCJDRSU Annual Report 2016 15

FIGURE 4 The conceptual model relating to the infection process 63

FIGURE 5 The conceptual model relating to patient outcome post infection 64

FIGURE 6 The prevalence of CJD prions within central nervous tissue 65

FIGURE 7 The proportion of residual mass transferred to a patient 67

FIGURE 8 The proportion of residual mass removed in a subsequent decontamination cycle 67

FIGURE 9 The reduction in infectivity in the first autoclaving cycle 69

FIGURE 10 The reduction in infectivity in the first detergent cycle 69

FIGURE 11 The proportion of autoclave cycle 1 log-reduction achieved by cycles 2 and 3 70

FIGURE 12 The proportion of detergent cycle 1 log-reduction achieved by cycle 2 70

FIGURE 13 The proportion of the incubation period during which the patient is infectious 74

FIGURE 14 The proportion of patients < 60 years with clinical CJD symptoms who are diagnosed with another neurodegenerative disease 76

FIGURE 15 The proportion of patients over 80 years with clinical CJD symptoms who are diagnosed with another neurodegenerative disease 76

FIGURE 16 The simulated proportion of patients aged between 60 and 80 years inclusive with clinical CJD symptoms who are diagnosed with another neurodegenerative disease 77

FIGURE 17 The likelihoods of the PSA configurations being compatible with the observed data (curves are drawn on top of each other) 81

FIGURE 18 Comparing the QALYs lost within the base case and when using an alternative assumption related to the distribution of surgical units following IPG196 and in keeping instruments moist 85

FIGURE 19 The probabilities that S1, S2, S3 and single-use instruments are the most cost-effective at a range of cost-per-QALY thresholds 88

FIGURE 20 The probabilities that S4, S5, S6 and single-use instruments are the most cost-effective at a range of cost-per-QALY thresholds 88

FIGURE 21 The distribution chosen to represent the experts' consensus judgements for parameter 1: the percentage of patients aged < 60 years whose death was due to CJD who are misdiagnosed as having died from another neurodegenerative disease, since 2005 126

FIGURE 22 The distribution chosen to represent the experts' consensus judgements for parameter 2: the percentage of patients aged ≥ 80 years whose death was due to CJD who are misdiagnosed as having died from another neurodegenerative disease, since 2005 128

FIGURE 23 The distribution chosen to represent the experts' consensus judgements for parameter 3: the percentage of patients aged 60–79 years, whose death was due to CJD who are misdiagnosed as having died from another neurodegenerative disease, since 2005 128

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 130

FIGURE 25 Alternative the distribution of incubation periods, constructed by perturbing the proportions of the population in each interval from the central estimates 130

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 131

FIGURE 27 The assumed age profile of patients undergoing brain surgery who are assumed to have normal life expectancy 133

FIGURE 28 The assumed age profile of patients undergoing brain surgery assumed to die at 18 months 133

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 134

FIGURE 30 The assumed age profile of patients undergoing neuroendoscopy 134

FIGURE 31 The assumed age profile of patients undergoing posterior eye operations 135

Glossary

ID_{50} The infectious dose required to infect 50% of individuals receiving the infectious agent.

MM Methionine homozygosity at codon 129.

MV Heterozygosity (methionine/valine) at codon 129.

VV Valine homozygosity at codon 129.

List of abbreviations

ABC	approximate Bayesian computation
ACDP	Advisory Committee on Dangerous Pathogens
BSE	bovine spongiform encephalopathy
CI	confidence interval
CJD	Creutzfeldt–Jakob disease
CJDAS	Creutzfeldt–Jakob disease Advisory Sub-Committee
CNS	central nervous system
CRD	Centre for Reviews and Dissemination
CrI	credible interval
CSEW	Coroners' Society of England and Wales
EEG	electroencephalography
FFI	fatal familial insomnia
FFPE	formalin fixed, paraffin embedded
FML	factor for efficiently maximising the likelihood
gCJD	genetic Creutzfeldt–Jakob disease
GSS	Gerstmann–Sträussler–Scheinker
HES	Hospital Episode Statistics
hGH	human growth hormone
hGN	human gonadotrophin
ICER	incremental cost-effectiveness ratio
iCJD	iatrogenic Creutzfeldt–Jakob disease
IHC	immunohistochemical
IP	interventional procedure
IPG196	Interventional Procedures Guidance 196
MRI	magnetic resonance imaging
NCJDRSU	National CJD Research and Surveillance Unit
NICE	National Institute for Health and Care Excellence
OR	odds ratio
PK	proteinase K
PMCA	protein misfolding cyclic amplification
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRNP	prion protein gene
PrP	prion protein
PrP^{res}	protease-resistant prion protein
PrP^{Sc}	prion protein scrapie
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life-year
RF	radiofrequency
RIO	rational impartial observer
RMEC	rapid multienzyme cleaner trial formulation
RML	Rocky Mountain Laboratory
RN	random number
RT-QuIC	real-time quaking-induced conversion
ScHARR	School of Health and Related Research
sCJD	sporadic Creutzfeldt–Jakob disease
SDS	sodium dodecyl sulfate
SI	supplementary instrument
SSBA	standard steel-binding assay
SSD	sterile service department
stCJD	surgically transmitted Creutzfeldt–Jakob disease
$TICU_w$	tissue culture infectious units on wires
TSE	transmissible spongiform encephalopathy
vCJD	variant Creutzfeldt–Jakob disease
VPL	violation of the permissible limit

Plain English summary

The aims of this report were to summarise evidence relating to surgically transmitted Creutzfeldt–Jakob disease and to explore the value for money of strategies to reduce the chance of any future surgically transmitted Creutzfeldt–Jakob disease 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 Creutzfeldt–Jakob disease occurs in around 1–2 per million people and that no definite cases of surgically transmitted Creutzfeldt–Jakob disease have been observed since the 1970s. The reviews also looked for information on the possibility of patients being infected with Creutzfeldt–Jakob disease 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 Creutzfeldt–Jakob disease, 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 surgically transmitted Creutzfeldt–Jakob disease. 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 surgically transmitted Creutzfeldt–Jakob disease cases. However, additional measures, such as using only 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

Background

Creutzfeldt–Jakob disease is a progressive, fatal disease affecting the brain. Creutzfeldt–Jakob disease is caused by an abnormal infectious protein called a prion. Surgical instruments can become contaminated with prions when a person who has Creutzfeldt–Jakob disease, but does not exhibit clinical symptoms, undergoes surgery on 'high-risk' tissues. Such surgery includes 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 Creutzfeldt–Jakob disease by surgical instruments, resulting in surgically transmitted Creutzfeldt–Jakob disease. Previous work involving authors of this report assessed the cost-effectiveness of sets of single-use instruments and other strategies to reduce future surgically transmitted Creutzfeldt–Jakob disease cases, evidence from which was considered by the National Institute for Health and Care Excellence in establishing Interventional Procedures Guideline 196 [National Institute for Health and Care Excellence (NICE). *NICE Interventional Procedure Guidance 196. Patient Safety and Reduction of Risk of Transmission of Creutzfeldt–Jakob Disease (CJD) Via Interventional Procedures*. London: NICE; 2008]. Interventional Procedures Guideline 196 includes recommendations on decontamination methods and guidance for set-keeping to ensure that instruments that are 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 either to be 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 Creutzfeldt–Jakob disease because of dietary exposure to bovine spongiform encephalopathy) and those born after 1996 (who were believed, at the time of writing Interventional Procedures Guideline 196, to be at zero risk of dietary exposure to bovine spongiform encephalopathy).

Objectives

To evaluate the expected risk of surgically transmitted Creutzfeldt–Jakob disease cases under present surgical conditions and to estimate the cost-effectiveness of strategies that may alter the anticipated risks of surgically transmitted Creutzfeldt–Jakob disease.

Methods

Review methods

Eight systematic reviews were conducted. Four questions were fundamental to understanding Creutzfeldt–Jakob disease and four were undertaken to understand the risks of transmission via surgery. Broadly, the reviews investigated Creutzfeldt–Jakob disease 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 the National Institute for Health and Care Excellence 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™ (Clarivate Analytics, Philadelphia, PA, USA)] 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 to ensure that methods used in previous potentially relevant papers could be incorporated. Titles and abstracts were examined by one reviewer, and 10% of randomly selected excluded citations were double-checked checked by a second reviewer. Where appropriate, full papers were reviewed for pertinent information.

Elicitation methods

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. 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 of the experts. Following discussion between the experts and the 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, revised. 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 surgically transmitted Creutzfeldt–Jakob disease 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 National Institute for Health and Care Excellence committee convened to provide national guidance, and conformed to the National Institute for Health and Care Excellence reference case, using a 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 surgically transmitted Creutzfeldt–Jakob disease infection; taking into account the possibility that patients with surgically transmitted Creutzfeldt–Jakob disease could be misdiagnosed with an alternative neurodegenerative disease; and setting a calibration target of these number of possible surgically transmitted Creutzfeldt–Jakob disease cases observed between 2005 and 2018. To reduce the impact of sampling error, 27 random number streams were used for each probabilistic sensitivity analysis configuration. Calibrating the model was complex and required the use of heuristics to initially rule out parameter configurations that were incompatible with the 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 National Institute for Health and Care Excellence committee, the following strategies were run:

- Do nothing, assuming that the current situation is maintained with respect to surgical centres' adherence to Interventional Procedures Guideline 196.
- Full adherence to Interventional Procedures Guideline 196, and guidance on keeping instruments moist for those units where this is not followed, with the exception of single-use neuroendoscopes.
- Full adherence to guidance on keeping instruments moist for those units where Interventional Procedures Guideline 196 is not followed.
- Removal of the requirements to have separate instrument sets for patients born after 1996.
- Modelling interventions that prohibit the possibility of surgically transmitted Creutzfeldt–Jakob disease. 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 observe at what price per operation sets of single-use instruments, or a completely effective cleaning solution, would need to be to reach cost per quality-adjusted life-year gained values of £30,000 (a typical threshold for cost-effectiveness used by the National Institute for Health and Care Excellence) and £300,000 (the maximum value used by the National Institute for Health and Care Excellence for highly specialised technologies). Further threshold analyses were undertaken to look at the maximum costs associated with following Interventional Procedures Guideline 196 to be at, or below, thresholds of £30,000 and £300,000 per quality-adjusted life-year gained. Additional analyses explored the affect 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 National Institute for Health and Care Excellence committee, modelling of decontamination products was not conducted other than that contained in strategy 5 (see *Review methods*). The reasons for this include the heterogeneity of the studies of decontamination products for Creutzfeldt–Jakob disease 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 Creutzfeldt–Jakob disease case is reported to be between 1 and 2 per million worldwide, but the rate of sporadic Creutzfeldt–Jakob disease cases is noted to be increasing in some countries. The prevalence of non-clinical Creutzfeldt–Jakob disease 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 surgically transmitted Creutzfeldt–Jakob disease cases since the 1970s and that the risk of iatrogenic Creutzfeldt–Jakob disease 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 period of Creutzfeldt–Jakob disease ranges between 1 and 42 years. The infectivity of Creutzfeldt–Jakob disease 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; however, the reduction of residual mass to ≤ 5 µg of 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 or not 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.

Although no data from the literature were directly used in the model, apart from a paper co-written by authors of this report that detailed, and updated, the evidence considered for Interventional Procedures Guideline 196, selected papers were used in discussion with clinical experts to inform the model parameters.

A key result from the cost-effectiveness analyses was that keeping instruments moist was expected to save money and to reduce the estimated number of surgically transmitted Creutzfeldt–Jakob disease cases; however, there was still a risk of Creutzfeldt–Jakob disease transmission. Based on probabilistic sensitivity analyses, keeping instruments moist was estimated to produce on average 2.36 surgically transmitted Creutzfeldt–Jakob disease cases between 2019 and 2023, with a maximum value of 47 surgically transmitted Creutzfeldt–Jakob disease cases across the 27 assumed surgical centres. From a position of keeping instruments moist, the cost per quality-adjusted life-year of introducing single-use instruments was in excess of £1.0M in all scenarios. From a position of implementing Interventional Procedures Guideline 196 and keeping instruments moist, the cost per quality-adjusted life-year of introducing

single-use instruments was in excess of £4.5M in all scenarios. From a position of keeping instruments moist, the cost per quality-adjusted life-year of implementing Interventional Procedures Guideline 196 was estimated to be in excess of £1.6M.

The threshold analyses indicated that with a cost-effectiveness threshold of £300,000 per quality-adjusted life-year, a single-use set (or completely effective detergent) would need to be $\leq$ £50 per operation, assuming that instruments were kept moist. At a cost-effectiveness threshold of £30,000 per quality-adjusted life-year, this value reduced to £15 per operation. Threshold analyses exploring the maximum cost associated with implementing Interventional Procedures Guideline 196 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 5-year period. Analyses undertaken indicated that there would not be a large change in the numbers of quality-adjusted life-years lost because of surgically transmitted Creutzfeldt–Jakob disease (< 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 because of the rare nature of Creutzfeldt–Jakob disease and the reliance on historical cases of surgically transmitted Creutzfeldt–Jakob disease, the lack of observational data, the case–control study designs and the use of animal data. The apparent increase in sporadic Creutzfeldt–Jakob disease cases noted in several papers is most probably because of improved case ascertainment, population increases and an ageing population. Recent studies of prior accumulation in human lymphoid tissue raise the possibility of either a low background prevalence of abnormal prion proteins or an extended period of bovine spongiform encephalopathy-related infection [see Public Health England. *Summary Results of the Third National Survey of Abnormal Prion Prevalence in Archived Appendix Specimens*. London: Public Health England; 2016; and Advisory Committee on Dangerous Pathogens TSE Subgroup. *Updated Position Statement on Occurrence of vCJD and Prevalence of Infection in the UK*. 2016. URL: www.clinicalvirology.org/news/acdp-tse-subgroup-updated-position-statement-on-occurrence-of-vcjd-and-prevalenceof-infection-in-the-uk/ (accessed 8 January 2020)]. The possibility of underdiagnosis of variant Creutzfeldt–Jakob disease also exists. Data on the likely incubation periods of Creutzfeldt–Jakob disease are limited to retrospective data from iatrogenic Creutzfeldt–Jakob disease, variant Creutzfeldt–Jakob disease or kuru cases. As Creutzfeldt–Jakob disease detection methods advance, more accurate confirmation of Creutzfeldt–Jakob disease 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 National Institute for Health and Care Excellence 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. Although running a greater number of probabilistic sensitivity analysis configurations would increase the accuracy in the incremental cost-effectiveness ratio related to uncertainty in parameter estimates, and running more random number streams would increase the accuracy for a given probabilistic sensitivity analysis configuration, the results appear sufficiently robust for decision-making. Keeping instruments moist is predicted to both save money and reduce the risk of future surgically transmitted Creutzfeldt–Jakob disease cases. All other strategies evaluated have incremental cost-effectiveness ratios in excess of £1M per quality-adjusted life-year 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 surgically transmitted Creutzfeldt–Jakob disease cases. Throughout the modelling there was a conscious decision to be pessimistic if a choice needed to be made, and, thus, the cost per quality-adjusted life-year estimates are likely to be underestimates rather than overestimates.

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 surgically transmitted Creutzfeldt–Jakob disease since the 1970s. Evidence implicating surgery as a risk factor for Creutzfeldt–Jakob disease is restricted to case–control designs, and the evidence on decontamination agents and processes has limited applicability. Owing 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 surgically transmitted Creutzfeldt–Jakob disease cases do not appear to be cost-effective as they have cost per quality-adjusted life-year gained estimates in excess of £1M. It is estimated that removing the requirement to operate on people born after 1996 with different instruments would not markedly increase the risk of surgically transmitted Creutzfeldt–Jakob disease cases.

The modelling indicates that a number of surgically transmitted Creutzfeldt–Jakob disease cases that could occur despite keeping instruments moist. In the event of multiple surgically transmitted Creutzfeldt–Jakob disease cases being identified, performing an urgent update of this review, with an amended calibration target is likely to be informative.

Study registration

This study is registered as PROSPERO CRD42017071807.

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Chapter 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 CJD is transmitted, 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 1 year of the symptoms appearing.

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

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

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

Variant CJD was observed following the exposure of the UK population during the late 1980s and early 1990s to bovine spongiform encephalopathy (BSE), which 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 since declined, with only two 'definite or probable' vCJD deaths reported since 2012. The majority of cases have occurred in a younger population compared with that observed in sCJD, with a mean age of 26 years. The median disease duration post diagnosis is longer in vCJD (14 months) than that observed in sCJD. All people who have contracted clinically observed vCJD have died.

Incidences of iCJD, which is the transmission of prion disease through medical procedures or equipment, have been recorded for procedures such as dura mater grafts, electroencephalography (EEG) needles and neurosurgery, and from 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 surgically transmitted CJD (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 transmitted 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 iCJD 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; estimations incorporated potential subclinical vCJD infections identified from a histopathological survey of lymphoreticular tissue to be 237 per million [95% confidence interval (CI) 49 to 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 Division[13] were used to inform the NICE Interventional Procedures Guidance 196 (IPG196) *Patient Safety and Reduction of Risk of Transmission of Creutzfeldt–Jakob Disease (CJD) Via Interventional Procedures*.[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 (SIs) 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 procedures 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] Although 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 that include:

- a finding of abnormal prion accumulation in the appendixes 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 that 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 number IP1553)[18,19] that informed NICE guidance IPG196[11] for the NICE Interventional Procedures (IPs) 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. To undertake modelling to estimate the cost-effectiveness of strategies to reduce the risk of transmission of CJD via surgical procedures.

Chapter 2 Clinical evidence

Methods for systematic reviews

The protocol for this project was developed in consultation with the NICE Interventional Procedures Advisory Committee and was registered on the Centre for Reviews and Dissemination (CRD) systematic review database (PROSPERO registration number CRD42017071807). The project aimed first 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 in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2009[20] standards.

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 and the infectious mass required to transmit CJD • Outcome: trends or themes in CJD infectivity • Study designs: empirical in vivo or in vitro studies

continued

TABLE 1 Eligibility criteria for each review question (*continued*)

Review question	Eligibility criteria for inclusion into the review
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, that is a 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 that 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.	

Search strategy

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

- MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations – via Ovid® (Wolters Kluwer, Alphen aan den Rijn, the Netherlands), 1946 to 2017
- EMBASE – via Ovid, 1974 to 2017
- Science Citation Index and Conference Proceedings Citation Index– Web of Science™ (Clarivate Analytics, Philadelphia, PA, USA), 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, because 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's 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 combined terms for:

1. 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' (see *Appendix 1*, search strategy lines 10–15) were combined with 'CJD' population terms (see *Appendix 1*, search strategy lines 1–9). The terms applied were identical to those used in appendices 1 and 3 in the original systematic review.[10]
2. 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' (see *Appendix 1*, search strategy line 27) and 'instrument decontamination' (see *Appendix 1*, search strategy lines 28–33) were combined with 'CJD' population terms in humans or non-human mammals (see *Appendix 1*, search strategy lines 18–25).
3. 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 that report on the extent to which surgical instruments remain in their original sets following use and decontamination. Terms for 'instrument decontamination' (see *Appendix 1*, search strategy lines 36–41) were combined with 'high-risk surgical procedures' (see *Appendix 1*, search strategy lines 42–56). A list of high-risk surgical procedures were taken from appendix C of NICE IPG196.[14]
4. Searches for the complication rates associated with the use of single-use versus reusable anaesthetic, diagnostic or surgical instruments.
   Electronic literature searches were performed to identify articles that report on complication rates associated with the use of single-use versus reusable anaesthetic, diagnostic or surgical instruments. Terms for 'disposable' or single-use' instruments (see *Appendix 1*, search strategy lines 60–63), including specifically named instruments recommended at the NICE committee meeting in June 2017 (see *Appendix 1*, search strategy line 63), were combined with 'high-risk surgical procedures' (see *Appendix 1*, search strategy lines 65–79) or 'complications' (see *Appendix 1*, search strategy lines 81–84).
5. Searches for the risk of future surgery following surgery.
   Electronic literature searches were performed to identify articles that report on the risk of future surgery following surgery. Terms for 'reoperation' or 'repeat surgery' were combined (see *Appendix 1*, search strategy lines 88–90) with 'high-risk surgical procedures' (see *Appendix 1*, search strategy lines 92–106). As the review question was reconceptualised 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 CJD.

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

- MEDLINE, MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations – via Ovid, 1946 to 2017
- EMBASE – via Ovid, 1974 to 2017
- The Cochrane Library (Wiley Online Library) 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 and Conference Proceedings Citation Index – Web of Science, 1990 to 2017.

The search strategy comprised Medical Subject Headings or Emtree thesaurus 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 [Clarivate Analytics (formerly Thomson Reuters), Philadelphia, PA, USA], 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 the 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 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 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 were double-checked by a second reviewer (LU). All full-text articles were independently assessed for inclusion by two reviewers (MS, and 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® (Microsoft Corporation, Redmond, WA, USA) 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 the 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 quality assessment tools available depending on the study type included; 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 (1) they are surveillance reports, thereby not constituting the traditional definition of a study or (2) 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 (CRD42017071807), was updated accordingly.[21] 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

Owing 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. 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 the 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.

Literature search results

The literature searches of bibliographic databases were performed on 14 August 2017 and yielded 8466 citations. During the screening process, a citation of potential relevance to review question 2 was identified that 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 2 October 2017, resulting in a further 310 citations. A total of 41 further citations were obtained and assessed for eligibility either from recommendations from NICE's 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). In total, 10% 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 was ultimately deemed 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*.

The incidence of Creutzfeldt–Jakob disease and the prevalence of Creutzfeldt–Jakob disease-related prions in humans in the UK

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

- the incidence of CJD (sporadic, genetic, variant and iatrogenic)
- 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);[22] however, this source was last updated in May 2015 and is therefore less up to date than the 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. A total of 69 published citations were identified as being relevant to the incidence of clinical CJD or the prevalence of subclinical CJD around the world.

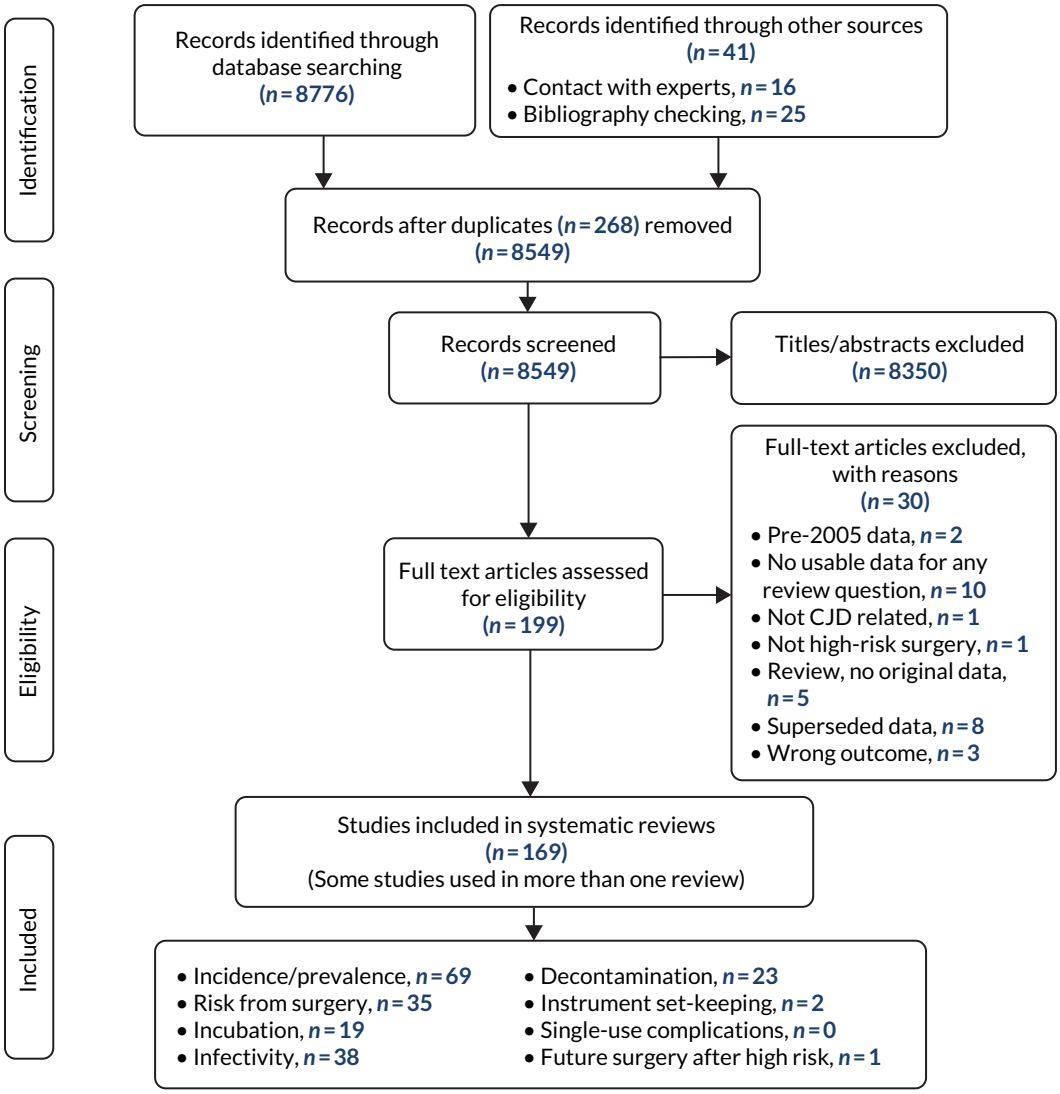

FIGURE 1 The PRISMA flow diagram of studies included in systematic reviews.

The incidence of Creutzfeldt–Jakob disease

The global incidence of CJD is typically reported to be around 1 to 2 cases per million per year,[22] based on surveillance studies published around the world from 2005 (*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. By contrast, a paper by Jeon *et al.*[28] 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.

A study by Gao *et al.*[29] does not report an incidence rate per million for CJD in China, but does report that during the period from 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.[29]

Increase in the UK sporadic Creutzfeldt–Jakob disease incidence over time

Between 1990 and 2017, the NCJDRSU recorded figures of iCJD [from receipt of human gonadotrophin (hGN), human-derived growth hormone or dura mater) and vCJD, which were relatively

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[22]
Australia	1993–2016	1.20	Sporadic	EuroCJD[22]
Belgium	1997–2017	1.19	Sporadic	EuroCJD[22]
Canada	1994–2017	1.03	Sporadic	EuroCJD[22]
Czech Republic	2000–17	1.16	Sporadic	EuroCJD[22]
Denmark	1993–2017	1.45	Sporadic	EuroCJD[22]
Estonia	2004–17	0.32	Sporadic	EuroCJD[22]
France	1993–2017	1.53	Sporadic	EuroCJD[22]
Germany	1993–2017	1.36	Sporadic	EuroCJD[22]
Hungary	1997–2017	1.07	Sporadic	EuroCJD[22]
Italy	1993–2017	1.44	Sporadic	EuroCJD[22]
Netherlands	1993–2017	1.21	Sporadic	EuroCJD[22]
Norway	1995–2017	0.96	Sporadic	EuroCJD[22]
Slovakia	1993–2017	0.85	Sporadic	EuroCJD[22]
Slovenia	1993–2017	1.38	Sporadic	EuroCJD[22]
Spain	1993–2017	1.30	Sporadic	EuroCJD[22]
UK	1993–2017	1.19	Sporadic	NCJDRSU 2016[1]
USA	2016	1.22	Excludes vCJD	US Centers for Disease Control and Prevention[23]
Japan	1999–2015	1.3	All types	Yamada *et al.*[24]
Australia	1993–2014	1.2	All types	Klug *et al.*[25]
Finland	1997–2013	1.45	Sporadic	EuroCJD[22]
Cyprus	1995–2013	0.70	Sporadic	EuroCJD[22]
Germany	1993–2013	1.33	Excludes vCJD	EuroCJD[22]
Holland	1993–2013	1.21	Excludes vCJD	EuroCJD[22]
Hungary	1997–2013	1.65	Excludes vCJD	EuroCJD[22]
Sweden	1997–2013	1.44	Excludes vCJD	EuroCJD[22]
Switzerland	1993–2013	1.72	Sporadic	EuroCJD[22]
Argentina	2008	0.85	All types	Begué *et al.*[26]
Greece	1997–2008	0.62	Sporadic	EuroCJD[22]
Taiwan	1998–2007	0.55	Sporadic	Lu *et al.*[27]

low compared with sCJD. *Figure 2* plots the number of deaths in the UK that have been attributed to definite or probable CJD between 1996 and 2017 (as of 2 May 2018) as reported by the NCJDRSU. An increase in sCJD cases is noted over the 27-year period, whereas iatrogenic, genetic and variant forms remain rare.

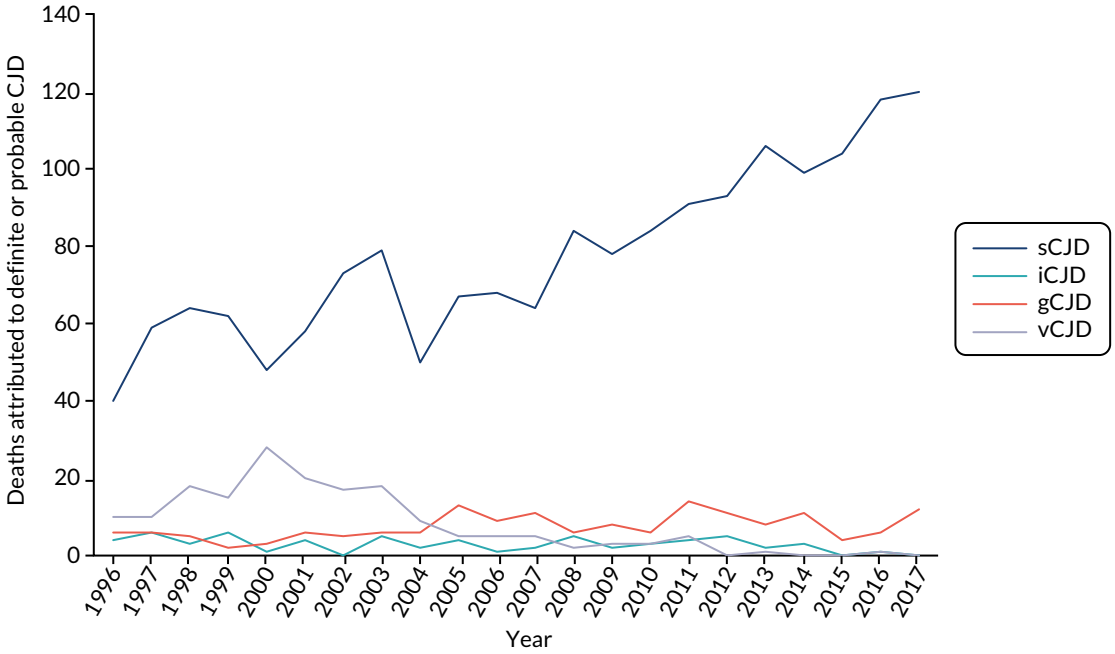

FIGURE 2 Deaths attributed to definite or probable CJD in the UK, using data from the NCJDRSU, between 1996 and 2017.[30]

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

- improved case ascertainment because of clinician awareness and/or improvements in diagnostic testing
- population increases
- an ageing population
- 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 the surveillance of CJD. Case ascertainment is likely to improve in areas where CJD surveillance is strong, where there is greater awareness among health-care professionals of CJD and where there are more neurologists who are 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, owing to the potential for iatrogenic transmission, there has been a focused collaborative effort to examine the evidence of transmission through different exposures by examining the links to confirmed CJD cases through retrospective 'lookback' studies.[31]

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 sporadic Creutzfeldt–Jakob disease incidence globally

Reports of increased rates of sCJD were noted from other countries. In Finland, an increased incidence of sCJD was noted between 1974 and 1989 of 0.6 per million to 1.36–1.44 per million in 2007–13, as reported in an abstract by Isotalo *et al.*[32] An abstract by Chen[33] reports that sCJD incidence rates in Taiwan doubled between 2008 and 2015. They also report that age at onset became younger. Chen[33] speculates that the 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[34] from Belgium noted a relevant trend of significantly increased age-specific incidence of sCJD patients between the age of 70 and 90 years in the period 2002–04 compared with 1998–2001, using retrospectively obtained data (1990–1997; $p < 0.01$). 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.*[35] report in a study abstract that the annual incidence of human prion diseases has increased since 1999, particularly so in older patients (aged ≥ 70 years), with cases of rapidly developing dementia increasingly being identified by domestic physicians.

One study from Slovenia reported an apparent fluctuation of sCJD cases in 2015, with seven definite and two probable sCJD cases resulting in an incidence of 4.36 per million for the country that year.[36]

Autopsy and biopsy in Creutzfeldt–Jakob disease

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 from neuropathology.[1] Despite the observed increase in sCJD cases over the last twenty years, autopsy is not performed routinely on sCJD 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 (aged 36 years), a pathological examination after death in February 2016 confirmed it to be vCJD despite the absence of clinical epidemiologic diagnostic criteria for probable or possible vCJD.[37] 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 explanation for the increasing number of sCJD 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 the transmission of sCJD by a number of epidemiological studies; a retrospective study by Urwin *et al.*,[38] described as ongoing, is seeking to investigate this risk factor further by reviewing UK sCJD cases.

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 that stringent infection control protocols are followed. Protocols for instrument decontamination are required for brain biopsy. For example, Shi *et al.*[39] state that although 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 and Phillips.[40] state that getting a biopsy in a timely manner is often not possible given the costly and aggressive nature of the diagnostic test and that the rigorous decontamination and sterilisation techniques for handling tissue at biopsy may make it impractical in a community setting.

Ethnic and geographical differences

Variations in CJD incidence according to ethnicity by Maddox *et al.*[41] and Holman *et al.*[42] were noted in the literature. In the USA, the age-adjusted CJD incidence for white people was reported as being 2.7 times higher than that for black people (1.04 and 0.40 per million, respectively). Similarly, the estimated incidence of CJD (0.7 per million) among Asians and Pacific Islanders in the USA between 2003 and 2009 was reported by Maddox *et al.*[43] as being significantly lower than that for white people ($p < 0.001$).

Nakatani *et al.*[44] noted that the occurrence of sCJD appeared to have regional variations 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. 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 are presented and, therefore, this particular phenomenon remains to be explored. Klug *et al.*[45] conducted a spatial and epidemiological analysis of

sCJD case-clusters in Australia. The authors concluded that the observed increase of sCJD cases in a geographic area is more 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.[46] Mitrova *et al.*[47] report that although gCJD represents approximately 10–15% of all CJD patients in the majority of countries, in Slovakia the rate of gCJD has been higher than 65% since 1975 owing to an accumulation of gCJD incidence in two clusters in central Slovakia. 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 the focal cluster. This finding indicates an unusual phenomenon of an increased prevalence of the E200K mutation linked to gCJD in the Slovak region. A study by Ladogana *et al.*[48] 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.

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

Diagnosis of Creutzfeldt–Jakob disease

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.*[49] report that post-mortem examination was not performed in any of the five cases of CJD occurring in Croatia between 2001 and 2011 owing to patient families' refusal of the procedure. More generally, Kosier[50] state anecdotally in a US case report that the diagnosis of CJD is often delayed because of clinician bias towards more obvious possible medical or psychiatric causes. Litzroth *et al.*[51] highlight that in Belgium, between 1998 and 2012, on average 60% of hospitalised patients who died with suspected CJD were captured by the surveillance system. 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. From a review of 21 referrals to the National CJD Centre in Ireland, Brett *et al.*[52] found that only five referrals were positive for CJD, with 12 being referred as part of their differential diagnosis. Brett *et al.*[52] cautioned that, more often than not, the clinical suspicion of CJD was not borne from 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.*[53] also raised 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 (50/96 referrals) were confirmed as definite CJD via tissue samples through biopsy or autopsy.[53] The authors proposed 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, its detection may have improved in the last 6 years. *Figure 3* is taken from the 25th Annual Report of the NCJDRSU[2] 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 those for 2005–9. However, if there are proportionately more older people in the more recent age band, the incidence will be inflated.

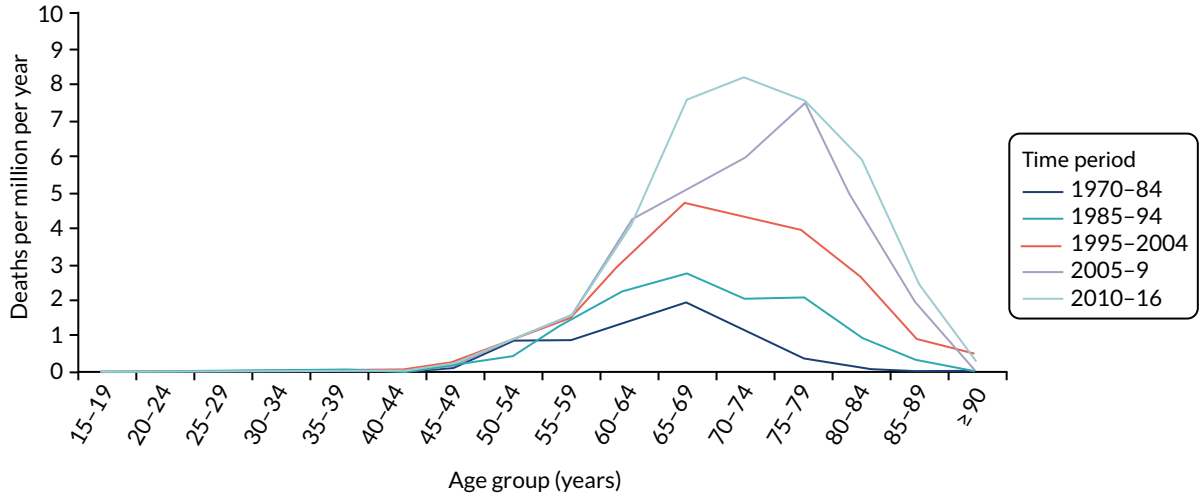

FIGURE 3 Age-specific mortality rates from sCJD in the UK 1970–2016: reproduced from NCJDRSU Annual Report 2016.[2] 1970–1984 mortality rates calculated using mid-1981 England and Wales population estimates based on the 1981 Census. 1985–1994 mortality rates calculated using mid-1991 UK population estimates based on the 1991 Census. 1995–2004 mortality rates calculated using mid-2001 UK population estimates based on the 2001 Census. 2005–2009 mortality rates calculated using mid-2001 UK population estimates based on the 2001 Census. 2010–2016 mortality rates calculated using mid-2011 UK population estimates based on the 2011 Census. Reproduced with permission from the National CJD Research & Surveillance Unit, University of Edinburgh.[2]

Owing to the median age at 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,[54,55] acute neuropathy,[56] hyperparathyroidism,[57] dementia,[51,58–61] Lewy body dementia,[51] encephalitis,[51] aphasia,[62] Alzheimer's disease,[51,60] psychiatric decompensation[50] and movement disorder.[63] 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.[64] 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 that 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. sCJD is commonly reported to have a disease duration of 4–7 months;[2,22,65–67] however, Nagoshi *et al.*[68] report that duration of disease was longer for sCJD in Japan than in Western countries. The authors state that sCJD, which represented 77.0% of cases of prion disease in their surveillance network between 1999 and 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 vCJD, which is 14 months from the onset of symptoms to death (NCJDRSU's 2016 annual report[2]) or indeed iCJD via human growth hormone (hGH), the median of which is reported as 16 months (mean 14 months) for 22 iCJD patients.[69] Nagoshi *et al.*[68] 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 GSS syndrome and FFI. Nagoshi *et al.*[68] 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 individuals with the MM genotype. Both methionine (MM) and valine (VV) homozygotes at codon 129 of *PRNP* are at an increased risk of sCJD.[70] In the north of Europe, the MM genotype represents 38% of the general population, whereas 11% of the population have the VV genotype and 51% are heterozygotes (methionine/valine; MV) at codon 129 of *PRNP*.[71] An epidemiological study by Giaccone *et al.*[72] of the *PRNP* genotype of 402 consecutive sCJD cases in Italy revealed that 70.4% ($n = 283$) had the MM genotype, 15.4% ($n = 62$) were MV and 14.2% ($n = 57$) were VV.[72] Although 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, Ironside *et al.*[73] re-analysed three of the appendixes identified (from the 12,674 appendix and tonsil samples analysed by Hilton *et al.*[7]) as positive for disease-associated PrP; two of the three were found to be VV genotype, which provided the first indication that the valine homozygotes are also susceptible to vCJD infection.[73] 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.*[74] from 16 positive appendix samples found that eight were MM, four were MV, and four were VV at codon 129 of *PRNP*, indicating that genetic susceptibility for subclinical CJD was more equally distributed in the population.

Heterozygosity at codon 129 of *PRNP* was generally believed to confer complete resistance to both sporadic and acquired prion diseases.[75] However, the most recent case of clinical vCJD in 2016 was heterozygous[37] and an additional possible vCJD case reported by Kaski *et al.*[76] in 2008 was also heterozygous, but this possible vCJD case was not confirmed by autopsy. Two case reports indicate that the MV genotype is susceptible to iCJD, but the cases were subclinical. First, the case of 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.*[77] This patient had received over 9000 units of factor VIII concentrate prepared from plasma pools known to include donations from a vCJD-infected donor. Second, a case in 2004 of subclinical vCJD from blood transfusion, who was heterozygous at codon 129, and died from a cause unrelated to CJD[78] 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 benefiting from apparent reduced transmission efficiency and longer asymptomatic incubation periods.[79]

Disease duration and genotype

Prion protein–gene data from 378 of the Japanese patients diagnosed with sCJD, reported by Nagoshi *et al.*,[68] showed that 364 cases (96.3%) had the MM genotype but that disease duration was longest for the 11 patients (2.9%) who were MV (mean, 32.2 months for MV vs. 16.6 months for MM and 13.2 months for VV).[68] Begué *et al.*[26] report data for the disease duration of sCJD from 59 definite cases in Argentina. Genotype analysis indicated that the MV genotype was associated with the longest disease duration (10.9 months), followed by the VV (5.6 months) and the MM genotypes (3.6 months).[26] Data from Rudge *et al.*[69] relating to CJD transmission via hGH in the UK also found that MM patients had the shortest disease duration; MM patients had a mean disease duration of 7.8 months, the VV patients 17 months and MV patients had a mean disease duration of 18.6 months (range 10–32 months). In addition, the duration of disease from first symptom was significantly longer in the MV patients ($p = 0.02$, two-tailed *t*-test). Although there were only four patients who were MM, three of these had the most rapid disease progression ($p = 0.04$, Mann–Whitney *U*-test). Yamada *et al.*[24] state that the majority of the general Japanese population (93%) carry the MM genotype. Considering that a large share of patients in the Argentinian sample also contained the 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,[68] Argentina,[26] and the UK[69] therefore indicate that the MV genotype is associated with the longest disease duration compared with homozygotes. Pennington and Knight[80] also reported disease duration to be significantly longer in codon 129 heterozygotes for gCJD.

Variant Creutzfeldt–Jakob disease

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.[37] A further 52 cases have been reported from other countries around the world, which brings the global total of clinical vCJD cases to 231.[81] Between 2005 and 2014, 68 vCJD cases were reported from 11 countries including the UK ($n = 29$), France ($n = 19$), Spain ($n = 5$), Ireland ($n = 3$), the USA ($n = 3$), Holland ($n = 3$), Portugal ($n = 2$), Italy ($n = 1$), Canada ($n = 1$), Saudi Arabia ($n = 1$) and Taiwan ($n = 1$).[22] A total of 3 out of the 178 cases in the UK that occurred up to 2016 are considered to have occurred through blood transfusion.[2] A 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.[78] Three further potential, but unconfirmed, cases of CJD transmission through blood transfusion are described by Chohan *et al.*[82] and Davidson *et al.*[83] A retrospective study by Molesworth *et al.*,[84] which was performed to identify situations where the transplantation of organs or tissues might have occurred in any of the 177 UK vCJD cases, found no evidence of transplant-associated vCJD in the UK.[84] The remaining 175 clinical vCJD cases are presumed to be related to dietary exposure to BSE.[85]

Iatrogenic Creutzfeldt–Jakob disease

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

In the UK, 85 cases of iCJD were identified between 1970 and December 2016, and are described by the NCJDRSU.[1] In total, eight cases were from dura mater grafts, 76 from hGH and one from hGN. All cases have since died, with a mean age at death for the hGH/hGN group of 35 years (range 20–51 years) and for the dura mater cases 46.5 years (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.*[86] The Urwin *et al.*[86] study referenced the Davidson *et al.*[83] paper but not the Chohan *et al.*[82] paper. These two papers discuss three potential, but unconfirmed, cases of CJD transmission via blood transfusion. Ward *et al.*[87] 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.[87] The evidence regarding the incidence of iCJD from surgery is discussed in the review on the risk of CJD transmission via surgery.

The estimated prevalence of subclinical variant Creutzfeldt–Jakob disease in the UK

In vCJD, prions appear to replicate extensively within lymphoid tissue; 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 is thought to represent a potentially background, but low, level of infection in the population.[88] 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.[89]

A key study conducted by Gill *et al.*,[74] referred to as the 'Appendix II' study, examined subclinical prion accumulation in excised peripheral tissues from general population cohorts born in 1941–60 and 1961–85.[74] 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[16] following completion of the most recent study of stored appendixes ('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 4200 people or 240 per million people.[15,16] This estimate is based on results of immunohistochemical (IHC) staining of appendixes from two birth cohorts, which are described in *Table 3*.

Variant Creutzfeldt–Jakob disease and bovine spongiform encephalopathy

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.[90] Moreover, a recent study by Diack *et al.*[91] examined two Spanish cases of vCJD: a mother and son who resided in a BSE-endemic area, who are thought to have ingested bovine brain.[91] 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[75,76] highlights that abnormally stained appendixes associated with vCJD prion accumulation have been confirmed in cohorts of people who were not considered to have had significant exposure to BSE because they were either from appendixes removed before the BSE epidemic in the UK (prior to 1980) or from appendixes from patients born after food safety measures to limit BSE were implemented (after 1996). The presence of seven 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 1980 and1996). Moreover, planned statistical analysis, as described by Gill *et al.*,[74] found no difference between the prevalence observed in the cohort considered to be most at risk of the BSE epidemic (people born 1961–85) and an older cohort (born 1941–60).

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 described in *Table 4*. Central estimates range between 0 and 493 per million people in the 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.*[94] This review includes the cross-sectional study by Hilton *et al.*[7] that estimated the prevalence in the sample population to be 120 per million from 11,228 appendixes.

TABLE 3 Results of the Appendix III study[16]

Appendix III cohort	IHC stain results	Central estimate
Appendixes removed between 1970 and 1979 and before the BSE epidemic	Two positive samples from 14,692 appendixes	1 in 7000
Appendixes removed from patients born after 1 January 1996 and after measures to remove BSE were in place	Five positive samples from 14,824 appendixes	1 in 3000

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

Study (first author and year of publication)	Design	Number of samples	Predicted/estimated prevalence	Description of estimation
Gill *et al.* (2013)[74]	UK histological analysis of appendix samples from the 1941–60 and 1961–85 birth cohorts	32,441	• 1 in 2000 or 493 per million (95% CI 282 to 801 per million) • 1941–60: 733 per million (95% CI 269 to 1596 per million) • 1961–85: 412 per million (95% CI 198 to 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 (2010)[92]	Two estimations based on UK tonsil tissue samples from the 1961–85 birth cohort	10,075	• High: 109 per million (95% CI 3 to 608 per million) • Low: 0 per million (95% CI 0 to 403 per million)	• One specimen showed both positive and negative results on further tests, so the two estimates reflect both positive and negative scenarios
Clewley (2009)[93]	UK estimation combining tonsil tissue samples	63,007 (32,661 from the 1961–95 cohorts)	• 1961–85 cohort: 0 per million (95% CI 0 to 289 per million) • 1961–1995 cohort: 0 per million (95% CI 0 to 113 per million) • 1986–95 cohort: 0 per million (95% CI 0 to 185 per million) • 1996–2007 cohort: 0 per million (95% CI 0 to 122 per million)	• No positive results from 63,007 tonsil specimens from the birth cohort in Britain, where most cases of vCJD have occurred

Obtaining definitive prevalence estimations

Subclinical vCJD can be detected through typical PrP staining in lymphoid tissue or through 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. To collect a truly accurate picture of the prevalence of CJD through abnormal prion protein in humans, the UK Health Protection Agency proposed the creation of a post-mortem tissue archive.[95] The study required tissue from a large number of post-mortems and 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.[96] The CSEW concluded that to participate in the study would 'adversely affect the independence of the coronial service and would further erode public confidence'.[97] McGowan and Viens[95] describe that as 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.

Discussion of the incidence and prevalence of Creutzfeldt–Jakob disease

The incidence of CJD is relatively stable around the world (between 1 and 2 cases per million people) but age-adjusted detection of sCJD is increasing in the UK as well as in 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 2000 people and the estimated prevalence of CJD-related prions in lymphoid tissues in the UK population who are not thought to be exposed to the BSE epidemic was 1 in 4200

people. 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.

The risk of Creutzfeldt–Jakob disease transmission via surgery

The literature searches retrieved no further published papers from the period 2005 to 2017 reporting confirmed cases of stCJD, further to the four neurosurgical cases which occurred between 1952 and 1974.[3] These four historical 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 that began in the late 1980s. The four historical surgical cases, therefore, represent a small proportion of the known iCJD cases (469 iCJD cases according to Brown *et al.*[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 dry instruments), the high levels of infectivity of CJD in the brain and a presumed subclinical underlying prevalence (albeit low) in the general population mean that there is a margin of uncertainty around detecting and quantifying the risk of CJD transmission via surgery.

Observational studies implicating surgery in Creutzfeldt–Jakob disease

Despite the absence of studies providing direct evidence of further cases of stCJD, a number of papers were identified which allude to a potential relationship between CJD cases and prior surgery. Papers that 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 and 2017

Study (first author and year(s) of publication)	Design	Source
Kobayashi (2015 and 2016)[98–100]	Two historical 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 a conference abstract
Gnanajothy (2013)[101]	Case report of 64-year-old man diagnosed with CJD (type of CJD not reported) 3 months after cataract surgery. The authors discuss the possibility that the visual symptoms that prompted the surgery might have represented onset of the disease rather than it being the case that the procedure itself transmitted the disease (i.e. the patient already had CJD)	Published paper
Tuck (2013)[102]	Case report of sCJD that was posited to be iCJD via surgery because of 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 ventriculoperitoneal shunt was placed at 11 years of age for hydrocephalus. Autopsy results were consistent with sCJD	Conference abstract
Moreno (2013)[103]	A surveillance study in Meixoeiro Hospital (Spain) reported 12 cases of CJD (10 sCJD and 2 gCJD) from 1997 to 2010, which represented a high average yearly rate of 4.6 per million people (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 people), only 3.9 cases would have been expected over a 14-year period. A total of 8 out of 12 CJD cases had undergone at least one surgical or invasive medical procedure	Published paper

TABLE 5 Studies reporting links between CJD and surgery published between 2005 and 2017 (*continued*)

Study (first author and year(s) of publication)	Design	Source
Puopolo (2011)[104]	A case–control study found that 'history of surgery' was more frequent in sCJD cases ($n = 13$, 2%; neurosurgery, $n = 12$; cornea transplantation, $n = 1$) vs. no-CJD cases ($n = 5$, 1%; neurosurgery $n = 5$) and none in genetic TSE patients. A crude OR of 1.57 (95% CI 1.14 to 2.16) was reported. Results did not reach statistical significance when adjusted for a 10-year time lag	Published paper (included in de Pedro-Cuesta *et al.*[112])
de Pedro-Cuesta (2011)[105] Mahillo-Fernandez (2008)[106]	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 with high-risk procedures (i.e. surgery to brain, spinal cord, retina and optic nerve) carried out > 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 ≥ 1 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-Cuesta *et al.*[112])
Hamaguchi (2009)[107,108]	A case–control study in Japan with 753 sCJD patients and 210 controls. 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% of patients. Among the neurosurgery cases, the symptoms of sCJD were misdiagnosed as those of other neurological diseases, and the surgeries were performed near disease onset. The authors concluded that, despite absence of empirical evidence of transmission via surgery, the risk of contracting CJD via surgery is still present because patients are operated on after disease onset	Two published papers (included in de Pedro-Cuesta *et al.*[112])
Ruegger (2009)[109]	A case–control study in Switzerland found that 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, had orthopaedic surgery, had ophthalmologic surgery after 1980, attended 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-Cuesta *et al.*[112])
Ward (2006)[110]	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-Cuesta *et al.*[112])
Ward (2008)[111]	A case–control study in the UK of 431 sCJD patients and 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: (1) skin stitches, (2) nose/throat operations and (3) 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-Cuesta *et al.*[112])

OR, odds ratio.

Issues of reliability and validity in case–control studies

Because sCJD is idiopathic, its aetiological basis is presumed to be spontaneous but this is not known with any certainty.[89] Therefore, case–control studies are a frequently encountered design in estimating possible and plausible risk factors for sCJD. de Pedro-Cuesta *et al.*[112] caution about the potential biases in these study designs in an assessment of 18 case–control studies of CJD. From a combined analysis of studies, the authors found that history of surgery or blood transfusion was associated with a risk of sCJD in some, but not all, recent studies using a 10-year or longer lag time, when controls were longitudinally sampled. Furthermore, they found that none of surgical history, blood transfusion, dental treatments or endoscopic examinations was linked to vCJD. However, the authors highlight that the validity of the findings in these case–control studies may be undermined by (1) the selection of control cases; (2) exposure assessment in lifetime periods of different durations; (3) disregarding 'at-risk' periods for exposure in the controls, or asymmetry between the case and control data; and (4) confounding by concomitant blood transfusion at the time of surgery. They also postulate that surgery at early clinical onset might be over-represented 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. Owing 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, the use of community controls and ascertainment of surgical exposures through the 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 Creutzfeldt–Jakob disease through occupational exposure for health-care professionals

In 2009, the Spanish CJD registry was notified of a case of sCJD in an experienced general pathologist/neuropathologist, which prompted investigation into the possible risks to health-care professionals in contact with CJD patients.[113] As a result, Alcade-Cabero *et al.*[113] reported the data requested from the EuroCJD surveillance network, which documented 65 physicians or dentists (including two pathologists) and 137 health-care workers from 8321 registered sCJD cases from 21 countries. Control data, which used 'non-cases' from five countries, recorded 15 physicians and 68 other health-care professionals among 2968 controls or non-cases, and suggested that there was no relative excess of sCJD among health-care professionals. The study authors also performed a literature review examining reports ($n = 12$) pertaining to 66 health-care 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 (OR 4.6, 95% CI 1.2 to 17.6)]. The authors concluded that a wide spectrum of medical specialties and health-care professions are represented in sCJD cases and that there is no evidence of an increased occupational risk for health-care 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-care professionals.

Risk of Creutzfeldt–Jakob disease in surgery and age

de Pedro-Cuesta *et al.*[114] performed a retrospective analysis of 167 cases of sCJD between 1987 and 2003. From a study of 167 probable or definite CJD cases and 835 matched controls, the authors suggest that a younger age at first surgery may increase the risks of acquiring sCJD: patients aged < 30 years (OR 12.80, 95% CI 2.56 to 64.00), patients aged 30–39 years (OR 3.04, 95% CI 1.26 to 7.33) and patients aged ≥ 40 years (OR 1.75, 95% CI 0.89 to 3.45), for anatomically classified surgical procedures. As highlighted by the same authors in a different study,[112] caution should be urged when interpreting conclusions from

analyses on indirect evidence in retrospective samples. Additionally, the ≥ 40-year 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.*[115] used a cross-sectional design to study surgical procedures in sCJD patients and controls to estimate subclinical and clinical risks to future surgery. 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[116] reinforces this concern by providing data from the Japanese CJD Surveillance registry. From an analysis of 760 CJD patients, Kobayashi[116] identify that six patients had undergone neurosurgery after the onset but before the diagnosis of CJD during the period from 1999 to 2008.[116]

Cases of suspected but unconfirmed Creutzfeldt–Jakob disease 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.[117] A study by Hall *et al.*[118] reports that 154 patients in the UK are considered to be 'at increased risk' of various forms of CJD following neurosurgery. This paper reports that of these 154 patients, only 129 have been informed that they are at an increased risk of CJD, either because of deaths before notification or because a local decision was taken not to inform the individual. Although no incidence of CJD has been reported within these 154 patients, the authors highlight that 'at-increased-risk' patients often have a relatively short life expectancy because of their medical conditions. Diagnosing asymptomatic infection requires testing specific tissues that are most readily available at post-mortem. Few post-mortems have been conducted when at-increased-risk individuals have died; therefore, some asymptomatic infections may have been missed.

Two published papers[119,120] from the USA report instances in which potential iCJD exposure via neurosurgery was investigated in hospitals; however, no confirmed cases of transmission were subsequently identified.

Risks in surgery other than neurosurgery

Prospective risks from surgery

A study by Baig and Phillips[40] describes a case report of a male patient (aged 66 years) who had surgical fixation of a hip fracture, most probably around the onset of CJD symptoms; therefore, given the lack of symptoms, the standard sterilisation method was appropriately used. The authors highlight that this standard decontamination method is typically not adequate for the eradication of the CJD prion protein, thus 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 instead highlights a circumstance where subsequent iatrogenic transmission may have occurred because of a lack of high-risk decontamination procedures. However, surgery of low infective tissues in individuals diagnosed with CJD is noted to be common and,[110,111] therefore, surgery that 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.*[121] found infectivity in the skin of sCJD patients, albeit at prion levels 1000–100,000 times lower than that in the brain and detectable only by an extremely sensitive assay.[121,122] However, a study using humanised transgenic mouse models demonstrated that the skin prions were infectious. The study authors argue that extra precautions should be taken during non-neurosurgeries in sCJD patients, particularly when instruments will be re-used, because infectivity through skin was previously unknown.

A study by Notari *et al.*[123] found from a neuropathological examination of a vCJD case in the USA 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.[123] The authors concluded 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.*[124] postulate that ocular tonometry is a risk factor for contracting sCJD from a case–control study conducted across 11 states in the USA. 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.[124]

Tullo *et al.*[125] document that there were 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.[125] At the time of publication, two recipients remained symptom-free of CJD, whereas one patient had died, aged 92 years (7 years after surgery), showing some signs of dementia that were not considered indicative of iCJD.

Jirsova *et al.*[126] conducted an analysis of brain tissue samples from the frontal lobe of 1142 eye donors obtained from three 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.*[127] used data from corneal transplantation and CJD deaths from 1990 to 2006 in a statistical analysis, to suggest that a case of coincidental sCJD will occur among the population of corneal transplant recipients approximately every 1.5 years.[127]

Risks in dentistry

Bourvis *et al.*[128] conducted a risk assessment of the transmission of sCJD in endodontic treatment in the absence of adequate prion inactivation. The authors developed a mathematical model, which incorporated experimental and observational data and expert consultation. They 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 is essential in dentistry, and even suggest that the cost–benefit of single-use endodontic instruments should be re-evaluated. Everington *et al.*[129] found no evidence of an increased risk of vCJD associated with reported dental treatments in a case–control study of UK vCJD patients.[129] However, the authors do not rule out the possibility that some cases may have resulted from secondary transmission via dental procedures. Azarpazhooh and Fillery[130] highlight that, although 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 dental procedures.[130]

Discussion/summary of risk of Creutzfeldt–Jakob disease transmission via surgery

Although no studies have identified a new case of stCJD 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 being relevant to CJD and surgery, including younger age at first exposure, increased risk of surgery around the time of symptom onset, the risk to health-care professionals, and the 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. When considering vCJD, surgical procedures (other than high-risk procedures) that could potentially be regarded as posing a risk of iatrogenic transmission include appendectomy and tonsillectomy. However, no direct evidence exits to highlight a serious risk from surgical procedures involving tissues that are not high risk.

Incubation periods of acquired transmissible spongiform encephalopathys

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.

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 (first author and year of publication)	Design	Population	Source of infection	Location	Number of cases
Ae (2016)[35]	Epidemiological surveillance	iCJD	Dura mater graft	Japan	149
Brown (2012)[3]	Epidemiological surveillance	iCJD	All	International	469
Brown (2015)[6]	Review	iCJD	Neurosurgery	International	6
Chohan (2010)[82]	Case study	iCJD	Blood products	UK	1
Collinge (2008)[131]	Epidemiological surveillance, cohort	Kuru	Ingestion	Papua New Guinea	11
Collinge (2008)[132]	Review	Kuru	Ingestion	Papua New Guinea	NA
Collinge (2006)[133]	Epidemiological surveillance, cohort	Kuru	Ingestion	Papua New Guinea	11
Collinge (2006)[134]	Letter: reply regarding Collinge *et al.*[134]	Kuru	Ingestion	Papua New Guinea	NA
Davidson (2014)[83]	Retrospective cohort	iCJD	Blood products	UK	9
Haïk (2014)[135]	Review	CJD	All	International	NA
Hamaguchi (2013)[136]	Epidemiological surveillance	iCJD	Dura mater graft	Japan and international	195
Heath (2006)[137]	Epidemiological surveillance	iCJD	Dura mater graft	UK	8
Hirst (2005)[138]	Epidemiological surveillance	iCJD	hGH	UK	1
Peden (2010)[77]	Case study	iCJD	Blood products	UK	3
Meissner (2009)[139]	Retrospective cohort	iCJD	Dura mater graft	Germany	10
Ritchie (2017)[140]	Epidemiological surveillance, retrospective cohort	iCJD	hGH, dura mater graft	UK	37
Rudge (2015)[69]	Epidemiological surveillance, cohort	iCJD	hGH	UK	22
Wroe (2006)[141]	Case study	iCJD	Blood products	UK	1

NA, not applicable.

The diagnosis of definite or probable iCJD depends on identification of the likely 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.

UK data on incubation

A summary of data on incubation periods for iCJD in the UK is presented in *Table 8*.

Dura mater grafts and genotypes

Frequency data and mean incubation periods by genotype are presented in *Table 8* for the UK subset of CJD cases that are known to be caused by dura mater. The worldwide number of iCJD cases due to dura mater surgery exceeds 200, and it is known that the majority have occurred in Japan ($n = 149$).[35]

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

Source of infection	Number of cases (*n*)		Incubation periods for overall data (years)		Studies/reports (first author and year of publication)
	Overall	UK	Mean	Range	
Primary transmission					
vCJD from ingestion/BSE	229	175[a]	12	–	Haik (2014);[135] NCJDRSU (2017)[2]
Kuru	–	0	12[b]	4–> 40	Haik (2014);[135] Collinge (2006);[133] Ritchie (2017)[140]
Secondary transmission					
Dura mater graft	228	8	12	1.3–30	Brown (2012);[3] Haik (2014)[135]
Neurosurgical instruments	4[c]	3	1.4	1–2.3	Brown (2015);[6] Brown (2012);[3] Haik (2014)[135]
EEG needles	2	0	–	1.3–1.7	Brown (2015);[6] Brown (2012);[3] Haik (2014)[135]
Corneal transplant	2	0	–	1.5–27	Brown (2012);[3] Haik (2014)[135]
Growth hormone	226	78	17	5–42[d]	Ritchie (2017)[140]
		21	20	8–31	Ritchie (2017)[140] – online table 1
Gonadotrophin	4	0	13.5	12–16	Brown (2012)[3]
Packed red blood cells	3	3	–	6.5–8.3[e]	Brown (2012);[3] Haik (2014)[135]
	2	2			Wroe (2006);[141] Peden (2004);[78] Ironside (2010);[146] Chohan (2010)[82]
Total (secondary transmission)	471	81			

a UK only: ACDP 2016; NCJDRSU,[2] $n = 178$ (but this includes the three cases of blood transfusion). However, no incubation data were provided.
b Collinge[132] reported 11 new cases from 1996 to 2004 with a much longer mean incubation period of 48.7 years (range 39–56 years) and with a much higher proportion of heterozygotes: 80% compared with < 50% in earlier samples (Cervenova *et al.*,[142] Klitzman *et al.*[143]).
c Possible additional cases of iCJD as a result of neurosurgery have also recently been identified (Brown and Farrell;[6] Kobayashi *et al.*;[144] Xiao *et al.*[145]), but no incubation data are available.
d Based on assumed midpoint date of multiyear periods of treatment, and the onset of symptoms (Ritchie *et al.*,[140] online table 1).
e Incubation data are available only for the three clinical cases; two cases were non-clinical, i.e. there was transmission by transfusion, but the patients died asymptomatic.

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

Source of infection	Number of cases (*n*)	Mean incubation period (years)	Range (years)	Studies/reports (first author and year of publication)
Dura mater graft 1990–2012[a]	8[b]	7.8[c]	3.8–14.8[c]	Heath (2006)[137]
	3	11[d]	8–15	[d]Ritchie (2017)[140]
Neurosurgical instruments	3	1.4	1.3–1.6	Brown (2015)[6]
EEG needles	0	NA	NA	–
Corneal transplant	0	NA	NA	–
Growth hormone 1990–2012[a]	78	NR	NR	Ritchie (2017)[140]
	65	20	7–39	Brown (2012)[3]
	21	19	11–31	[d]Ritchie (2017)[140]
Gonadotrophin	0	NA	NA	–
Packed red blood cells	3	–	6.5–8.3	Brown (2012)[3]
				Haik (2014)[135]

NA, not applicable; NR, not reported.
a Sample with frozen tissues from patients who died in 1990–2012.
b One of which was a porcine not human source of graft.
c Data reported as months, calculated by the reviewer as years.
d Supplementary online table 1.

Frequency data and mean incubation periods by genotype, extracted from Brown *et al.*,[3] are also presented in *Table 9* for subsets of the worldwide (excluding Japan) and Japanese affected populations. Hamaguchi *et al.*[147] reported a mean incubation period of 12.1 years (range 1–30 years) for 142 patients in Japan and 11.3 years (range 1–23 years) for a subset of 53 patients with published data from the other countries, although this subset did not include a Dutch case of dura mater-related iCJD that had an incubation period of 28 years, which is the longest reported incubation period outside Japan.[148]

Meissner *et al.*[139] reported on a sample of 10 cases (nine from Germany and one from Croatia) of iCJD related to dura mater, which were identified between 1993 and 2006. The median incubation period was 18 years (range 9 to 23 years), with 90% of cases being homozygotes, the majority of which were the MM genotype (80%). This study also reviewed published evidence from the literature on 27 international patients with iCJD because of dura mater grafts who had 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, mainly 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 CJD cases caused by hGH. It is reported that one particular preparation of hGH was most probably responsible for cases of iCJD caused by hGH in the UK, to date.[3,69]

As reported in *Table 7*, 78 cases had been reported in the literature for the UK as of 2017,[140] an increase from the 65 cases reported previously.[69] Ritchie *et al.*[140] 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, whereas the VV genotype had the shortest mean incubation period. The heterozygous genotype MV was the most frequently identified genotype in both subsets. There is potential for some crossover of data between the included studies, which cannot be accounted for in this review.

TABLE 9 Mean incubation periods by genotype for iCJD because of dura mater grafts

Location	Number of cases (*n*)	Genotype							
		Homozygotes						Heterozygotes	
		MM		VV		Total		MV	
		Frequency (%)	Incubation period (years)	Frequency (%)	Incubation period (years)	Frequency (%)	Incubation period (years)	Frequency (%)	Incubation period (years)
Not Japan[3,136]	54[a]	65	12	15	12	80[a]	12	20	16
[b]Japan[3,136]	54[c]	96	16	0	–	96	16	4	13

a Hamaguchi[136] reports data for a subset of 29 patients with both MM and MV having a mean incubation period of 13 years, with 74.3% of a subset of 35 patients being homozygotes.
b 142 out of 228 known worldwide cases are from Japan.[3,136] Note: according to an abstract by Ae *et al.*[35] 149 cases now reported in Japan, with a mean incubation period of 13 years and a maximum period of 30 years.
c Hamaguchi[136] reports the same figures for 58 patients.

TABLE 10 Mean incubation periods reported from included studies by genotype for iCJD caused by human growth hormone

Location	Cases with genotype data/total known cases	Genotype									
		MM		MV		VV		Homozygotes		Heterozygotes	Study (first author and year of publication)
		Frequency, *n* (%)	Incubation period (years)	Frequency, *n* (%)	Incubation period (years)	Frequency, *n* (%)	Incubation period (years)	Frequency	Incubation period (years)	Incubation period (years)	
UK	21/78 (1990–2012)[a]	2 (10)	30	12 (57)	18.5	7 (33)	15.7	43%	19	19 years	[b]Ritchie (2017)[140]
UK	37	10%		68%		22%		32%			Ritchie (2017)[140]
UK	56/65	8 (14)	30.8	33 (59)	23.4	15 (27)	14.3	41%		23	Rudge (2015)[69]
UK	22 (2000–2014)	4 (18)	31.8	17 (77)	28.6	1 (5)	20.6	23%		29	Rudge (2015)[69]
UK	28	1 (4)	21	13 (50)	23	14 (46)	18	54%	20	23	Brown (2012)[3]
France	111/119	54%	12			15%	9	69%	11	17	Brown (2012),[3] Haik (2014)[135]
USA	11/29	55%	21			18%	18	73%	20	23	Brown (2012)[3]

a Sample with frozen tissues from patients who died in 1990–2012. Hirst[138] reports a case of hGH with an incubation period of 24 years.
b Online tables 1 and 3.

These findings were broadly similar to those reported for another subset analysis of iCJD patients using imaging, molecular and autopsy data.[69] Rudge *et al.*[69] present data on a subset of 22 patients from 56 patients with genotypic data available. They studied a cohort of 22 patients diagnosed between 2000 and 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.*[69] 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 (1) mean 25.9 years (range 18.3–33.6 years); (2) mean 29.3 years (range 20.6–37.6 years); and (3) mean 32.8 years (range 23.2–43.3 years).[69] Incubation times between the cohort of 22 patients and a large subset of the UK group as whole were also compared.[69] The mean incubation times were longer in the latter cohort, but there was a noteworthy change in the proportion of MM and VV homozygote genotypes between the two periods; there was only one case of the VV genotype in the period 2000–14 compared with 14 occurring before 1998, whereas seven of the eight MM homozygotes occurred after 2004.[69] 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 caused by dura mater grafts appear shorter and are dominated by the MM genotype (see *Table 9*). The group with iCJD affected by hGH are equally distinct in terms of genotype, from individuals with sCJD.[140]

Discussion/summary of incubation data

The incubation periods for CJD reported in the published literature range from 1 to 42 years, with the shortest durations occurring in stCJD and the longest durations occurring in kuru or iCJD via hGH. Different incubation times might occur because of the resistance of different genotypes. Evidence from kuru studies[132,133] indicates that incubation times are shorter and mortality risk is significantly greater in those with the homozygous genotype (MM or VV) compared with the heterozygous genotype (MV), which has longer incubation times; older survivors are, therefore, more likely to be MV.[131,134] 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 the proportions of heterozygotes and homozygotes are similar across countries or groups but the incubation times are different, it has been proposed that differences in these incubation times might be because of infection with different strains or subtypes of the CJD agent.[135,140] For example, most cases of hGH iCJD in France were of the MM genotype, whereas in the UK the VV and MV genotypes predominated. Infections that appear to affect certain genotypes in a particular location may reflect an absence of genotypic resistance to a particular strain and, thus, have 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.[3]

Diagnoses of sCJD could potentially be made that are actually iatrogenic in origin. Correct identification can be difficult if cases of iCJD initially present as sCJD. Ritchie *et al.*[140] and Kobayashi *et al.*[144] 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.[140] 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.

The infectivity of Creutzfeldt–Jakob disease

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.

Studies discussing the infectivity of Creutzfeldt–Jakob disease

Infectious mass required to transmit Creutzfeldt–Jakob disease

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_{50}.

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 the risk of vCJD transmission via surgery[12,13] and implemented in IPG196[14] are reported in *Table 11*.

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.*[149] used protein misfolding cyclic amplification (PMCA) with beads to propagate abnormal prion protein scrapie (PrP^{Sc}) (infectious isoform/protease K-resistant prion protein) in Syrian hamsters. 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.*[150] also found that it was possible to detect higher levels of vCJD infectious titre in a human spleen using a novel bioassay than with a gold-standard immunoblot bioassay. As methods for end-point titration improve, it is therefore likely that some variation in 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; however, the phenotype (or observable physical properties) for MV and VV cases has been noted to be less predictable because of reduced transmission efficiency and increased incubation periods.[79,89] The vCJD prion or agent appears to replicate in lymphoid tissues during the asymptomatic phase of the incubation period.[151] A study[152] of abnormal prion protein accumulation in peripheral tissues from MV individuals has been undertaken to understand the infectivity and the risk of horizontal transmission. Bishop *et al.*[152] inoculated

TABLE 11 Estimated infectious titre of human tissue by surgical procedure in NICE IPG196[14]

Risk of CJD transmission	Surgical procedure	Infectivity
High	Brain and pituitary gland	10^{8} ID_{50s}/g
	Posterior eye, retina and optic nerve	
	Intradural spine operations	
	Neuroendoscopy	
Medium	Spinal cord	10^{6} ID_{50s}/g
	Tonsils	$10^{5.5}$ ID_{50s}/g
	Spleen	$10^{5.5}$ ID_{50s}/g
	Lymphoid tissue	$10^{4.5}$ ID_{50s}/g
	Anterior eye	$10^{3.5}$ ID_{50s}/g
	Peripheral nerves	

mice with brain and spleen samples from a subclinical vCJD recipient and the clinical vCJD donor. They found transmission of vCJD from the spleen to the mice 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 concluded that spleen tissue from the MV genotype can propagate the vCJD agent and that the infectious agent can be present in the spleen without central nervous system (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.*[150] in their evaluation of novel methods for end-point titration of 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 potential silent carriers of vCJD in lymphoid tissue as a key issue.[150]

Subtype or phenotype of Creutzfeldt–Jakob disease

In sCJD, an interaction between the host genotype at codon 129 and the causative agent identified as either PrP^{Sc} type 1 or PrP^{Sc} type 2 produces different clinical and histopathological phenotypic expressions, which may be influenced by other factors such as route of infection or locations of the initial PrP^{Sc} conversion.[153] In sCJD, six major subtypes carrying diverse clinical and pathological features have been identified: (1) MM1/MV1, (2) VV2, (3) MV2 with kuru plaques (MV 2K), (4) MM2-cortical (MM2C), (5) MM2-thalamic (MM2T) or sporadic fatal insomnia and (6) VV1.[154] In mice studies, all subtypes have been found to be transmissible to at least one genotype.[155] Four major prion strains have been proposed to underlie sCJD, iCJD, kuru and some gCJD cases, which are termed M1, V2, M2 and V1.[89] Variant CJD, however, can be distinguished from other categories of CJD owing to the unique PrP^{res} biochemical glycotype referred to as type 2B or type 4, which are also found in cases of natural BSE and other BSE-related conditions.[90]

Definitive information on the phenotype can be identified only following neuropathological examination, which provides the opportunity to establish whether or not CJD may have been acquired as opposed to being sporadic or genetic causes. Kobayashi *et al.*[98] propose the distinctive combination of the MM genotype at codon 129, kuru plaques and intermediate-type PrP^{Sc} as a reliable criterion for the identification of iatrogenically acquired CJD cases among presumed sCJD cases. Additionally, some studies highlight that, although exclusive type 1 (sCJDMM1) or type 2 (sCJDMM2) cases do exist, a frequent co-occurrence has been noted of both PrP^{Sc} type 1 and type 2 in sCJD in different areas, or the same area, of the brain from a single sCJD patient.[156] This finding complicates the diagnosis and the current classification of sCJD,[153] with Parchi *et al.*[154] highlighting the importance of assessing the cerebral cortex from each of the four lobes (striatum, hippocampus, thalamus and cerebellum) to avoid misclassification of disease. For example, Jansen *et al.*[157] 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. Similarly, an abstract by Mackay *et al.*[158] reports that 26 out of 108 sCJD patients (24%) had both type 1 and type 2 proteins on Western blot analysis. Mackay *et al.*[158] argue that the lack of distinct clinical or pathological findings in the six discrete subtypes suggests 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 the phenotypic variability and help to disclose the aetiology of CJD strains and efficiency of transmission, where possible.

Route of transmission

The route of transmission may also be relevant to the infectivity of iCJD. A study of five dura mater iCJD cases conducted by Iwasaki *et al.*[159] indicated that the initial symptoms at perceived sCJD onset appeared 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. Sakai *et al.*[160] also support the finding of a relationship between the initial clinical manifestation and the site of graft in patients with dura mater graft-associated CJD.[160] Beringue *et al.*[161] demonstrated in a study of transgenic mice that prion strain divergence can occur on transmission of human primary vCJD, and that peripheral exposure in mice resulted in inefficient neuroinvasion with asymptomatic, life-long infection of the lymphoid compartment.[161]

Beringue *et al.*[162] 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. Cali *et al.*[163] demonstrated that novel phenotypes may arise as a result of the adaptation of heterologous prion strains of sCJD through contaminated growth hormone.[163] A conference abstract by Peden *et al.*[164] also described that human-to-human transmission of prion disease may affect the seeding properties of the PrP^{Sc} associated with the disease. 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.*,[67] which 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.[67]

Detection of Creutzfeldt–Jakob disease

Whether or not and when asymptomatic carriers of CJD become infectious is important in understanding the potential risks of contamination during surgery. Bougard *et al.*[165] described an assay that detected prions 1.3 and 2.6 years before the clinical onset of disease in plasma samples from two blood donors who later developed vCJD. The authors report that the ability to identify presymptomatic ($n = 2$) and symptomatic ($n = 18$) vCJD-positives in a blinded cohort of 256 plasma samples comprising sCJD, Alzheimer's disease, Parkinson's, other neurological diseases and healthy controls 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 vCJD. However, the reliability of this marker for representing subclinical or indeed, clinical, vCJD has been questioned. Mead *et al.*[166] 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 a biopsy and at autopsy showed minimal deposition of disease-associated prion protein in tonsil tissue.[166] 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 because of the sensitivity of the CJD assay employed. Examination of 14-3-3 proteins in both the cerebrospinal fluid and a RT-QuIC assay are commonly employed tests that are considered to be sensitive and specific for sCJD detection, although less so for vCJD.[167] For example, the identified heterozygous clinical vCJD patient, aged 36 years in 2016,[37] tested negative for the 14-3-3 protein, RT-QuIC assay and vCJD-focused 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.*[168] used a highly sensitive PMCA assay to assess abnormal prion accumulation in the identified heterozygous subclinical vCJD patient, aged 82 years in 2017. Previous investigations had not detected abnormal prion protein or infectivity in the brain, indicating a lack of CNS involvement at the time of death.[78,152] However, using this assay they found vCJD prions in all lymphoid organs and a wide variety of other tissues, including the 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 neurological 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.*[152,169] reported that spleen tissue from the MV genotype 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.[152,169] However, Wadsworth *et al.*[170] found from an animal study of transgenic mice that, although vCJD prion infection was readily reported following inoculation with frozen vCJD brain or appendix, and formalin-fixed, paraffin-embedded (FFPE) brain, no infectivity was detected from FFPE vCJD spleen or FFPE appendix samples.[170] The authors caution that the absence of detectable infectivity in fixed, known positive vCJD lymphoreticular tissue does not definitively prove that vCJD transmission cannot occur through appendix specimens, as the assays used were not able to detect the low levels of infectivity previously found in the positive control lymphoreticular tissue following formalin fixation by Hilton *et al.*[7] However, in contrast, Halliez *et al.*[150] more recently found that lymphoid tissue exhibits higher capacity than the brain to replicate prions using novel detection methods.

Infectivity of genetic Creutzfeldt–Jakob disease

The potential for horizontal transmission of gCJD, as discussed previously, was raised by the unusually high prevalence of gCJD in Slovakia.[47] Ritchie *et al.*[171] report from an animal study of squirrel monkeys that no clinical or pathological signs of CJD were observed following blood transfusion of either sCJD or vCJD of the intracerebral-inoculated monkeys after euthanasia at 7 years. 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. Ritchie *et al.*[17] 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.[171] The infectiousness of CJD via blood is not directly relevant to the current decision problem of CJD risk via surgery. However, consideration of the 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 a sequence of amino acids and other proteins that demonstrate heterogeneity, which is specific for an individual but more common in an ethnic group. The relative contribution of each PrP allotype to the infectious disease associated with the abnormal isoform of prion protein (PrP^{Sc}) is unknown. Moore *et al.*[172] 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.[172] However, an analysis of six heterozygous cases of iCJD found that the composition of PrP^{Sc} iCJD was more homogenous and tended to contain a higher proportion of PrP^{Sc}-V129 than 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 (sCJD and iCJD), the PrP^{Sc} allotype ratio had no correlation with CJD type, age at clinical onset or disease duration. This evidence suggests that, therefore, factors other than PrP^{Sc} allotype abundance must influence the clinical progression and phenotype of heterozygous cases of CJD.

Discussion/summary of infectivity of Creutzfeldt–Jakob disease

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 the genotype at *PRNP* codon 129, infecting prion strain, route of transmission and location of *PRNP* conversion. Moreover, the method of detection and the analysis of CJD is crucial in obtaining detailed and accurate neuropathological confirmation of CJD type in order to posit the most plausible explanations for acquisition of iCJD.

Although few data regarding infectious dose or infectious titre in humans have been published to supersede the information used to populate the model built by ScHARR in 2005,[12] some animal studies using advanced detection methods indicate that infectious doses > 10^8 ID_{50} are possible.

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, that is 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,[173] a potentially effective decontaminant (Rely+On®; DuPont, Midland, MI, USA) to be used prior to autoclaving experienced barriers to its uptake in the NHS owing to (1) the perceived low risk of iCJD through surgical transmission and (2) resistance to the inclusion of an additional step in the decontamination process.[173] It should therefore be noted that, first, based on the number of known cases, the risk of iCJD through 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.

Decontamination studies

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

Five studies[174–178] reported log-reductions of prion infectivity after autoclaving with and without other decontamination processes (*Table 12*). In terms of prion strain, three studies used 10% brain homogenate of 263K hamster scrapie,[174–176] two used vCJD,[176,177] and the following prion strains were investigated in only a single study: 127S,[177] M1000[178] and BSE 6PB1.[176] All studies used steel wires contaminated with the prion (one study also used steel sheets[176]) and all studies investigated autoclaving at 121 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 hydroxide (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[174] to > 5–6,[176] 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.[176] Autoclaving at 134 °C for 5 minutes combined with alkaline cleaners or 0.2% SDS or 0.3% NaOH at different concentrations and/or different durations, also produced log-reductions of > 5.5 for the 263K prion strain.[175]

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

Study (first author and year of publication)	Prion strain(s)	Source material (% w/v)	Steel	Decontamination methods		Assay used
				Autoclaving	Other	
Belondrade (2016)[177]	127S scrapie and vCJD	BH (10)	Wires	• 121 °C: 20 minutes • 134 °C: 20 minutes	• 0.1 N NaOH: 15 minutes • 1 N NaOH: 60 minutes • 0.2% NaOCl: 15 minutes • 2% NaOCl: 15 minutes • 0.2% SDS /0.3% NaOH: 10 minutes	PMCA
Lawson (2007)[178]	M1000	BH (10)	Wires	• 121 °C: 20 minutes • 134 °C: 18 minutes	• RMEC A (enzymatic detergent) • RMEC B (enzymatic detergent) • 1.0M NaOH: 60 minutes	Tga20 mice WB
Lehmann (2009)[174]	263K scrapie	BH (10)	Wires	• 134 °C: 18 minutes	• H_2O_2: 30 minutes • AF: 10 minutes • Np-Np-H_2O_2/Cu: 10 minutes – 5 minutes – 15 minutes) • Dp-Dp-H_2O_2/Cu: 10 minutes – 5 minutes – 15 minutes • Np-Dp-H_2O_2/Cu: 10 minutes – 5 minutes – 15 minutes • Nmp-Nmp-PAA/Cu: 10 minutes – 5 minutes – 15 minutes, at 40 °C	Syrian golden hamsters
Lemmer (2008)[175]	263K scrapie	BH (10)	Wires	• 134 °C: 5 minutes	• 1.0M NaOH: 60 minutes at 23 °C • 2.5% NaOCl: 60 minutes at 23 °C • Alkaline cleaner 0.5% and 1%: 5/10 minutes at 55 °C • 0.2% SDS/0.3% NaOH: 5/10 minutes at 23 °C • Disinfectant with 0.2% PAA/0.075–0.225% NaOH: 120 minutes at 23 °C	Syrian golden hamsters
Rogez-Kreuz (2009)[176]	263K scrapie, vCJD[a] and BSE 6PB1[a]	BH (10 or 20)	Wires, sheets[a]	• 134 °C: 18 minutes	• 1 N NaOH: 60 minutes • H_2O_2: 10 or 20 minutes • 2% enzymatic detergent: 10 minutes at 37 °C • 1% alkaline detergent A: 10 minutes at 70 °C • 1% alkaline detergent B: 10 minutes at 55 °C	Syrian golden hamsters, WB[a]

AF, alkaline detergent, surfactants, chelatant; BH, brain homogenate; Dp, detergent and disinfectant for manual process; NaOCl, sodium hypochlorite; NaOH, sodium hydroxide; Nmp, detergent for washer (machine) process (used at 40 °C); Np, detergent for manual process; PAA, peracetic acid; RMEC, rapid multienzyme cleaner trial formulation; SDS, sodium dodecyl sulfate; WB, Western blot; w/v, weight/volume.
a In vitro only.

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 0.3% rapid multienzyme cleaner trial formulation (RMEC) B at 60 °C for 30 minutes.[178]

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

Study (first author and year of publication)	Prion strain	Decontamination methods		Log reduction	Transmission rate, *n/N* (%)	Incubation period days, *n* (SD)
		Autoclaving	Other			
Belondrade (2016)[177]	127S	121 °C: 20 minutes		≥ 5	10/12 (83)	NR
		134 °C: 20 minutes		FE	0/12 (0)	NR
	vCJD	121 °C: 20 minutes		5	1/8 (12.5)	NR
		134 °C: 20 minutes		FE	0/8 (0)	NR
Lawson (2007)[178]	M1000	121 °C: 20 minutes		1.6	100%	106 (2)
		134 °C: 3 minutes		1.5	100%	104 (3)
		134 °C: 18 minutes		2.2	100%	120 (5)
		134 °C: 3 minutes	0.3% RMEC B: 60 °C for 30 minutes	≥ 4.5	10%	166 (NR)
		121 °C: 20 minutes	0.3% RMEC B: 60 °C for 30 minutes	> 5	0%	–
Lehmann (2009)[174]	263K	134 °C: 18 minutes		4.11	57%	140
[a]Lemmer (2008)[175]	263K	134 °C: 5 minutes	0.5% alkaline cleaner: 5 minutes at 55 °C	≥ 5.5	NR	NR
		134 °C: 5 minutes	0.5% alkaline cleaner: 10 minutes at 55 °C	≥ 5.5	NR	NR
		134 °C: 5 minutes	1% alkaline cleaner: 5 minutes at 55 °C	≥ 5.5	NR	NR
		134 °C: 5 minutes	1% alkaline cleaner: 10 minutes at 55 °C	≥ 5.5	NR	NR
		134 °C: 5 minutes	0.2% SDS/0.3% NaOH: 5 minutes at 23 °C	≥ 5.5	NR	NR
		134 °C: 5 minutes	0.2% SDS/0.3% NaOH: 10 minutes at 23 °C	≥ 5.5	NR	NR
		134 °C: 5 minutes	Disinfectant with 0.2% PAA/ 0.075–0.225% NaOH: 120 minutes at 23 °C	> 2 to < 3	NR	NR
Rogez-Kreuz (2009)[176]	263K	134 °C: 18 minutes		≥ 5 to 6	50%	428 ± 103
		134 °C: 18 minutes	1 N NaOH: 60 minutes	≥ 5 to 6	28%	554 ± 197
		134 °C: 18 minutes	2% enzymatic detergent: 10 minutes at 37 °C	4	100%	131 ± 17
		134 °C: 18 minutes	1% alkaline detergent A: 10 minutes at 70 °C	≥ 5 to 6	0%	525 ± 149
	263K in vitro	134 °C: 18 minutes		≥ 5.4	NR	NR

FE, fully efficient as no positive wires found; NR, not reported; PAA, peracetic acid; RMEC, rapid multienzyme cleaner trial formulation.
a Bioassay 2 only (bioassay 1 = 2004 data).

The aim of some studies is development of a prion detection assay, rather than the development of the decontaminant.[177]

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

Eleven studies reported log-reductions of prion infectivity after various decontamination processes, principally enzymatic detergents that did not use autoclaving (*Table 14*). In terms of prion strain, seven studies used 10% or 20% brain homogenate of 263 K hamster scrapie,[174–176,179–182] three used vCJD,[177,179,180] two used ME7[183,184] and the following prion strains were investigated in only a single study: Rocky Mountain Laboratory (RML),[185] BSE 6PB1 and TGB1,[181] M1000[178] and 127S.[177] Nine studies used steel wires contaminated with the prion, one study used steel tokens[183] and one used steel sheets.[176]

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

Study (first author and year of publication)	Prion strain	Source material (% w/v)	Steel	Decontamination methods other than autoclaving	Assay used
Beekes (2010)[179]	263K scrapie, vCJD (MM1), sCJD	BH (10)	Wires	• 0.2% SDS/0.3% NaOH in 20% or 30% *n*-propanol	Hamsters, WB
Bellon (2014)[180]	263K, vCJD (mouse adapted)	BH (20)	Wires	• 0.1–0.45 mol/l NaOH: 4–45 °C for 5–240 minutes	Hamsters, WB
Belondrade (2016)[177]	127S scrapie, vCJD	BH (10)	Wires	• 0.1 N NaOH: 15 minutes • 1 N NaOH: 60 minutes • 0.2% NaOCl: 15 minutes • 2% NaOCl: 15 minutes • 0.2% SDS/0.3% NaOH: 10 minutes	Surf-PMCA
Edgeworth (2011)[185]	RML	BH (10)	Wires	• Rely+On • Prionzyme® (Genecor, Rochester, NY, USA) • 0.8% and 1.6% Hamo® 100 PID • 2 M NaOH • 20% NaOCl	Tga20 mice, Tg20 mice SSBA
Fichet (2007)[181]	263K scrapie, 6PB1 BSE, TGB1 BSE	BH (10)	Wires	• 6% liquid H_2O_2: 20 °C for 60 minutes • 2 mg/l gaseous H_2O_2: 30 °C (3 pulses) • 2 mg/l gaseous H_2O_2: 30 °C (6 pulses)	Animal, WB
[a]Hervé (2010)[182]	263K scrapie	NR	Wires	• Cold atmospheric plasma	Animal
Hervé (2010)[183]	ME7	BH (NR)	Tokens	• Four unspecified enzyme cleaning products, commonly used in UK SSDs: 43 or 50 °C for 5 minutes	EDIC/EF and WB
Howlin (2010)[184]	ME7	BH (10)	Wires	• Presoak, plus unspecified enzyme pretreatment (containing proteases), plus alkaline detergent (includes potassium hydroxide) (Hamo® 100)	EDIC/EF and WB

continued

TABLE 14 Studies reporting log-reductions in prion contamination on steel surfaces after decontamination processes other than autoclaving (*continued*)

Study (first author and year of publication)	Prion strain	Source material (% w/v)	Steel	Decontamination methods other than autoclaving	Assay used
Lawson (2007)[178]	M1000	BH (10)	Wires	• RMEC A (enzymatic detergent) • RMEC B (enzymatic detergent) • 1 M NaOH: 60 minutes	Tga20 mice, WB
Lehmann (2009)[174]	263K scrapie	BH (10)	Wires	• H_2O_2: 30 minutes • AF: 10 minutes • Np-Np-H_2O_2/Cu: 10 minutes – 5 minutes – 15 minutes • Dp-Dp-H_2O_2/Cu: 10 minutes – 5 minutes – 15 minutes • Np-Dp-H_2O_2/Cu: 10 minutes – 5 minutes – 15 minutes • Nmp-Nmp-PAA/Cu: (10 minutes – 5 minutes – 15 minutes, 40 °C)	Hamsters
Lemmer (2008)[175]	263K scrapie	BH (10)	Wires	• 1 M NaOH: 60 minutes at 23 °C • 2.5% NaOCl: 60 minutes at 23 °C • 0.5% and 1% alkaline cleaner: 5/10 minutes at 55 °C • 0.2% SDS/0.3% NaOH: 5/10 minutes at 23 °C • Disinfectant with 0.2% PAA /0.075–0.225% NaOH: 120 minutes at 23 °C	Hamsters
Rogez-Kreuz (2009)[176]	263K scrapie, vCJD,[b] BSE 6PB1[b]	BH (10 or 20)	Wires, sheets[b]	• 1 N NaOH: 60 minutes • H_2O_2: 10 minutes, 20 minutes • 2% enzymatic detergent: 10 minutes at 37 °C • 1% alkaline detergents A: 10 minutes at 70 °C • 1% alkaline detergents B: 10 minutes at 55 °C	Hamsters, WB

AF, alkaline detergent, surfactants, chelatant; BH, brain homogenate; Dp, detergent and disinfectant for manual process; EDIC/EF, episcopic differential interference contrast/epifluorescence microscopy; Nmp, detergent for washer (machine) process (used at 40 °C); Np, detergent for manual process; NR, not reported; PAA, peracetic acid; PMCA, protein misfolding cyclic amplication; SSBA, standard steel-binding assay; SSDs, sterile service departments; surf, stainless-steel wire surfaces as carriers of prions; WB, Western blot; w/v, weight/volume.
a Abstract only.
b In vitro only.

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.*[185] 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 plus 2 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

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

Study (first author and year of publication)	Prion strain	Decontamination methods	Log-reduction	Transmission rate	Incubation period days, *n* (SD)	Other (e.g. $TICU_w$)
Beekes (2010)[179]	263K	0.2% SDS/0.3% NaOH in 20% *n*-propanol	≥ 5.5	0/10	503	
		0.2% SDS/0.3% NaOH in 30% *n*-propanol	≥ 5.5	0/9	503	
	vCJD	0.2% SDS/0.3% NaOH in 20% *n*-propanol	3.3	NR	NR	
	sCJD	0.2% SDS/0.3% NaOH in 20% *n*-propanol	3.3	NR	NR	
Bellon (2014)[180]	vCJD	0.1–0.45 mol/l NaOH: 25–45 °C for 5–240 minutes	≥ 3.8	0/8	NR	
	263K	0.45 mol/l NaOH: 4 °C for 60 minutes	4.9	2/8	441	
		0.2 mol/l NaOH: 15 °C for 15 minutes	5	1/5	237	
		0.2 mol/l NaOH: 15 °C for 60 minutes	≥ 5	0/8	NR	
		0.45 mol/l NaOH: 15 °C for 30 minutes	≥ 5.2	0/8	NR	
		0.45 mol/l NaOH: 15 °C for 60 minutes	≥ 5.2	0/8	NR	
		0.15 mol/l NaOH: 25 °C for 60 minutes	4.1	5/9	215	
		0.45 mol/l NaOH: 25 °C for 60 minutes	4.7	3/10	382	
		0.45 mol/l NaOH: 25 °C for 240 minutes	≥ 5.4	0/8	NR	
		0.45 mol/l NaOH: 40 °C for 5 minutes	≥ 5.3	0/8	NR	
		0.45 mol/l NaOH: 40 °C for 15 minutes	5.1	1/6	364	
		0.1 mol/l NaOH: 45 °C for 5 minutes	≥ 5.4	0/8	NR	
		0.1 mol/l NaOH: 45 °C for 15 minutes	≥ 5.4	0/8	NR	
Belondrade (2016)[177]	127S	0.1 N NaOH: 15 minutes	≥ 3	12/12	NR	
	vCJD	0.1 N NaOH: 15 minutes	3	6/8	NR	
Edgeworth (2011)[185]	RML	Rely-On PI[a]	5.5	0/19	> 250	
		Rely-On PI[b]	8	NR	NR	< 0.003 $TICU_w$
		Prionzyme plus 2 M NaOH[b]	8	NR	NR	< 0.003 $TICU_w$
		2 M NaOH[b]	8	NR	NR	< 0.003 $TICU_w$
		0.8% Hamo 100[b]	NR	NR	NR	0.3[c]
		1.6% Hamo 100[b]	NR	NR	NR	0.07[c]

continued

TABLE 15 Results of studies reporting log-reductions in prion contamination on steel surfaces by processes other than autoclaving (*continued*)

Study (first author and year of publication)	Prion strain	Decontamination methods	Log-reduction	Transmission rate	Incubation period days, *n* (SD)	Other (e.g. $TICU_w$)
Fichet (2007)[181]	263K	6% liquid H_2O_2: 20 °C for 60 minutes	1	11/11 (100%)	114 (13)	
		2 mg/l gaseous H_2O_2: 30 °C (3 pulses)	> 5.5	0/8	> 540	
		2 mg/l gaseous H_2O_2: 30 °C (6 pulses)	> 5.5	0/8	> 540	
	6PB1 BSE	2 mg/l gaseous H_2O_2: 30 °C (3 pulses)	> 5.5	0/9	> 540	
	TGB1 BSE	2 mg/l gaseous H_2O_2: 30 °C (3 pulses)	> 5.3	0/9	> 540	
[d]Hervé (2010)[182]	263K	Cold atmospheric plasma	> 6	NR	NR	
Hervé (2010)[183]	ME7	Cleaner 4 (most efficient): 50 °C for 5 minutes	3	NR	NR	99.21% of initial prion amyloid load removed
Howlin (2010)[184]	ME7	Unspecified enzyme pretreatment (containing proteases) without presoak	Approximately 2 log greater reduction in prion amyloid than presoak alone even if allowed to dry and 3 log-reduction if process was started immediately after contamination (wet)			
		Unspecified enzyme pretreatment (containing proteases) with presoak	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 0.001 ng/mm,^{2} wet or dry			
Lawson (2007)[178]	M1000	1 M NaOH: 60 minutes	2.7	100%	130 (19)	
		1% RMEC A: 50 °C for 30 minutes	≥ 4.5	80%	204 (18)	
		0.3% RMEC B: 60 °C for 30 minutes	≥ 3.5	60%	147 (13)	
Lehmann (2009)[174]	263K	H_2O_2: 30 minutes	≥ 5.25	0%	≥ 370	
		AF: 10 minutes	≥ 5.25	0%	≥ 370	
		Np-Np-H_2O_2/Cu: 10 minutes – 5 minutes – 15 minutes	4.55	43%	133	
		Dp-Dp-H_2O_2/Cu: 10 minutes – 5 minutes – 15 minutes	≥ 5.25	20%	159	
		Np-Dp-H_2O_2/Cu: 10 minutes – 5 minutes – 15 minutes	≥ 5.25	0%	≥ 370	
		Nmp-Nmp-PAA/Cu: 10 minutes – 5 minutes – 15 minutes, at 40 °C	3.43	67%	102	

TABLE 15 Results of studies reporting log-reductions in prion contamination on steel surfaces by processes other than autoclaving (*continued*)

Study (first author and year of publication)	Prion strain	Decontamination methods	Log-reduction	Transmission rate	Incubation period days, *n* (SD)	Other (e.g. $TICU_w$)
Lemmer (2008)[175]	263K	1.0 M NaOH: 60 minutes at 23 °C	≥ 5.5	NR	NR	
		2.5% NaOCl: 60 minutes at 23 °C	≥ 5.5	NR	NR	
		0.5% alkaline cleaner: 5 minutes at 55 °C	≥ 4 to < 5	NR	NR	
		0.5% alkaline cleaner: 10 minutes at 55 °C	> 5 to ≤ 5.5	NR	NR	
		1% alkaline: 5 minutes at 55 °C	> 5 to ≤ 5.5	NR	NR	
		1% alkaline cleaner: 10 minutes at 55 °C	≥ 5.5	NR	NR	
		0.2% SDS/0.3% NaOH: 5 minutes at 23 °C	≥ 5.5	NR	NR	
		0.2% SDS/0.3% NaOH: 10 minutes at 23 °C	≥ 5.5	NR	NR	
		Disinfectant with 0.2% PAA/0.075–0.225% NaOH: 120 minutes at 23 °C	> 5 to ≤ 5.5	NR	NR	
Rogez-Kreuz (2009)[176]	263K	H_2O_2: 10 minutes	≥ 5 to 6	50%	443 ± 140	
		H_2O_2: 20 minutes	≥ 5 to 6	50%	428 ± 142	
		2% enzymatic detergent: 10 minutes at 37 °C	1.1	100%	95 ± 0	
		1% alkaline detergent A: 10 minutes at 55 °C	≥ 5 to 6	11%	446 ± 153	
		1% alkaline detergent B: 10 minutes at 55 °C	≥ 5 to 6	0%	524 ± 42	
		Sterrad NX1 (Advanced Sterilization Products Services Inc, Irvine, CA, USA) advanced cycle	≥ 5 to 6	0%	570 ± 18	
		Sterrad NX2 continuous advanced cycles	≥ 5 to 6	0%	574 ± 0	
		1% alkaline detergent A (10 minutes at 55 °C) plus Sterrad NX1 advanced cycle	≥ 5 to 6	0%	559 ± 22	
		1% alkaline detergent B (10 minutes at 55 °C) plus Sterrad NX1 advanced cycle	≥ 5 to 6	0%	562 ± 16	
	263K in vitro	Sterrad NX1 advanced cycle	≥ 5.4	NR	NR	

NR, not reported; PAA, peracetic acid; TICUw, tissue culture infectious units on wires; w/d, wet or dry.
a By bioassay in Tga20 mice alone.
b By SSBA.
c By far the least effective: more ineffective than autoclaving or Rely-On for Prionzyme, or 2 M NaOH. Note that Prionzyme'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 highly hazardous.[185]
d In vivo.

manufacturer's instructions), that is 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 process 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 0.2% SDS/0.3% NaOH in 20% or 30% *n*-propanol;[179] 0.2 mol/l NaOH at 15 °C for 60 minutes; 0.45 mol/l NaOH at 15 °C for 15 or 30 minutes; 0.45 mol/l NaOH at 25 °C for 240 minutes; 0.45 mol/l NaOH at 40 °C for 5 minutes; 0.1 mol/l NaOH at 45 °C for 5 or 15 minutes;[180] 2 mg/l gaseous H_2O_2 at 30 °C for 3 or 6 pulses;[181] H_2O_2 for 30 minutes; AF (alkaline detergent, surfactants, chelatant) for 10 minutes; and combinations of enzymatic detergents and disinfectants Np-Dp-H_2O_2/Cu (for 10 minutes – 5 minutes – 15 minutes),[174] the alkaline detergent B at 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 at 1% for 10 minutes at 55 °C, in combination with the Sterrad NX1 advanced cycle,[176] and cold atmospheric plasma.[182] According to Rogez-Kreuz *et al.*,[176] no insoluble prion (PrP^{res}) 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 three pulses.[181] None of the treatments for the ME7, vCJD, 127S or M1000 prion strains reported a log-reduction of ≥ 5 and a transmission rate of 0%.[177,178,182,184]

Supplementary evidence: studies reporting outcomes other than log-reductions after autoclaving with/without other processes

Six studies[185–190] reported outcomes other than log-reductions (*Table 16*). In terms of prion strain, two studies used 10% or 20% brain homogenate of RML[186] and two studies investigated sc237 and sCJD,[187,188] with the following prion strains investigated in only a single study: 263K scrapie,[189] and 301 V BSE and cattle BSE.[188] Five studies used steel wires contaminated with the prions and one study[189] used steel spheres. All studies investigated autoclaving at 121, 134 or 137 °C for specified amounts of time as a decontamination procedure; one study investigated autoclaving at 65 and 121 °C.[188]

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 (first author and year of publication)	Prion strain	Source material (% w/v)	Steel	Decontamination methods		Assay used
				Autoclaving	Other	
Baxter (2005)[189]	263K	BH (20)	Spheres	• 137 °C: 18 minutes	• Trigene (MediChem International (Manufacturing) Ltd, Queenborough, UK) disinfectant • Radio-frequency gas plasma	Hamsters
Edgeworth (2011)[185]	RML	BH (10)	Wires	• 134 °C: 18 minutes	• Rely+On • Prionzyme • 8% and 1.6% Hamo 100 PID • 2 M NaOH • 20% NaOCl	SSBA
Giles (2007)[188]	Sc237 sCJD	BH (10)	Wires	• 65 °C: 30 minutes, 120 minutes and 18 hours • 121 °C: 15, 30 and 120 minutes	• 2% SDS plus 1% AcOH	Tg7 and Tg23372 mice
Giles (2008)[190]	301V BSE Cattle BSE	BH (10)	Wires	• 65 °C: 8 minutes • 121 °C: 120 minutes • 134 °C: 120 minutes	• 4% SDS plus 1% AcOH	Tg2091 mice Tg4092 mice

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 (*continued*)

Study (first author and year of publication)	Prion strain	Source material (% w/v)	Steel	Decontamination methods		Assay used
				Autoclaving	Other	
Jackson (2005)[186]	RML	BH (10 and 20)	Wires	• 121 °C: 20 minutes • 134 °C: 20 minutes	• Enzymes: SDS-PK-Pronase • 2 M NaOH • LpH, LpHse • Endozyme Plus (Ruhof, Mineloa, NY, USA)	Tg20 mice, CD-1 mice, WB
	RML	BH (10)	Wires	• 134 °C: 20 minutes	Enzymes	Tg20 mice, CD-1 mice, WB
Peretz (2006)[187]	Sc237 sCJD	BH (10)	Wires	• 121 °C: 15, 30 and 120 minutes • 134 °C: 15, 30 and 120 minutes	• 2% SDS plus 1% AcOH • 4% SDS plus 1% AcOH	Tg7 and Tg23372 mice Micro BCA Protein assay (Pierce, Rockford, IL, USA)

AcOH, acetic acid; BH, brain homogenate; PK, proteinase K; WB, western blot; w/v, weight/volume.

The efficiency of autoclaving was assessed alone and in combination with a range of other decontaminants. These included SDS, acetic acid (AcOH), NaOH, radiofrequency (RF) gas plasma, Trigene disinfectant and various other enzymatic detergents. Selected results from these investigations are reported in *Table 17*.

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 (first author and year of publication)	Prion strain	Decontamination methods		Transmission rate	Incubation period days, *n* (SD)
		Autoclaving	Other		
Baxter (2005)[189]	263K	137 °C: 18 minutes	Trigene disinfectant	5/5	202 ± 28
			Trigene disinfectant	0/5	466[a]
			RF gas plasma	0/5	466[a]
Edgeworth (2011)[185]	RML	134 °C: 18 minutes	NR	5%	NR
[b]Giles (2007)[188]	Sc237 in Tg7 mice	65 °C: 30 minutes	2% SDS + 1% AcOH	100%	82 ± 0.7
		65 °C: 120 minutes	2% SDS + 1% AcOH	68%	269 ± 3.2
		65 °C: 18 hours	2% SDS + 1% AcOH	0%	> 400
		121 °C: 15 minutes	NR	100%	160 ± 7.3
		121 °C: 30 minutes	NR	20%	> 400
		121 °C: 120 minutes	NR	0%	> 400
		121 °C: 15 minutes	2% SDS + 1% AcOH	0%	> 400
		121 °C: 30 minutes	2% SDS + 1% AcOH	0%	> 400
		121 °C: 120 minutes	2% SDS + 1% AcOH	0%	> 400

continued

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 (*continued*)

Study (first author and year of publication)	Prion strain	Decontamination methods		Transmission rate	Incubation period days, *n* (SD)
		Autoclaving	Other		
	sCJD in Tg23372 mice	65 °C: 30 minutes	2% SDS + 1% AcOH	86%	354 ± 1.6
		65 °C: 120 minutes	2% SDS + 1% AcOH	44%	> 500
		65 °C: 18 hours	2% SDS + 1% AcOH	25%	> 500
		121 °C: 15 minutes	NR	22%	> 500
		121 °C: 30 minutes	NR	0%	> 500
		121 °C: 120 minutes	NR	73%	414 ± 15
		121 °C: 15 minutes	2% SDS + 1% AcOH	0%	> 500
		121 °C: 30 minutes	2% SDS + 1% AcOH	0%	> 500
		121 °C: 120 minutes	2% SDS + 1% AcOH	0%	> 500
Giles (2008)[190]	301V	134 °C: 15 minutes	NR	96%	161
		134 °C: 30 minutes	NR	57%	438
		134 °C: 120 minutes	NR	14%	> 600
		NR	1% AcOH: 65 °C for 18 hours	100%	117
		NR	4% SDS: 65 °C for 18 hours	100%	127
		NR	4% SDS + 1% AcOH: 65 °C for 30 minutes	73%	267
		NR	4% SDS + 1% AcOH: 65 °C for 120 minutes	33%	> 600
		NR	4% SDS + 1% AcOH: 65 °C for 18 hours	58%	410
		134 °C: 15 minutes	4% SDS + 1% AcOH	5%	> 600
		134 °C: 30 minutes	4% SDS + 1% AcOH	0%	> 600
		134 °C: 120 minutes	4% SDS + 1% AcOH	0%	> 600
	BSE	134 °C: 15 minutes	NR	84%	384
		134 °C: 30 minutes	NR	100%	375
		134 °C: 120 minutes	NR	89%	420
		NR	1% AcOH: 65 °C for 18 hours	91%	354
		NR	4% SDS: 65 °C for 18 hours	100%	368
		NR	4% SDS + 1% AcOH: 65 °C for 30 minutes	42%	> 500
		NR	4% SDS + 1% AcOH: 65 °C for 120 minutes	26%	> 500
		NR	4% SDS + 1% AcOH: 65 °C for 18 hours	4%	> 500

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 (*continued*)

Study (first author and year of publication)	Prion strain	Decontamination methods		Transmission rate	Incubation period days, *n* (SD)
		Autoclaving	Other		
		134 °C: 15 minutes	4% SDS + 1% AcOH	0%	> 500
		134 °C: 30 minutes	4% SDS + 1% AcOH	0%	> 500
		134 °C: 120 minutes	4% SDS + 1% AcOH	0%	> 500
Jackson (2005)[186]	RML (20% w/v) Tg20 mice	121 °C: 20 minutes	NR	0/6[a]	NR
		134 °C: 20 minutes	NR	0/4[b]	NR
		NR	LpH	5/5	91 (SEM 2.6)
		NR	LpHse	3/5[c]	70 (0)
		NR	Endozyme Plus	5/5	81 (1)
		NR	Enzymes SDS-PK-Pronase: 40 °C for 60 minutes	0/3	NR
		121 °C: 20 minutes	Enzymes SDS-PK-Pronase: 40 °C for 60 minutes	0/5[d]	NR
		134 °C: 20 minutes	Enzymes: SDS-PK-Pronase: 40 °C for 60 minutes	0/4	NR
	RML (20% w/v) CD-1 mice	134 °C: 20 minutes	NR	0/9	NR
		134 °C: 20 minutes	2 M NaOH	0/10	NR
		134 °C: 20 minutes	Enzymes SDS-PK-Pronase: 40 °C for 60 minutes	0/8	NR
		NR	Enzymes SDS-PK-Pronase: 40 °C for 60 minutes	0/10	NR
	RML (10% w/v) Tg20 mice	134 °C: 20 minutes	NR	13/13[c]	108 (12.4 SEM)
		NR	Enzymes SDS-PK-Pronase: 40 °C for 60 minutes	1/18 (101)	NR
Peretz (2006)[187]	Sc237 in Tg7 mice	121 °C: 15 minutes	NR	*n* = 10, 100%	160 ± 7.3
		121 °C: 30 minutes	NR	20%	> 400
		121 °C: 120 minutes	NR	0%	> 400
		121 °C: 15 minutes	2% SDS + 1% AcOH	0%	> 400
		121 °C: 30 minutes	2% SDS + 1% AcOH	0%	> 400
		121 °C: 120 minutes	2% SDS + 1% AcOH	0%	> 400
		134 °C: 15 minutes	NR	87%	96 ± 0.6
		134 °C: 30 minutes	NR	55%	262 ± 10
		134 °C: 120 minutes	NR	9%	> 400
		134 °C: 15 minutes	4% SDS + 1% AcOH	0%	> 400
		134 °C: 30 minutes	4% SDS + 1% AcOH	4%	> 400
		134 °C: 120 minutes	4% SDS + 1% AcOH	0%	> 400

continued

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 (*continued*)

Study (first author and year of publication)	Prion strain	Decontamination methods		Transmission rate	Incubation period days, *n* (SD)
		Autoclaving	Other		
	sCJD Tg23372	121 °C: 15 minutes	NR	*n* = 10, 22%	> 500
		121 °C: 30 minutes	NR	0%	> 500
		121 °C: 120 minutes	NR	73%	414 ± 15
		121 °C: 15 minutes	2% SDS + 1% AcOH	0%	> 500
		121 °C: 30 minutes	2% SDS + 1% AcOH	0%	> 500
		121 °C: 120 minutes	2% SDS + 1% AcOH	0%	> 500
		134 °C: 15 minutes	NR	73%	218 ± 4.1
		134 °C: 30 minutes	NR	63%	242 ± 2.8
		134 °C: 120 minutes	NR	46%	> 500
		134 °C: 15 minutes	4% SDS + 1% AcOH	0%	> 500
		134 °C: 30 minutes	4% SDS + 1% AcOH	0%	> 500
		134 °C: 120 minutes	4% SDS + 1% AcOH	0%	> 500

NR, not reported; SEM, standard error of mean; w/v, weight/volume.
a All animals in these groups were clinically sound when euthanized at 466 days.
b The data for decontamination at 121°C are the same data as reported in Peretz 2006.[187]
c Wires being placed in partially sealed glass tubes appears to have impaired the autoclaving process.
d Total numbers infected (but only apparent post-mortem): a = 2/6, b = 1/4; c = 4/5, d = 1/5.

Only one study reported the outcome 'tissue culture infectious units on wires' ($TICU_w$).[185] 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 301 V BSE prion strain were 96% and 57%, respectively, and for cattle BSE they were 84% and 100%, respectively.[190] 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.[186] 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.[186] 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%, respectively.[187,188] 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%, respectively.[187]

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 and 1% AcOH for the 301 V, cattle BSE,[190] Sc237 and sCJD prions strains;[187] autoclaving at 121 °C for 15, 30 or 120 minutes plus 2% SDS and 1% AcOH for the 301 V and cattle BSE prion strains;[190] and autoclaving at 65 °C for 18 hours plus 2% SDS and 1% AcOH for the Sc237 and sCJD prions strains.[188] Autoclaving at 134 °C for 20 minutes plus SDS-proteinase K (PK)-Pronase at 40 °C for 60 minutes also produced a 0% transmission rate for RML prion strains.[186]

Without autoclaving Trigene disinfectant and RF gas plasma, and SDS-PK-Pronase at 40 °C for 60 minutes, also produced transmission rates of 0% in the 263K and the RML prion strains, respectively.[186,189]

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

Nine studies[183,191–198] reported this outcome after autoclaving with and without other decontamination processes (*Table 18*): seven studies[192–198] for surgical instruments and two studies for endoscopes.[183,191] All studies were conducted in the UK. Seven studies[183,193–198] reported on protein residue on instruments acquired between one and nine NHS trusts; the number of trusts involved was not reported in two studies.[191,192] All studies reported that cleaning essentially involved conventional procedures for the equipment concerned. With the exception of two studies,[192,193] the assay appears to have involved detection of protein in situ on the instruments. Where reported, the number of instruments ranged from 2 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.*[193] reported a mean amount of protein per instrument of 71.67 µg (range 8–91 µg); Baxter *et al.*[192] reported a median range of 163–756 µg per instrument; Lipscomb *et al.*[194,195] reported residual contamination using an unvalidated 'contamination index' and reported that 56% of instruments (out of a total of 23) from a single NHS trust showed severe contamination (contamination index score of > 3–4) in at least one of the sample regions, whereas 66% of instruments ($n = 260$) from nine NHS primary care trusts showed equivalent severe contamination (contamination index score of > 3–4). According to this contamination index, a classification of 3 represents 0.42–4.2 µg of protein/mm^2 and a classification of 4 is > 4.4 µg of protein/mm^2. The most recent study,[196] reported residue 'per instrument side' for evaluated instruments from craniotomy sets ($n = 187$): 87% of instruments were found to have < 5 µg per instrument side and 96% were found to have < 10 µg per instrument side. Two papers did not explicitly quantify the residual protein but only noted its presence.[197,198] The studies assessing endoscopes reported either < 10 ng of protein/mm^2 after processing[183] or the 'equivalent to 1–4 µg of proteins per channel, except in one channel which harboured … equivalent to almost 33 µg of residual proteins for the whole channel'.[191]

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 precleaning 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: 1 µl drops of ME7-infected brain homogenate. Detection was made of in situ contamination using the same techniques: SYPRO® (Life Technologies Corporation, Carlsbad, CA, USA) ruby protein stain and episcopic differential interference contrast/epifluorescence microscopy. Across the studies, drying times before assessment ranged from 15 minutes[200] to 24 hours.[200,201]

The process to keep steel tokens or wires 'wet' was different in each study: Secker *et al.*[98] used a 'wet bag' (Humibag), that is a sealed bag containing 35 ml of distilled water for set time periods; Secker *et al.*[201] used an air-tight container lined with moist tissue for 17 hours; Howlin *et al.*[184] treated steel wires immediately, rather than allowing them to dry; and Lipscomb *et al.*[199] treated steel tokens with one of four presoak 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';[200] air dry for 24 hours;[201] air dry for 16 hours;[184] and air dry for 17 hours.[199] Different temperatures were evaluated but this text will focus only on the findings for room temperature (or the closest available data) across studies. Three of the four studies used the enzymatic cleaner Klenzyme (Steris, Mentor, OH, USA).

Both Secker *et al.* studies[200,201] reported on protein residue after 24 hours at room temperature before cleaning: 324.7 ± 15.0 ng of protein/mm^2 for the air dry conditions compared with 6.0 ± 3.5 ng of protein/mm^2 for the wet conditions (98.2% reduction compared with air dry; $p \leq 0.001$)[201] and 1000 ± 205.0 ng of protein/mm^2 for the air dry conditions compared with 31.9 ± 5.3 ng of protein/mm^2

TABLE 18 Study characteristics and results

Study (first author and year of publication)	Country	Source	Surgical instruments (number)	Cleaning cycle	Assay/in situ	Residual protein contamination of surgical instruments after conventional cleaning and sterilisation in a sterile service department	
						Mean protein per instrument (µg)	Median protein per instrument (µg)
Baxter (2006)[192]	UK	SSDs from a random sample of NHS trusts	Five trays ($n = 120$)	*Routine hospital cleaning and sterilisation*	Ninhydrin/acid stripping of surfaces and hydrolysing of proteins	NR	163–756 µg (range)[a]
[b]Lipscomb (2006)[194]	UK	SSD from one NHS trust	Ranged in shape and size ($n = 23$)	*Traditional machine washer-disinfector cleaning procedures*	SYPRO ruby protein stain and EDIC/EF microscopy Unclear[c]	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 contamination index value for all the instruments was 2.8	
[b]Lipscomb (2006)[195]	UK	SSDs from nine anonymous NHS primary care trusts	Nine sets ($n = 260$)	*Traditional machine washer-disinfector cleaning procedures*	SYPRO ruby protein stain and EDIC/EF microscopy In situ	Levels of soiling (scores averaged for each instrument): severe (66%: contamination index score, > 3 to 4); moderate (17%: contamination index score, > 2 to 3); low level (7%: contamination index score, 0 to 2). Across the nine trays, the mean contamination index per instrument set ranged from 2.4 to 3.6; overall mean contamination index value for all the instruments was 3.2. Contamination index: class 3 is 0.42–4.2 µg of protein/mm^2 and class 4 is > 4.4 µg of protein/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	

Study (first author and year of publication)	Country	Source	Surgical instruments (number)	Cleaning cycle	Assay/in situ	Residual protein contamination of surgical instruments after conventional cleaning and sterilisation in a sterile service department	
						Mean protein per instrument (µg)	Median protein per instrument (µg)
Murdoch (2006)[193]	UK	Five Department of Health and Social Care hospitals	A range of instruments ($n = 43$)	*Autoclaved*	'Protein extraction and quantification methods', i.e. levels of protein removed from instruments and identified in the 'buffer' or 'wash'	71.67 µg[d] 8–91 µg (range)[e]	NR
Baxter (2006)[197]	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' plus RF gas plasma, $n = 3$	EDX Unclear[c]	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 (2009)[198]	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 (2018)[196]	UK	One NHS trust. Some instruments 'artificially soiled' with Edinburgh soil	The five most-commonly used neurosurgery sets ($n = 1000$)	'Automated washer disinfector' in SSD (untreated), plus instruments treated with two types of wetting agents [PreKlenz (Steris, Mentor, OH, USA) and sterile water]	SDS extraction and OPA, ProReveal (Synoptics, Cambridge, UK). Unclear[c]	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[f]	NR

continued

TABLE 18 Study characteristics and results (*continued*)

Study (first author and year of publication)	Country	Source	Surgical instruments (number)	Cleaning cycle	Assay/in situ	Residual protein contamination of surgical instruments after conventional cleaning and sterilisation in a sterile service department	
						Mean protein per instrument (µg)	Median protein per instrument (µg)
						Different sets: instruments $n = 187$ (ProReveal assay): 87% (163/187): < 5 µg of protein per instrument side; 96% (179/187): < 10 µg per instrument side	
Hervé (2013)[183]	UK	Manufacturer, contaminated with 'Edinburgh soil'	Endoscopes (n = NR)	An 'enzymatic cleaner used in a number of endoscopy units'	SYPRO ruby protein stain and EDIC/EF microscopy Unclear	Contamination was < 10 ng/mm^2 after standard cleaning (see figure 3 in Hervé and Keevil,[183] for details)	
Hervé (2016)[191]	UK	Unknown number of 'hospital-based endoscopy units' ($n = 6$)	Endoscopes ($n = 6$)	An 'enzymatic cleaner: Enzol' (Enzol, Johnson & Johnson, New Brunswick, NJ, USA)	SYPRO ruby protein stain and EDIC/EF microscopy Unclear	Level of microcontamination absorbed into the luminal surface of the endoscope: 0.1–0.9 µg of protein/m. With the exception of one endoscope channel (with protein residues equivalent to almost 33 µg), most protein residues remained under the equivalent of 1–4 µg per channel	

EDIC/EF, episcopic differential interference contrast/epifluorescence microscopy; EDX, energy-dispersive X-ray spectroscopy; NR, not reported; OPA, orthophthaladehyde; SSD, sterile service department.
a A significant difference was observed in mean levels of protein contamination between trays ($p < 0.0001$).
b Contamination index.
c Unclear: not reported in Methods, but detection methods indicate evaluation of proteins in situ.
d Calculated from table II: 3082 [total protein µg per instrument/43 (total number of instruments)].[194]
e A significant difference was observed in mean levels of protein contamination between hospitals ($p < 0.0001$).
f Smith *et al.* (2018),[196] Supplemental table XV.
Note
Contamination index: class 3 is 0.42–4.2 µg of protein/mm^2 and class 4 is > 4.4 µg of protein/mm^2.

TABLE 19 Study characteristics and results

Study (first author and year of publication)	Country	Contaminant	Steel medium	Pretreatment	Assay/in situ	Dry	Wet	Differences in residual protein (ng/mm²) contamination of wires or tokens	
								Dry	Wet
Lipscomb (2007)[199]	UK	1-µl drops of ME7-infected BH	Surgical 316L grade SS tokens (10 × 25 mm)	Klenzyme®; Endozyme AW; Enzol; Liquid 52 (Hamo Liquid 52, Steris, Mentor, OH, USA)	SYPRO ruby and EDIC/EF microscopy; in situ	DT = 17 hours. No presoak/ pretreatment	DT = 17 hours 5 minutes for each: Klenzyme, 8 ml/l; Endozyme AW, 4 ml/l; Enzol, 8 ml/l; liquid 52, 8 ml/l	Final residual protein contamination at 22 °C:[a] • Control = 100%	Percentage of final residual protein contamination compared with control at 22 °C:[a] • Klenzyme = 19% • Endozyme AW = 36%; • Enzol = 4%; • Liquid 52 = 17%
Howlin (2010)[184]	UK	1-µl drops of ME7-infected BH	Surgical 316L grade SS wires (5 × 0.16 mm)	Klenzyme; Pre-Klenz (presoak gel)	Western blot; in situ[b]	DT = 16 hours followed by pretreatments	DT = 0 hours (immediate treatment)	Total protein removal (ng/mm²): immediate treatment with Pre-Klenz, produced a 2 log-reduction compared with 'dry' controls	
[a]Secker (2011, 2010)[201,202]	UK	1-µl drops of ME7-infected BH	Surgical 316L grade SS tokens (25 × 75 mm)	Klenzyme; Endozyme	SYPRO ruby protein stain and thioflavin T (Sigma Aldrich, St Louis, MO, USA), EDIC/EF microscopy; in situ[b]	DT = 24 hours; air RT or F (4–8 °C)	DT = 24 hours; moist: air-tight container lined with moist tissue; RT or F (4–8 °C)	• RT = 324.7 ± 15.0 ng/mm² • F = 243.8 ± 17.9 ng/mm² • Klenzyme applied after 2 hours: RT = 18.0 ± 9.3 ng/mm² (90.1% reduction compared with untreated air-dry control) • Endozyme applied after 2 hours: RT = 194.3 ± 7.9 ng/mm²	• RT = 6.0 ± 3.5 ng/mm² (98.2% reduction compared with dry; $p \leq 0.001$) • F = 56.8 ± 12.9 ng/mm² (76.7% reduction compared with dry; $p \leq 0.001$)

continued

TABLE 19 Study characteristics and results (*continued*)

Study (first author and year of publication)	Country	Contaminant	Steel medium	Pretreatment	Assay/in situ	Dry	Wet	Differences in residual protein (ng/mm^2) contamination of wires or tokens	
								Dry	Wet
Secker (2015)[200]	UK	1-µl drops of ME7-infected BH (equivalent to 1 µg total protein)	Surgical 316L grade SS tokens (10 × 30 mm)	Prolystica 2 × alkaline detergent, working pH 10.1 or Progenica (Serchem Ltd, Telford, UK) detergent, working pH 10.9	SYPRO ruby protein stain and thioflavin T; EDIC/EF microscopy; in situ[b]	Air for (DT): • 15 minutes • 30 minutes • 1 hour • 2 hours • 24 hours • (RT and F)	Wet bag: sealed bag with 35 ml of distilled water for (DT): • 15 minutes • 30 minutes • 1 hour • 2 hours • 24 hours • (RT and F)	24 hours' humidity: • RT, 55–70% • F, 46–69% Protein absorption precleaning (RT): • 15 minutes, 15.3 ± 4.8 ng/mm^2 • 24 hours, 1000 ± 205.0 ng/mm^2 Prolystica (RT): • 1 hour, 54.8 ± 13.7 ng/mm^2 • 2 hours, 918.6 ± 54.0 ng/mm^2 • 24 hours, 1026.1 ± 92.5 ng/mm^2 Prolystica (F): • 1 hour, NR • 2 hours, NR • 24 hours, 605.1 ± 89.5 ng/mm^2	24 hours' humidity: • RT, 90% • F, 90% Protein absorption precleaning (RT): • 15 minutes, 18.5 ± 4.2 ng/mm^2 • 24 hours, 31.9 ± 5.3 ng/mm^2 Prolystica (RT): • 1 hour, NR • 2 hours, NR[c] • 24 hours, NR[c] Prolystica (F): • 1 hour, NR • 2 hours, NR[c] • 24 hours, NR[c] Progenica (RT): • 1 hours, NR • 2 hours, NR • 24 hours, NR[c]

Study (first author and year of publication)	Country	Contaminant	Steel medium	Pretreatment	Assay/in situ	Dry	Wet	Differences in residual protein (ng/mm²) contamination of wires or tokens	
								Dry	Wet
								Progenica (RT): • 1 hour, NR • 2 hours, 112.0 ± 41.4 ng/mm² • 24 hours, 743.2 ± 155.5 ng/mm² Progenica (F): • 1 hour, NR • 2 hours, 1095.6 ± 359.1 ng/mm² • 24 hours, 1247.9 ± 132.1 ng/mm²	Progenica (F): • 1 hours, NR • 2 hours, NR • 24 hours, NR[c]
						Dry bag: tied, clear polythene bag for (DT): • 15 minutes • 30 minutes • 1 hour • 2 hours • 24 hours • (RT and F)		24 hours humidity: • RT, 55–80% • F, 47–90% Protein absorption pre-cleaning (RT): • 15 minutes, 30.6 ± 27.7 ng/mm² • 24 hours, 785.6 ± 310.8 ng/mm²	(Repeat from above) 24 hours humidity: • RT, 90% • F, 90% Protein absorption pre-cleaning (RT): • 15 minutes, 18.5 ± 4.2 ng/mm² • 24 hours, 31.9 ± 5.3 ng/mm²

continued

TABLE 19 Study characteristics and results (*continued*)

Study (first author and year of publication)	Country	Contaminant	Steel medium	Pretreatment	Assay/in situ	Dry	Wet	Differences in residual protein (ng/mm^2) contamination of wires or tokens	
								Dry	Wet
								Prolystica (RT): • 1 hour, 84.7 ± 30.9 ng/mm^2 • 2 hours, NR[c] • 24 hours, NR[c] Prolystica (F): • 1 hour, NR • 2 hours, NR[c] • 24 hours, 181.5 ± 39.4 ng/mm^2[c] Progenica (RT): • 1 hour, NR • 2 hours, NR • 24 hours, 154.5 ± 7.0 ng/mm^2[c] Progenica (F): • 1 hour, NR • 2 hours, NR • 24 hours, NR[c]	Prolystica (RT): • 1 hour, NR • 2 hours, NR[c] • 24 hours, NR[c] Prolystica (F): • 1 hour, NR • 2 hours, NR[c] • 24 hours, NR[c] Progenica (RT): • 1 hour, NR • 2 hours, NR • 24 hours, NR[c] Progenica (F): • 1 hour, NR • 2 hours, NR • 24 hours, NR[c]

BH, brain homegenate; DT, drying time; EDIC/EF, episcopic differential interference contrast/epifluorescence microscopy; F, refrigerated. NR, not reported; RT, room temperature; SS, stainless steel.

a Data for 30 °C too but 'efficacy changes little between the ambient temperatures'.[201]

b Unclear: not reported in methods, but comments in discussion sections of papers indicate measurement was of in situ proteins, e.g. Howlin *et al.*:[184] 'A concentration of 0.03 ng/mm^2 prion-associated amyloid was detected in situ on the wires'; Secker *et al.*:[200] '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'.

c Level of difference is $p \leq 0.05$ compared with the room temperature. Air sample for same time point (data for dry bag and wet bag indicate statistically significantly reduced levels of residual protein).

for wet conditions.[200] After the application of presoaks or cleaners, Lipscomb *et al.*[199] reported a reduction in protein between 64% and 96% on the presoaked or treated tokens compared with the dry, untreated controls and Howlin *et al.*[184] reported a reduction of approximately 2 logs in protein residue for tokens treated immediately (not allowed to dry) with the PreKlenz presoak compared with wires that were allowed to dry for 16 hours. Secker *et al.*[200] and Lipscomb *et al.*[199] also reported that the longer the drying times, the more difficult it was to remove the contamination.

Discussion/summary of studies on residual mass and decontamination

The published evidence suggests that standard cleaning practices within SSDs do not achieve levels of ≤ 5 µg residual protein per instrument for all instruments, as required by current guidance.[203]. However, these published data are based on different assays and detection methods and the most recent data[196] suggest that as much as 87% of assessed instruments might have protein residue of < 5 µg per instrument side, and 96% might have residue of < 10 µg per instrument side. Recent papers[200,201] 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 with dry conditions ($p \leq 0.001$).[201] Standard cleaning in SSDs might, therefore, be expected to produce residual protein levels of ≤ 5 µg 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.[183]

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, with highly variable transmission rates (ranging from 0% to 100%) that are generally > 50%. It is generally accepted that autoclaving alone only partially inactivates TSE prions.[119,204–207] The majority of studies published in 2004 and earlier focused on the 263K scrapie prion strain, whereas the more recent data have investigated efficiency of autoclaving on a wider range of prions, for example 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, 301 V, cattle BSE, Sc237 and sCJD prions strains, alkaline detergents,[176] 0.2% SDS/0.3% NaOH,[175] RMEC B,[178] 4% SDS plus 1% AcOH,[187,190] H_2O_2 and gas plasma (Sterrad NX1 and 2 cycles).[176] It has been reported that, based on the evidence, the following should be sufficient to achieve adequate levels of inactivation and decontamination of 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.[205]

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 ≥ 5 and/or 0% transmission across a range of prion strains. These include Rely-On PI (DuPont) and Prionzyme (Genecor);[185] NaOH;[180,185] Trigene disinfectant and RF gas plasma;[189] SDS-PK-Pronase;[186] H_2O_2 and gas plasma;[174,176]; and combinations of enzymatic detergents and disinfectants.[174] However, it has also been stated that NaOH and NaOCl, although effective, 'are not compatible with various pieces of medical equipment, and … present a serious handling hazard for healthcare employees',[174] although NaOH is reported to be less corrosive than NaOCl.[119,205] A combination of immersion in NaOH or NaOCl followed by autoclaving is recommended by the World Health Organization.[4,119]

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 assay, 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.[119,176,186,204,205,208] Such differences also make direct comparison between findings

difficult for human prions and other TSE prions.[177] 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 SSDs,[189,193,209] but they report contamination only with proteins (not prions) after standard decontamination processes. Although 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.[206,209]

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 ACDP TSE subgroup estimated that the likelihood of at least one instrument migrating in or out of a neurosurgical set is 50%.[117] This document contains a project report and guidance for the Department of Health and Social Care 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, this could potentially promote a self-sustaining epidemic of CJD or vCJD.

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 (first author and year of publication)	Country	Time period	Design	Strategy	Details
Belay (2013)[119]	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)[210]	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

NR, not reported.

Only two studies were identified that provided any evidence on whether or not instruments for procedures on high-risk tissues remain in their original sets.[119,210] In 2013, an article was published by Belay *et al.*[119] 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 Centers for Disease Control and Prevention. 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 1 and 12 sets of instruments for neurosurgery, that 12 of the 19 affected hospitals had multiple sets and that 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.[210] 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, that is 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 SIs and the increased use of single-use instruments. It is important to note that the report provided no quantitative evidence on whether or not 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 (first author and year of publication)	Findings
Belay (2013)[119]	• By the time of a CJD diagnosis, the identification of contaminated instruments had become almost impossible in some hospitals, in part because 12 out of 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; therefore, it was also not possible to determine the exact number of patients exposed to the instruments used on the index patient in these hospitals

NICE (2016)[210]	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 at a 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 SIs, which might migrate between sets, has been stopped

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

Very little research has been undertaken to evaluate whether or not 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.[119] The second study[210] was performed in the highly relevant setting of the NHS, but is unpublished and its methodology was poorly reported. It did not report quantitative evidence on whether or not 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 SIs 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 Department of Health and Social Care guidance report[117] 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.

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 with reusable instruments for high-risk procedures. Safety was to be determined by the relative frequency of complications. This review excluded instruments, including anaesthetic equipment, that would not normally come into contact with high-risk tissues[205,211] or that are now single use.[210] 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.

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.

Discussion/summary of complication rates for single-use versus reusable instruments

An unpublished report produced for NICE in 2016[210] explored the barriers to and facilitators of 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 before, 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 are therefore unknown.

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 and Social Care[212] reported that 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 CNS or posterior eye). 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.

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[213] (*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 5 years previously, in order to explore the prevalence of subclinical vCJD. To do this, the article analysed the relationship between mortality rates and reoperation rates by procedure. The annual incidence of mortality in this cohort ≥ 5 years after the first instance of neurosurgery was as low as 3% for certain procedures that would not be considered as 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).

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.[213] Two additional potentially relevant procedures from this paper have also been included here: unspecified excision of brain and excision of brain lesion(s); this is because of their low 5-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.*[213] 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 related only 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*).

The data indicate that the proportion of individuals in this sample having a second or third procedure (or more) within 5–10 years after an initial neurosurgical procedure differed depending on the index procedure (see *Table 23*). This ranged from 10.7% for individuals having one 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, the majority (57.2%) of those who had subsequent procedures were also likely to have more than one additional procedure.

TABLE 22 Characteristics of included studies

Study (first author and year of publication)	Country	Time period	Design	Type of surgery	Details
Bird (2009)[213]	UK (Scotland)	1993–2001	Audit and evaluation	Neurosurgery	Neurosurgery (and proportions of patients experiencing more than one procedure) and mortality

TABLE 23 Findings of Bird *et al.*[213] 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*/*N*)	More than one subsequent procedure, % (*n*/*N*)	Proportion of individuals with a subsequent procedure who underwent more than one, % (*n*/*N*)
Drainage of extra- and sub-dural haematoma[a]	8.3 (221/2654)	2.4 (63/2654)	22.2 (63/284)
Cerebral aneurysm operations	14.8 (264/1782)	7.1 (127/1782)	32.5 (127/391)
Creation of ventricular shunts	21.2 (191/900)	28.3 (255/900)	57.2 (255/446)
Excision of brain: unspecified[a]	12.1 (110/911)	6.9 (63/911)	36.4 (63/173)
Excision of brain lesion (e.g. frontal[a])	13.0 (139/1072)	5.6 (60/1072)	30.2 (60/199)

a Not specified as high risk.

Discussion/summary of risk of future surgery in high-risk procedures

The Bird *et al.*[213] paper is a UK (Scottish-based) 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.*[213] paper to inform the model is limited, as the paper 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.

Chapter 3 Cost-effectiveness

Background

Previous modelling work assessing the risks of surgical transmission of CJD was undertaken by 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), which produced IPG196.[214] 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 should be established for patients born after 1 January 1997 (who are unlikely to have been exposed to the BSE epidemic).

An update of the previous work was undertaken by ScHARR. 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 appendixes 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 sCJD, fCJD and iCJD. Throughout the report, any CJD cases that have been caused by surgical transmission will be abbreviated to stCJD.

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 reconducted to address possible 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 18 January 2018; the results of the elicitation exercise are in *Appendix 4*.

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 the experts) 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 judgements. 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 formed his/her own probability judgements. It was for the experts to decide how much weight a 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 or not the fitted distribution was an acceptable representation of RIO's uncertainty and whether or not 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 (PSA).

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

Cost-effectiveness literature review

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

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, where they had 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 by Bennett *et al.*[13] a publication was identified, which was not conceptually different from Stevenson *et al.*[12] but used a system dynamics approach. Bennet *et al.*[13] had three broad aims: (1) to clarify the possible scale of vCJD infection via surgical instruments, (2) to identify the most important factors contributing to this risk and (3) to help prioritise scientific research. Conclusions from the Bennet *et al.*[13] paper were 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.*[13] was published earlier than that of Stevenson *et al.*[12] (2005 compared with 2009), this was not preferred to the previous modelling structure.

A further paper by Garske *et al.*[215] was identified that reported that key determinants of future cases of CJD 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 that 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.*[215] paper (which was published in 2006) and thus this model was not deemed preferable to that of Stevenson *et al.*[12]

Based on the authors' critique of Bennett *et al.*[13] and Garske *et al.*,[215] 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 *Key model parameters*. *Figure 4* depicts the flows of patients, instrument sets and SIs that have the potential to transmit CJD surgically. Patients have been categorised into three discrete groups: (1) patients who are not infected with CJD; (2) patients who are infected with CJD who are not infectious; and (3) 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 to be outside the modelling process. Across time, patients can move (1) from the non-infected state to the infectious but asymptomatic state following an operation with a contaminated instrument, and (2) to the infected and infectious state when the incubation period of the disease for that patient has been reached; additionally, 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.

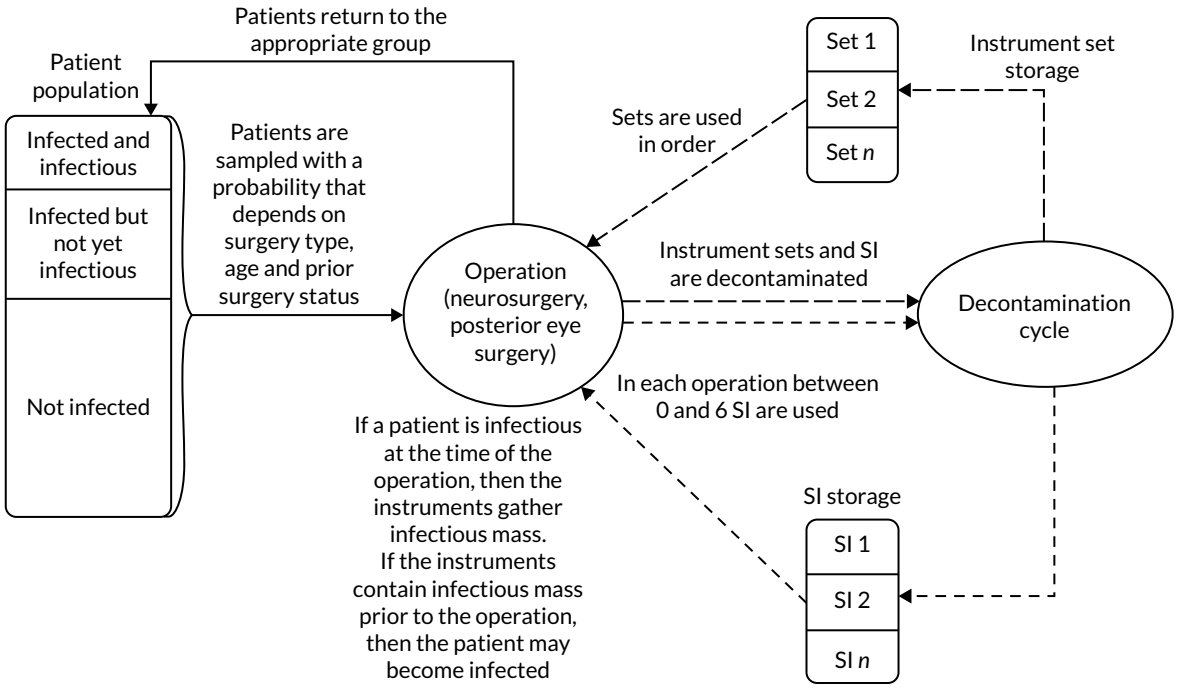

FIGURE 4 The conceptual model relating to the infection process. Reproduced from Stevenson *et al.*,[12] with permission from *Journal of the Operational Research Society*.

During the operation, decontamination process and 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 with 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, whereas 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 1 January 2004, the year at which a proportion of key distributions within the model were elicited, to 2018 in the calibration period. This duration included a 1-year warm-up period from 1 January 2004 to 1 January 2005, which allowed 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 with those potentially observed in the UK to establish plausible bounds for use within the PSA and then subsequently to determine likelihood ratios for each PSA configuration. This process is described in further detail in a later section (see *Appendix 7*).

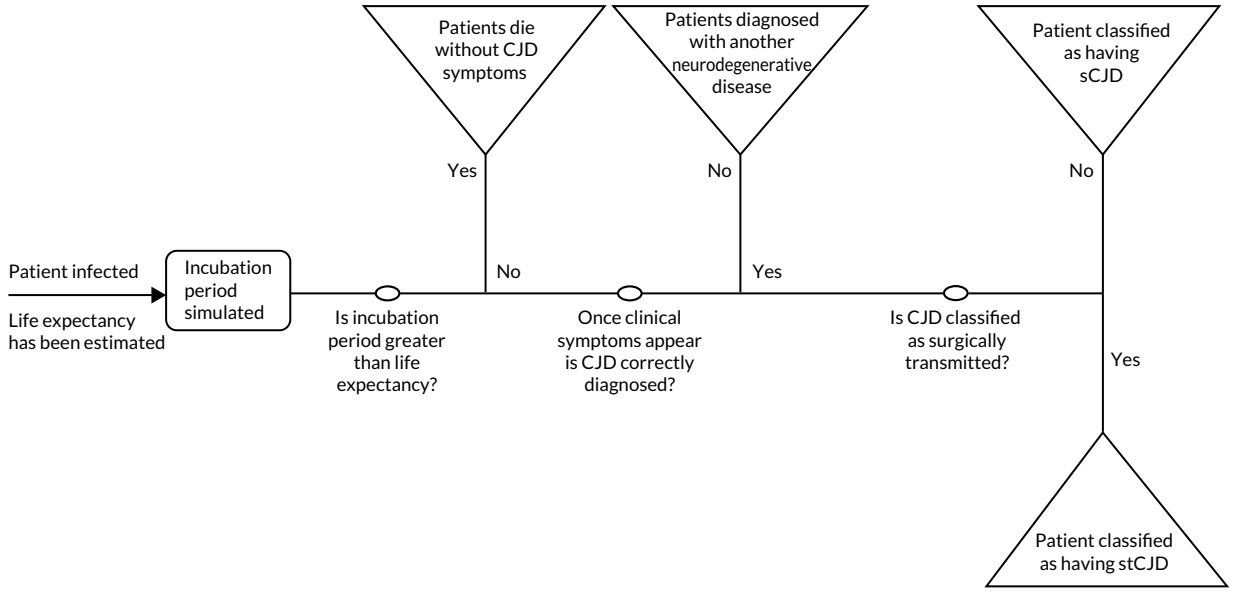

FIGURE 5 The conceptual model relating to patient outcome post infection.

Having established parameter configurations that were plausibly consistent with the number of stCJD cases potentially observed, the model was run for a further 5 years to look at the potential loss of health because of stCJD associated with each strategy evaluated. The 5-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 it did not limit the committee to a decision which could not be changed in the longer term if required. The 5-year period matched the value used by 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 5-year period.

The model was constructed in Simul8 (© 2017 Professional Edition Simul8 Corporation, Glasgow, UK). A NHS and Personal Social Services perspective was taken and both costs and benefits were discounted at 3.5% per annum as recommended by NICE.[216]

Key model parameters

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

The underlying probability of Creutzfeldt–Jakob disease 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 years in 2005 could still be used for the prevalence of CJD prions in central nervous tissue in 16- to 39-year-olds in the current analysis; although, they acknowledged that the range would produce an overestimate as the probability in all tissue would be greater than that confined to just the CNS. The experts disagreed with the previous experts in whether or not the prevalence would be greatest in the 16–39 years age group compared with the 0–15, 40–69 and ≥ 70 years age groups. The current experts believed that the elicited distribution should be used for all age groups. The distribution used to populate the model is shown 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.

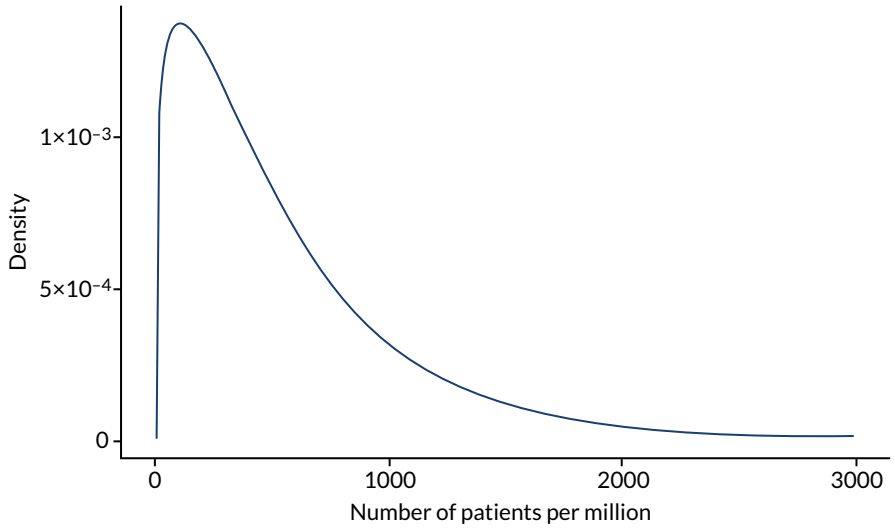

FIGURE 6 The prevalence of CJD prions within central nervous tissue.

The NICE committee asked for two scenarios to 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 they were assumed unlikely to have been exposed to the BSE epidemic; in an alternative scenario it was assumed that the P96 group had the same probability of being infectious as the general population.

The residual mass per surgical instrument

The ScHARR report[11] assumed that the mass on an individual instrument was 2.88 mg of wet-tissue equivalent for instruments used for tonsillectomies, and 1.26 mg 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*',[11] with these data reported in a different form within Baxter *et al.*[192] It was assumed that the tonsillectomy value was generalisable to the residual mass on a brain and posterior eye surgery. When multiplied by the number of instruments assumed to be in each set, this 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 2.88 mg. These values were assumed fixed.

During discussions on the parameterisation of residual mass, a committee member highlighted a recently published article,[196] which suggested that the residual protein mass is likely to be < 5 µg protein mass per instrument side. This is considerably less than that used in the previous ScHARR report,[11] which was 576 µg of protein mass (2.88 mg of wet-tissue equivalent).

A preliminary inspection of articles discussing residual mass was undertaken, which indicated that protein mass ranged between 163 and 756 µg (120 instruments) in Baxter *et al.*[192] and between 8 and 91 µg (mean 71.67 µg; 43 instruments) in Murdoch *et al.*[193] Lipscomb *et al.*[195] presented further evidence, which was based on a set from each of nine NHS trusts (260 instruments in total), and reported that 66% of all instruments showed severe contamination in at least one sample area, equating to > 4.4 µg of protein/mm^2.

Examining the data in Baxter *et al.*[192] and Murdoch *et al.*,[193] the mean residual protein mass per instrument in 2004 was set to 200 µg (95% CI 150 to 250 µg) in consultation with NICE committee members.

However, the data reported in Smith *et al.*,[196] and further data marked as academic-in-confidence obtained from a NICE committee member (anonymous, May 2018), indicate 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 that had adhered to IPG196. Following discussion with committee members, the mean residual mass for those units that were compliant with guidance to keep instruments moist was assumed to be 10 µg. In 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 200 µg of residual mass 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 5% (10/200) of the mass assumed to be harvested prior to 2012. Any infectious mass already on an instrument was assumed to remain on the instrument following measures to keep instruments moist.

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, which was undertaken to inform the previous work 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 0.4% to 87.1%, showing considerable uncertainty.

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, which was undertaken to inform the previous work by ScHARR.[11] A depiction of the distribution for the proportion of mass transferred to the patient is provided in *Figure 8*. This has a mean of 0.9% and a 95% CrI of 0.0% to 4.0%.

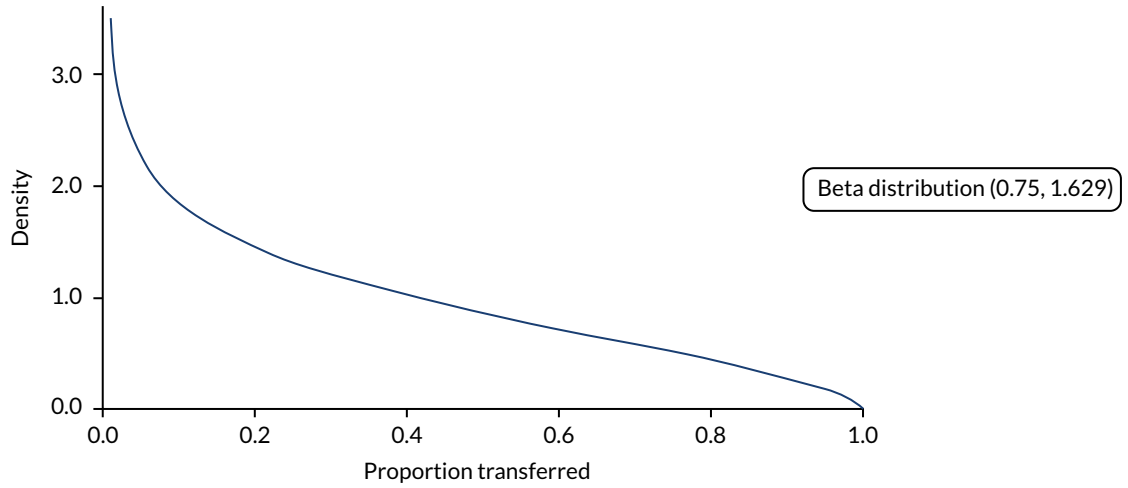

FIGURE 7 The proportion of residual mass transferred to a patient.

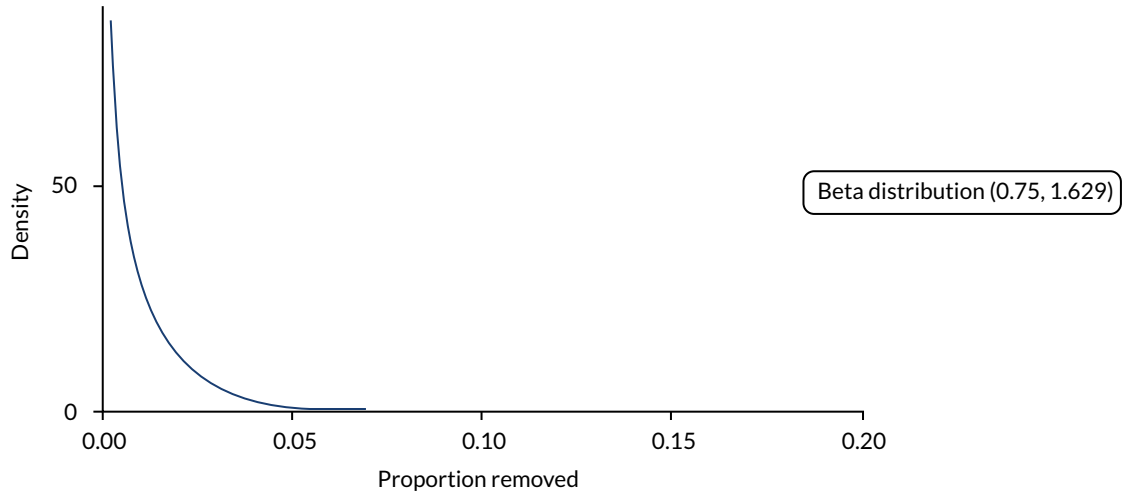

FIGURE 8 The proportion of residual mass removed in a subsequent decontamination cycle.

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. Therefore, 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 SIs that were used were assumed to gather the same mass as instruments in the main set.

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 the mass that was reported in table 11 of the ScHARR report,[11] with the former being 10 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*.

Parameters relating to the decontamination of surgical instruments

The assumed infectious titre of tissues containing Creutzfeldt–Jakob disease prions

In the previous modelling undertaken,[11] brain and posterior eye tissue were assumed to have 10^8 ID_{50} per gram, with this value assumed to be 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. First, the mean infectious titre was varied between 10^7 and 10^9 ID_{50} per gram, assuming a uniform distribution. Second, 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_{50} per gram.

TABLE 24 Information relating to the 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)

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: (1) the effectiveness of infectivity reduction in the first decontamination cycle, (2) the effectiveness of infectivity reduction in subsequent decontamination cycles and (3) 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.

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 log-reduction of 1.42 to 3.58.

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

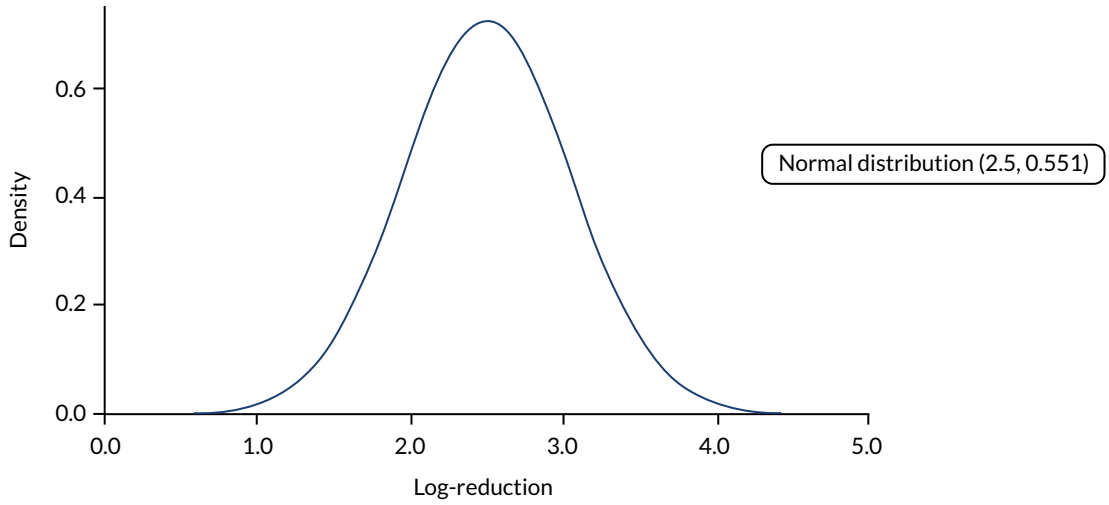

FIGURE 9 The reduction in infectivity in the first autoclaving cycle.

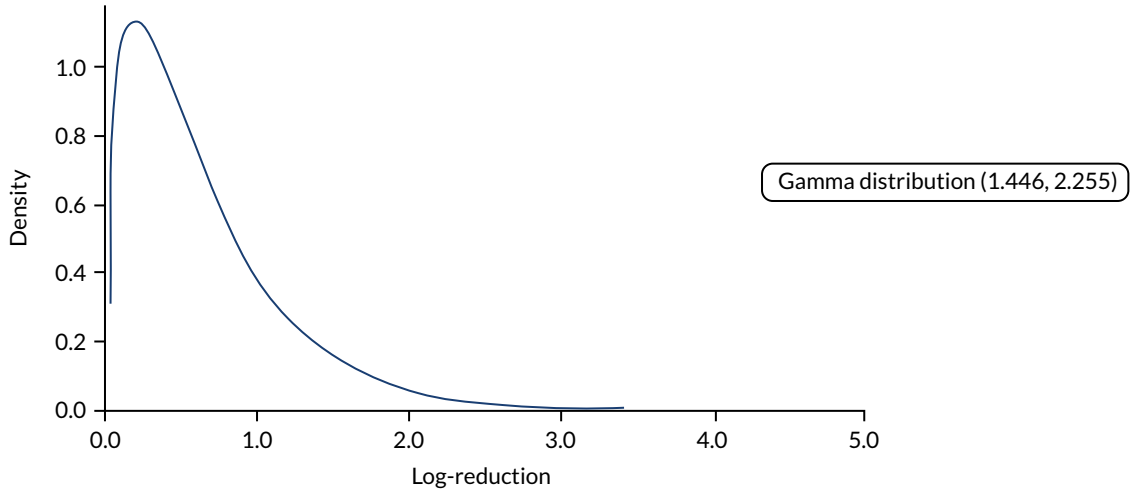

FIGURE 10 The reduction in infectivity in the first detergent cycle.

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 further 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 of 0.043 to 0.330.

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 of 0.047 to 0.931.

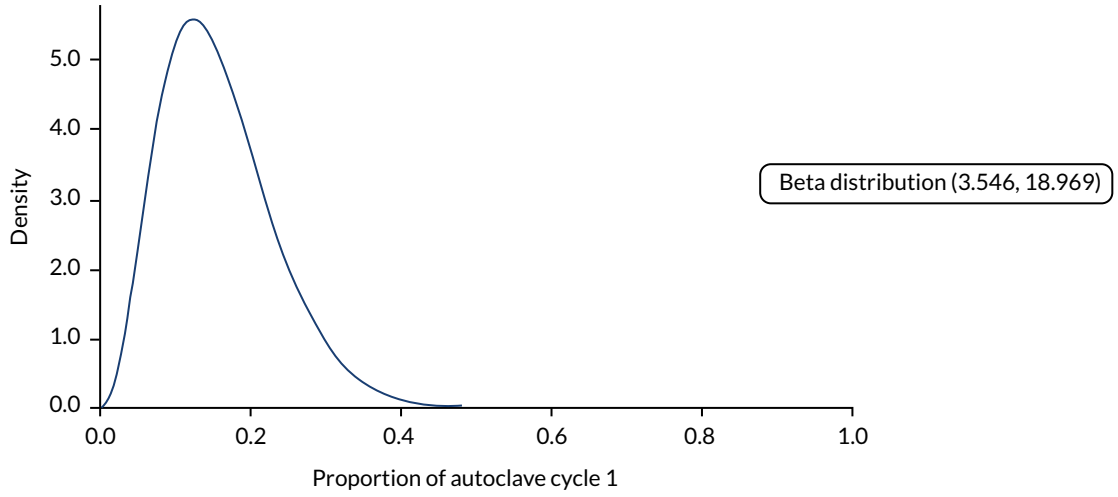

FIGURE 11 The proportion of autoclave cycle 1 log-reduction achieved by cycles 2 and 3.

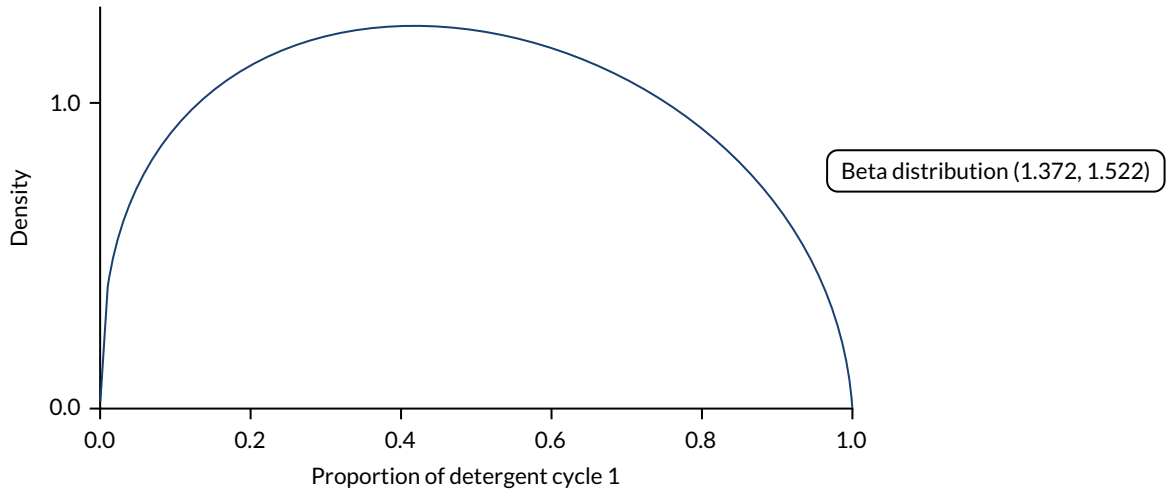

FIGURE 12 The proportion of detergent cycle 1 log-reduction achieved by cycle 2.

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

This has been detailed in *The proportion of residual mass on brain and posterior instruments that is removed in a subsequent decontamination cycle* for brain and posterior eye instruments and in *Residual mass, proportion transferred to a patient, proportion removed during the operation and the mass harvested during neuroendoscopy* for neuroendoscopes.

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 1/200–1/300) 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 1/2000–1/3000.

For each instrument that was 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 (6.0% and 12.5%, respectively) were chosen such that it was close to the proportion of the set that one instrument comprised. This is (see *Parameters relating to instrument migration, costs and safety*) a 1/14 probability (7%) for an instrument in a neurosurgery set and a 1/9 probability (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.

Parameters relating to instrument migration, costs and safety

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; and 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 instruments (previously 18).

For brain and posterior eye sets, the instrument 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 that were used in rotation. During each operation, each SI had a 20% chance of being required.

For neuroendoscopy, IPG196[214] recommended that all neuroendoscopy accessories became 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 SI was used in all operations. If a large number of deaths was observed related to neuroendoscopy, this assumption would be amended.

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%, while the set was undergoing the decontamination process. This value was selected following discussion with clinicians and review of evidence. 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 in set B being moved 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 uncertainty around the proportion of mass contained on individual instruments.
2. That when a SI was used, there was a 50% chance that this instrument would join the set with a similar instrument from the set becoming the 'new' 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 as a result of 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,[214] 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 remain with the set to which they have been introduced. However, owing to logistical and/or financial problems in implementing IPG196,[214] 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.

The costs associated with single-use instruments

A NICE committee member stated 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 (anonymous, May 2018).

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[11] 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. Although 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, disposable rigid neuroendoscopes, but that these have since been withdrawn. This puts downwards 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.

The costs associated with decontaminating reusable instruments

Data provided by a committee member indicated that the cost of decontaminating a reusable instrument was, on average, £0.60 in Scotland (personal communication, May 2018). 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.

The costs associated with disposing 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 (£350–500), the authors of this report deemed that this simplifying assumption would not cause significant inaccuracy.

The costs associated with keeping instruments moist

Data reported in Smith *et al.*[196] state that the cost of NHS bags would be £440 per 7355 neurosurgical trays reprocessed, equating to £0.06 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 £0.06 per tray. Thus, it has been assumed that the cost of keeping instruments moist was £0.12 per set conditional on using NHS bags, tap water and a tray liner.

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.

The costs associated with systems to allow instruments to be tracked

NICE committee members provided data from an unpublished Society for British Neurosurgeons survey and from costs recorded at their own units, which indicated that £750,000 across a 5-year period, including necessary equipment, would be a reasonable estimate (anonymous, May 2018). Sensitivity analyses were intended using £500,000 and £1,000,000.

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

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

In the earlier ScHARR model,[11] 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_{50} per gram, where an ID_{50} is the dose required to infect 50% of the susceptible population). It was assumed that the relationship between the number of ID_{50} and the probability of infection was:

$$\text{Probability of infection} = \text{MIN}(\text{Number of } ID_{50}\text{transferred} \times 50\%, 100\%), \quad (1)$$

such that 2 ID_{50} or more would result in a certain infection. In the earlier ScHARR model, the use of a geometric sequence was used, such that 2 ID_{50} would result in only 75% of patients being infected ($1–0.5^2$). However, the committee did not want to use this assumption because the dose to infection was not robustly known and high levels of ID_{50} 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 *The proportion of residual mass on brain and posterior instruments that is transferred to a patient* and the assumed infectious titre per gram is detailed in *Parameters relating to the decontamination of surgical instruments*.

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.

The incubation period following surgically transmitted Creutzfeldt–Jakob disease infection

The incubation period associated with stCJD was elicited from clinical experts in January 2018 (see *Appendix 4*). 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 given 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 was 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 (1) 0.25 to 2 years, (2) 2 to 10 years, (3) 10 to 20 years and (4) 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%, whereas the probability of being in the fourth interval (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[217]), the patient would display clinical symptoms. Otherwise, the patient would die without CJD symptoms. Each year a proportion of patients incubating CJD die as a result of non-CJD-related reasons, in line with data reported by the Office for National Statistics.[217] The probability of non-CJD-related death was dynamic between 2005 and 2014, using the appropriate life table, but was assumed to use life tables from 2014 to 2023.

The infectious period following surgically transmitted Creutzfeldt–Jakob disease 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 infectious for only the last 20% of the incubation

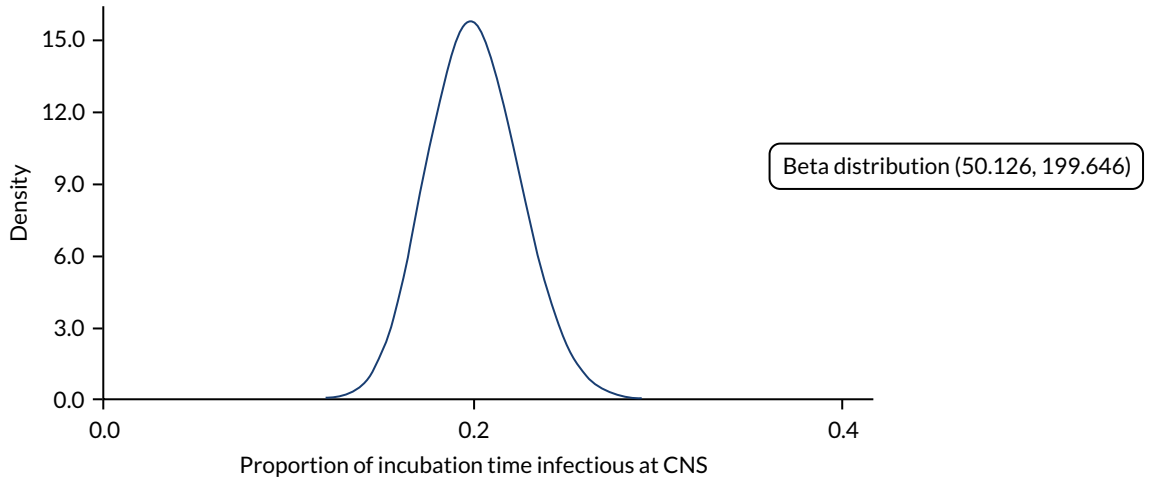

FIGURE 13 The proportion of the incubation period during which the patient is infectious.

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.

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; Zellis, Hemel Hempstead, UK) 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.

The assumed costs and quality-adjusted life-years associated with Creutzfeldt–Jakob disease

Once clinical symptoms have developed, it is assumed that patients accrue no further QALYs as a result of 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,[218,219] 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 and McLean[220] indicate that costs of additional care and/or equipment were 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 cost, from a NHS and Personal Social Services perspective, in 2017–18 for a CJD case was £50,000.

The probability that a person with Creutzfeldt–Jakob disease symptoms are not diagnosed with Creutzfeldt–Jakob disease

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 who 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, with the experts willing to allow the misdiagnosis in the aged 60–80 years category to be the average of the two other age bands: those aged < 60 years and those aged > 80 years. The distribution for those patients aged < 60 years is shown in *Figure 14*.

The mean value is 13.0% with a 95% CrI 0.4% to 26.8%. The distribution for those patients aged > 80 years is shown in *Figure 15*. The mean value is 55.0% with a 95% CrI of 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 (see *Figure 32*), which showed similar age-specific mortality rates between 2005–9 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 2005–9, which could be indicative of better ascertainment in recent years. The assumption of equal ascertainment would favour single-use instruments.

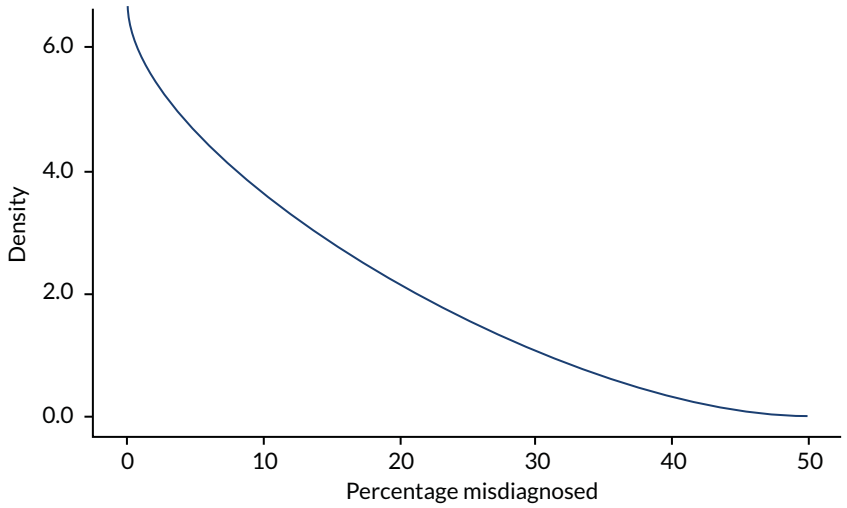

FIGURE 14 The proportion of patients < 60 years with clinical CJD symptoms who are diagnosed with another neurodegenerative disease.

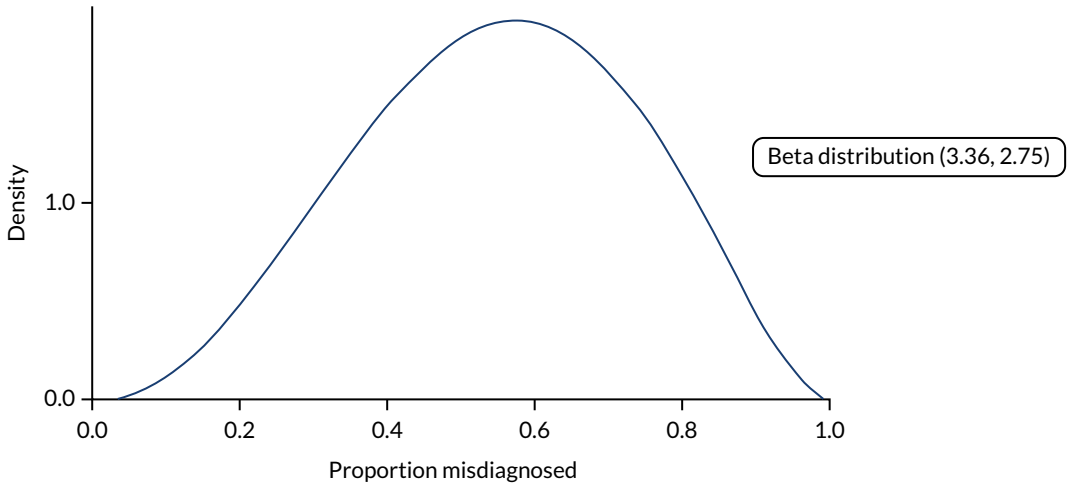

FIGURE 15 The proportion of patients over 80 years with clinical CJD symptoms who are diagnosed with another neurodegenerative disease.

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 *The potentially unobserved number of surgically transmitted Creutzfeldt–Jakob disease cases between 2005 and 2018*.

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

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 5*. 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.

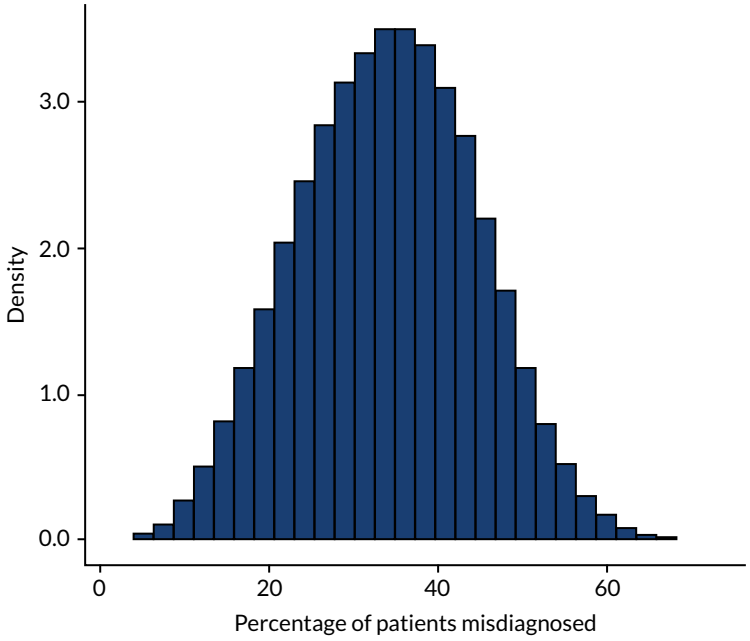

FIGURE 16 The simulated proportion of patients aged between 60 and 80 years inclusive with clinical CJD symptoms who are diagnosed with another neurodegenerative disease.

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 1 January 2005 is provided in *Table 25*. For future years, the average number of operations in the last 3 years was 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.

Hospital Episode Statistics data provide age breakdowns for each code, with more granularity from the year 2012 than prior to this date. Analysis of these data indicated that the age profile of patients remained relatively stable across time for each of the three brain operation groupings, for neuroendoscopy and for posterior eye operations. Therefore, for simplification, the age profile within 2016–17 was assumed to apply throughout the model. Depictions of each assumed age profile are provided in *Appendix 6*.

Calibration targets

The observed number of surgically transmitted Creutzfeldt–Jakob disease cases between 2005 and 2018 and the potentially unobserved number of surgically transmitted Creutzfeldt–Jakob disease cases

The observed number of surgically transmitted Creutzfeldt–Jakob disease cases between 2005 and 2018

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

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

Year	Brain 1[a]	Brain 2[b]	Brain 3[c]	NE	PE
2005–6	19,554	5346	1684	302	4629
2006–7	21,451	5317	1069	311	4098
2007–8	19,302	5517	1062	338	6164
2008–9	18,406	5557	1107	354	8415
2009–10	19,404	5706	1101	389	7660
2010–11	20,323	5755	1121	488	7796
2011–12	21,288	5889	1217	497	5081
2012–13	21,110	5887	1151	500	13,296
2013–14	22,497	5905	1110	539	13,060
2014–15	22,508	6013	1087	532	5378
2015–16	22,916	6106	1110	527	5226
2016–17	23,029	6114	968	518	5481
Numbers assumed subsequent to 2017[d]	22,818	6078	1055	526	5362

NE, neuroendoscopy; PE, posterior eye.
a Brain 1 denotes operations with assumed normal life expectancy.
b Brain 2 denotes operations with assumed death within 12 months.
c Brain 3 denotes operations with a 50% chance of death within 12 months and a 50% chance of normal life expectancy.
d Estimated as an average of the numbers between 2014 and 2017.
Note
These data are inflated by 15% within the model to account for operations not coded as the main procedure and to account for operations conducted privately at non-NHS hospitals.

The potentially unobserved number of surgically transmitted Creutzfeldt–Jakob disease 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 *The costs associated with decontaminating reusable instruments*. The second way that stCJD can be misdiagnosed 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 NCJDRSU, which detailed whether or not patients who had a diagnosis of CJD since 2005 had a history of neurosurgery or posterior eye surgery, as well as 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 or not the 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 is limited, which would result in an overestimated calibration target.

For posterior eye surgery, there were potentially 24 individuals who had undergone 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, there were potentially 13 individuals who had undergone operations that could have transmitted CJD. There were no dates provided for the

operations and thus it was assumed that the proportion of operations conducted in 2005 or later that were observed for posterior eye surgery (10/24) were applicable to neurosurgery, which equates to a possible five 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 that had been misdiagnosed as another form of CJD, or just over one case per year on average.

Categorisation of surgical units, establishing probabilistic sensitivity analysis configurations that are plausible and generating likelihood functions for plausible probabilistic sensitivity analysis configurations

Categorisation of surgical units

Based on the heterogeneity in surgical units adhering to IPG196 and the analyses varying the assumption of whether or not the P96 group (patients born after 1996) could be infectious from birth, six categories of surgical units were defined (denoted 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 or not 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 60% of units neither followed IPG196 nor kept instruments moist. These probabilities were altered in a scenario analysis.

Employing a heuristic to rule out probabilistic sensitivity analysis configurations that would produce implausible results

Owing to the time required for each run [approximately 12 seconds per 'plausible' (defined later) PSA configuration] and the number of PSA configurations, random number (RN) streams, scenarios and 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 7* 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.

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

$$FML = 10^{A} \times B \times C, \quad (2)$$

in which

- A = 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
- B = residual mass on an instrument × (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 12 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 a 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.

Running further analyses to remove probabilistic sensitivity analysis configurations that are potentially consistent with the observed data but generate an implausible number of transmissions when run through the model

In total, 2000 PSA configurations with a FML value of $\leq e^{12}$ were sampled. For each configuration, the first RN stream was run, assuming a S3 surgical unit and determining whether or not there was a violation of the permissible limit (VPL) of clinical transmissions for patients aged ≤ 60 years. It was noted that the clinical experts had stated 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, the PSA configuration was deemed to be inconsistent with the observed data and the PSA run was discarded. If there was not a VPL, 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, while 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. From RN streams 7 to 13, the VPL threshold was increased to 40; from RN streams 14 to 17, the VPL threshold was increased to 45; from RN streams 18 to 23, the VPL threshold was increased to 55; and for RN streams 24 to 27 the VPL threshold was increased to 66. This resulted in 509 out 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.

Calculating the likelihood of each plausible probabilistic sensitivity analysis 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 zero 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 transmissions that result in clinical symptoms would have a likelihood of 1, whereas any PSA configuration that produced > 30 transmissions that result in clinical symptoms, in patients than < 60 years of age, 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.

Generating estimates of the expected numbers of future surgically transmitted Creutzfeldt–Jakob disease, life-years lost and quality-adjusted life-years lost

The likelihoods associated with each PSA sample were 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.

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 use the average value multiplied by the likelihood of the PSA rather than the maximum value. Generating CIs around the mean of each output was more complex owing 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 1 and then using statistical techniques to estimate a CI.

Exploring the probability that each type of surgical unit was the most cost-effective

Exploratory analyses were undertaken to provide indicative probabilities that each type of surgical unit (one of 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 a S3 (S6), meaning 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 that 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.

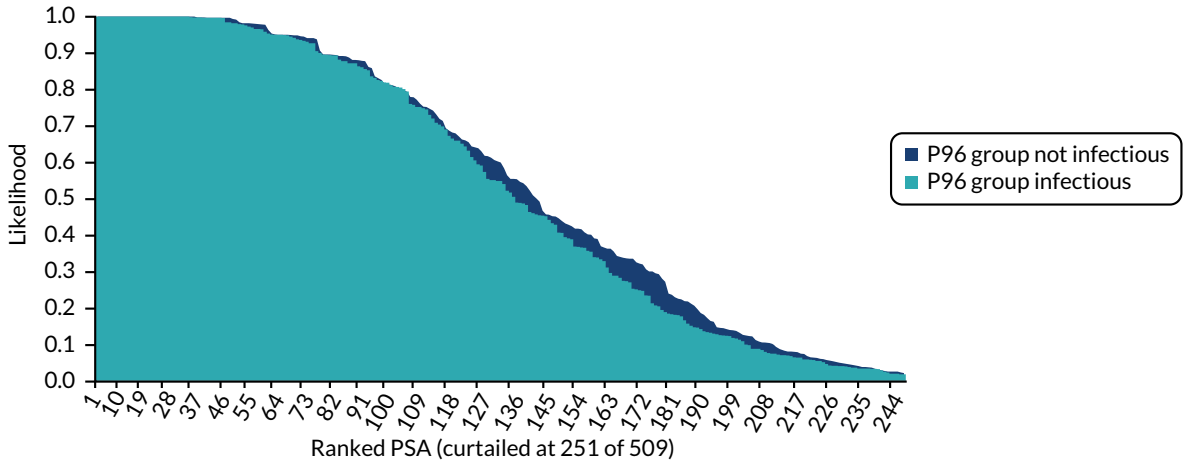

FIGURE 17 The likelihoods of the PSA configurations being compatible with the observed data (curves are drawn on top of each other).

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 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%, respectively. Thus, in this scenario analysis half of surgical units both followed IPG196 and kept instruments moist.

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 that prohibit the possibility of stCJD. These are likely to take the form of the introduction of 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. First, 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 and infectivity detection method used. Second, the findings for some agents inevitably differed both within and between studies, owing to the described heterogeneity (see results for Rely+On depending on the assay or NaOH depending on the prion strain). Identifying the most 'efficacious' decontaminant, requiring comparison across agents, was, therefore, not possible. Third, as far as we could tell, the majority of the decontaminants (and combinations thereof) were not commercially available but had been developed for the laboratory tests, whereas others that did exist as distinct products were few and, in some cases, were no longer on the market, for example Rely+On. Fourth, uptake of additional decontaminant solutions might be very low in practice owing to requiring an extra step in the sterilisation process. Therefore, major concerns 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 5.

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 *Categorisation of surgical units*) to represent the combinations of the unit's adherence to IPG196; whether or not instruments are kept moist; and whether or not it is assumed that the P96 group is infectious. It has been assumed that there are 27 units in England.

It is assumed that the answers produced will contain Monte Carlo sampling errors 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.

Base-case results

The base-case results are provided in *Table 26* and relate to the period 2019–23, as agreed with the NICE committee. The estimated values are presented in columns two to four; these are calculated using all PSA configurations ($n = 509$) and all RN streams ($n = 27$). The values of simulated deaths as a result of CJD infection, which were weighted by their likelihood that the transmissions of CJD modelled between 2005 and 2018, matched the observed data. The final column contains a value that 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.

Interpretation of the base-case results

As anticipated, fewer deaths as a result of stCJD were estimated when IPG196 was followed and when residual mass was reduced. Thus, in terms of future deaths as a result of stCJD, S1 had fewer deaths than S2, which had fewer deaths than S3, and S4 had fewer deaths than S5, which had fewer deaths than S6. Furthermore, as anticipated, when the P96 group was assumed not to be infectious there were fewer projected deaths as a result of stCJD; that is, S1 had more deaths than S4, S2 had more deaths than S5 and S3 had more deaths than S6.

Those units that 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 as a result of stCJD of 0.035 when the P96 group was deemed infectious from birth and 0.040 when the P96 group was not deemed infectious from birth. Assuming IPG196 was not followed, failure to keep instruments moist was associated with an increase in the estimated numbers of future deaths compared with not following IPG196 increased by 0.343 when the P96 group

TABLE 26 Base-case results per surgical unit[a]

Surgical unit	Average number of future deaths caused by infections between 2019 and 2023, total (non-P96 group/P96 group)[b]	Average number of future undiscounted life-years lost caused by infections between 2019 and 2023	Average number of future discounted QALYs lost caused by infections between 2019 and 2023	Maximum number of future deaths across the PSAs caused by infections between 2019 and 2023 multiplied by likelihood, total (non-P96 group/P96 group)[b]
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)

a The values need to be multiplied by 27 to provide numbers for England rather than surgical units.
b Numbers may appear discrepant as a result of rounding.

was deemed infectious from birth and 0.310 when the P96 group was not deemed infectious from birth. 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 number 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 while in the subclinical 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 were associated with the prevalence of CJD prions in their tissue being very low: < 1 per 200,000 people had prions in their tissue. In these PSA runs, no infectious people had entered the system between 2004 and 2018; this resulted in no infections and thus these PSA runs have a likelihood of 1 of matching the observed data. In the 2019–23 period, infectious people were simulated to have an operation in some RN streams, which resulted in infections and deaths. The number of deaths was 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 10 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 *Exploring the uncertainty in the results produced within the base-case analyses* 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 for each of the two groups 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%. The 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.

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 comprised strategies to follow IPG196 and/or reduce the residual mass on instruments, and estimated the effect 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.

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 RNs exhausted within a simulation. For example, in the scenario analysis that changed a unit from S2 to S1, at the start of 2019 this model run will have used significantly more RNs than a comparison with S1 alone. This is a result of the RNs required in selecting from 2012 onwards, the SIs used in an operation and the migration of instruments between sets (which is a feature of S2 but not of S1). This misalignment of RNs 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, which offers support that the values are relatively robust. However, caution is advised in trying to interpret differences in the results of the scenario analyses (see *Table 27*) and

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

Surgical unit	Average number of future deaths caused by infections between 2019 and 2023, total (not P96 group/P96 group)[a]	Average number of future undiscounted life-years lost caused by infections between 2019 and 2023	Average number of future discounted QALYs lost caused by infections between 2019 and 2023	Maximum number of future deaths across the PSAs caused by infections between 2019 and 2023 multiplied by likelihood, total (non-P96 group/P96 group)[a]
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[b]	0.041 (0.041/0.000)	1.661	0.484	0.556 (0.444/0.111)
S4[b]	0.037 (0.037/0.000)	1.543	0.451	0.556 (0.444/0.111)

a Numbers may appear discrepant as a result of rounding.
b Removing the necessity for the P96 group to have to use a different instrument set.

the base-case results (see *Table 26*), as these differences could be artefacts of the RNs selected. Significantly more computational time would be required to provide an accurate comparison of the scenario analyses and the base-case results; this was beyond the time scales of the project.

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

As described in *Exploring the probability that each type of surgical unit was the most cost-effective*, the distribution that was 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 for the expected number of QALYs lost as a result 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.

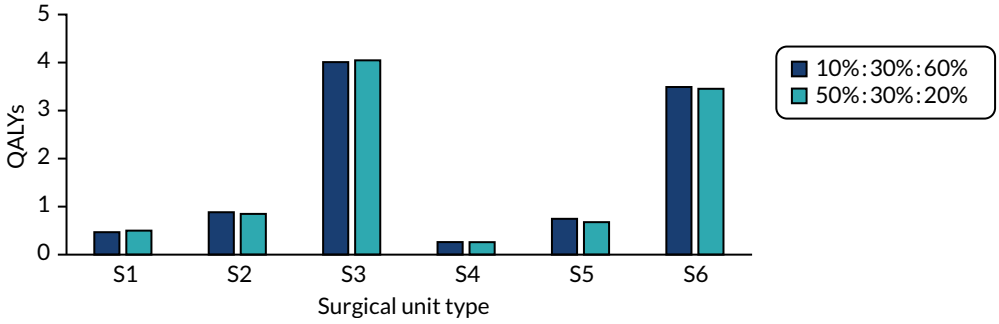

FIGURE 18 Comparing the QALYs lost within the base case and when using an alternative assumption related to the distribution of surgical units following IPG196 and in keeping instruments moist. The percentages in the figure key refer to the proportion of units that are S1/S4, S2/S5 and S3/S6, respectively. S1 and S4 are assumed to follow both 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.

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 that change the values of parameters and threshold analyses have been performed to determine at what price for 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 symptomatic stCJD.

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,[216] and between £100,000 and £300,000 for highly specialised technologies.[221]

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 owing to the relatively small values involved.

TABLE 28 Parameter values used within the cost-effectiveness analyses

Parameter	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

The base-case cost-effectiveness of strategies for reducing the likelihood of surgically transmitted Creutzfeldt–Jakob disease

Results for S1 and S4 units

For surgical units that adhere to IPG196 and keep 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 a S1 unit that the additional net cost 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 £4.0M. For a S4 unit, the net cost was similar (£1,814,545) with fewer QALYs gained (0.275), resulting in a cost per QALY gained of £6.7M. Both cost-per-QALY estimates are markedly higher than the thresholds commonly used by NICE.

Results for S2 and S5 units

For surgical units that do not adhere to IPG196 but keep 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 a S2 unit that the additional net cost 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 a 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 a S2 unit, adherence to IPG196 is estimated to have a net cost of approximately £750,000 and provide an increase in QALYs of 0.415, resulting in a cost per QALY of approximately £1.8M. For a S5 unit, adherence to IPG196 is estimated to have 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 £1.6M. Both cost-per-QALY estimates are markedly higher than the thresholds commonly used by NICE.

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 a 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 a 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 a 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 dominant (lower costs and more QALYs produced). For a S6 unit, there was also an expected cost saving of an increase in QALYs of 2.749, resulting in keeping instruments moist being dominant.

For a 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 £1.8M per QALY gained. For a S6 unit having moved to a S5, the cost per QALY gained of adhering to IPG196 would be in the region of £1.6M.

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

The probabilities of each surgical unit and using single-use instruments being the 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) have the highest probability of being cost-effective, followed by units that continue to ignore IPG196 and those that do not keep 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) that are estimated to be the most cost-effective.

Sensitivity analyses performed on the base-case results

Having observed the ICERs that were presented in terms of cost per QALY gained produced in the base case, the sensitivity analyses that was performed explored a combination of all of the values that were more favourable to single-use instruments. Thus, the cost of a CJD case was increased to £70,000; the average cost of a 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 to be constant.

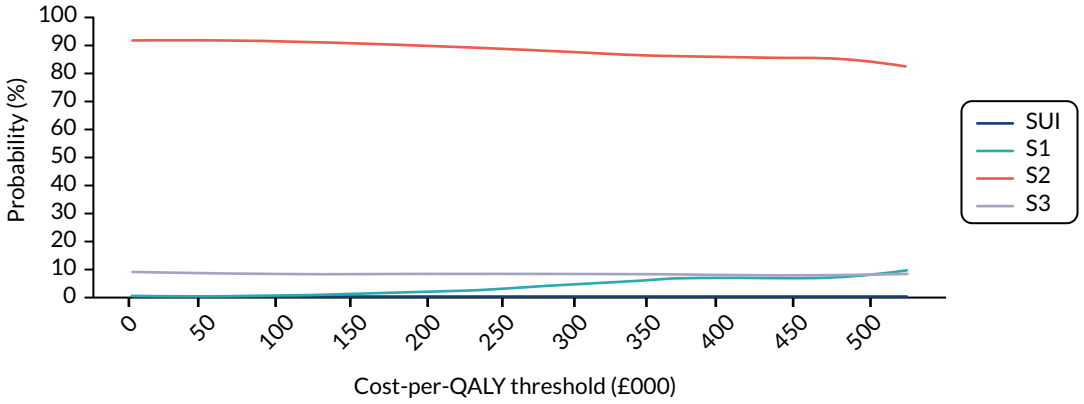

FIGURE 19 The probabilities that S1, S2, S3 and single-use instruments are the most cost-effective at a range of cost-per-QALY thresholds. SUI, single-use instrument.

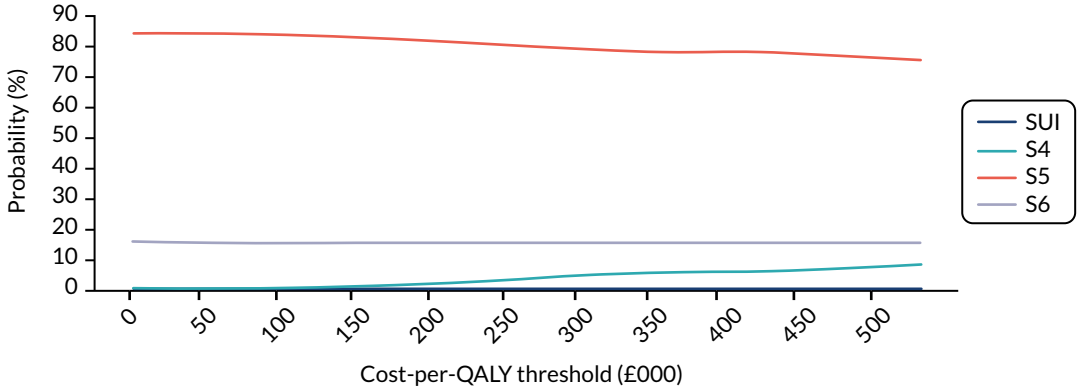

FIGURE 20 The probabilities that S4, S5, S6 and single-use instruments are the most cost-effective at a range of cost-per-QALY thresholds. SUI, single-use instrument.

Sensitivity analyses results for S1 and S4 units

The ICER for single-use instruments for a S1 unit became £2.9M, whereas the ICER for a S4 unit became £4.9M. Neither value was below the commonly used NICE thresholds.

Sensitivity analyses results for S2 and S5 units

The ICER for single-use instruments for a S2 unit became £2.4M, whereas the ICER for a S5 unit became £2.9M. Neither value was below the commonly used NICE thresholds.

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

Sensitivity analyses results for S3 and S6 units

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

For a 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 £1.2M per QALY gained. For a S6 unit, the cost-per-QALY of adhering to IPG196 would be in the region of £1.1M, which is similar to moving from a S5 to a S4 unit. 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.

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 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 that was 100% effective at removing CJD prions, as both approaches (single-use instruments and the cleaning solution) 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 that was more favourable to reusable instruments and a completely effective cleaning solution. The results are presented in *Table 29*. Caution must be used in interpreting these results, as options other than single-use instruments or a completely effective cleaning solution exist. For example, moving from a S6 to a S5 (or S3 to a S2) is estimated to be a dominant strategy and thus the thresholds for single-use sets for a S6 unit or a S3 unit are redundant, although these have been presented for information.

It is seen that in units where instruments were kept moist, a single-use set price would need to be 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.

Threshold analyses on the costs of adhering to IPG196

For S2 and S5 units, analyses were performed to indicate 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 a completely effective cleaning solution. The results are presented in *Table 30*. The estimated cost of implementing IPG196 is estimated to be £750,000, which is greater than the threshold values provided in *Table 30*.

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

		Cost-per-QALY threshold (£)			
Surgical unit	Assumptions	30,000	50,000	100,000	300,000
S1	Base case	11.21	12.70	16.43	31.32
	Favourable	11.60	13.09	16.81	31.71
S2	Base case	13.44	16.28	23.36	51.71
	Favourable	13.91	16.75	23.83	52.18
S3	Base case	30.66	43.67	76.19	206.27
	Favourable	31.91	44.92	77.44	207.53
S4	Base case	10.25	11.14	13.37	22.30
	Favourable	10.61	11.50	13.73	22.66
S5	Base case	12.70	15.09	21.06	44.93
	Favourable	13.15	15.53	21.50	45.37
S6	Base case	27.90	39.21	67.48	180.55
	Favourable	29.07	40.38	68.65	181.72

Favourable denotes assumptions that are more favourable to single-use and effective detergents.

TABLE 30 Threshold analyses on the cost of implementing IPG196

		Cost-per-QALY threshold (£)			
Surgical unit	Assumptions	30,000	50,000	100,000	300,000
S2	Base case	13,746	22,038	42,766	125,678
	Favourable	14,270	22,561	43,290	126,202
S5	Base case	15,122	24,333	47,360	139,466
	Favourable	15,645	24,856	47,882	139,988

Favourable denotes assumptions that are more favourable to single-use and effective detergents.

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

The data reported in *Tables 26* and *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 as a result of the misalignment of RNs. Conversely, where the requirement for different instrument sets is 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 the number of deaths (which may be equal in both scenarios) and the 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.

Chapter 4 Discussion and conclusions

The purpose of the systematic review was to summarise the most up-to-date published evidence about CJD with regards to the 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 because of the rare nature of CJD. As a result, the eight systematic reviews are heavily reliant on historical cases of stCJD, observational data, case–control study designs and animal data.

This 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.[11] 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. Although 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, detected using vCJD-specific immunostaining, has also been detected in stored anonymised appendix tissue samples in cohorts of people considered not to have had significant exposure to the BSE epidemic, as reported in the recent Appendix III study.[16] 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 appendixes without transmission to the CNS. Therefore, the assumption that a prevalence of non-clinical prion accumulation in peripheral tissue represents disease that will go on to become clinical CJD has yet to be substantiated. As CJD detection methods advance, more accurate confirmation of CJD pathology will be possible from autopsy and excised tissue samples. Data on the likely incubation periods of CJD are limited to retrospective data from iCJD, vCJD or kuru cases. These data indicate that very long incubation periods that exceed life expectancy are possible. Although 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, to our knowledge no reports of observed cases of stCJD have been published. Although 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_{50} per gram are possible.

Evidence on the decontamination of surgical instruments is fragmented with no single study assessing the efficacy of all strategies, which include reducing residual mass, keeping instruments moist, autoclaving and sterilisation. Comparison of included studies is also problematic as a result of these being conducted under different conditions and in laboratory settings that 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 owing 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 was used alongside heuristics that increased the efficiency of the

available computational time. The results produced suggest that although 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 cases. Not adhering to keeping instruments moist had a higher mean number of cases (approximately 11) and a maximum among the simulations undertaken of 115. As such, keeping instruments moist should be undertaken wherever possible.

Although 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 modelled strategies, 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 affect 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 (< 0.08; see *Table 27*) having kept instruments moist, noting that these cases would appear in the future and may be misdiagnosed.

Running a greater number of PSA configurations would increase the accuracy in the ICER related to uncertainty in parameter estimates, and running more RN 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 (3) 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.[203]

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 the 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 5-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.

Furthermore, 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 among 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 of the aspects deemed important by the NICE advisory committee and was calibrated to the potential number of stCJD cases that have been observed between 2005 and 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, 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 time scale of the project, it was only possible to elicit opinion from four experts, which may be a limitation. It is highlighted that the model focused 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.

Although the work undertaken suggests that (1) keeping instruments moist is a dominant strategy compared with not, and (2) that all other ICERs are in excess of £1 million per QALY gained, there remains a possibility of future stCJD cases using 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 HES 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 cases that have been observed in England. Historical data are unlikely to provide further insight; however, prospectively assessing whether or not patients diagnosed with

alternative neurodegenerative diseases have a history of high-risk surgery could improve the ascertainment rates of stCJD. Furthermore, 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 appendixes tested for prions may allow an improved estimate of the prevalence of asymptomatic CJD in the UK population.

Further studies of the effectiveness of keeping surgical instruments moist 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 (see *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.

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Contributions of authors

Matt Stevenson (https://orcid.org/0000-0002-3099-9877) led the project, undertook the review of cost-effectiveness literature, constructed the mathematical model and interpreted the results.

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Data-sharing statement

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

Patient data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

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Appendix 1 Clinical effectiveness search strategies

MEDLINE, MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations

Date range searched: 1946 to 2017 (via Ovid).

Date searched: 14 August 2017.

Search strategy

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

Date range searched: 1974 to 11 August 2017.

Date searched: 14 August 2017.

Search strategy

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. 96 remove duplicates from 95

Science Citation Index (SCI-E) and Conference Proceedings Citation Index (CPCI)

Date range searched: 1990 to 2017 (via Web of Science).

Date searched: 14 August 2017.

Search strategy

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 searches

Supplementary searches were carried out in October 2017.

MEDLINE, MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations

Date range searched: 1946 to 2017 (via Ovid).

Date searched: 2 October 2017.

Search strategy

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

Date range searched: 1974 to 2017 October.

Date searched: 2 October 2017.

Search strategy

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)

Date range searched: 1990 to 2017 (via Web of Science).

Date searched: 2 October 2017.

Search strategy

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

Date range searched: 1946 to 2017 (via Ovid).

Date searched: 7 June 2017.

Search strategy

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

Date range searched: 1974 to 6 June 2017.

Date searched: 7 June 2017.

Search strategy

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)

Date range searched: 1990 to 2017 (via Web of Science).

Date searched: 11 July 2017.

Search strategy

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 AM, Akuku O. Creutzfeldt–Jakob disease in Kenya. *Trop Med Int Health* 2005;**10**:710–12	Data from pre 2005
Allen CT, Sonnen J, Leslie MJ, Kidoguchi L, Harris C, Gambetti P, Montine TJ. Washington statewide pathology surveillance for prion disease. *Ann Neurol* 2007;**61**:371–72	Superceded data
Amour J. Comparison of single-use and reusable metal laryngoscope blades for orotracheal intubation during rapid sequence induction of anaesthesia: a multicenter cluster randomised study. *Anaesthesiology* 2010;**112**:325–32	Not high-risk surgery
Brandel JP, Salomon D, Capek I, Vaillant V, Alperovitch A. Epidemiological surveillance of Creutzfeldt–Jakob in France. *Rev Neurol* 2009;**165**:684–93	Review with no original data
Chandra SR, Issac TG, Philip M, Gadad V. Creutzfeldt–Jakob disease phenotype and course: our experience from a tertiary centre. *Indian J Psychol Med* 2016;**38**:438–42	No usable data for any review question
Checchi M, Hewitt PE, Bennett P, Ward HJ, Will RG, Mackenzie JM, Sinka K. 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 Sang* 2016;**111**:325–32	No usable data for any review question
Chen CC, Wang YH, Wu KY. Consumption of bovine spongiform encephalopathy (BSE) contaminated beef and the risk of variant Creutzfeldt–Jakob disease. *Risk Anal* 2013;**33**:1958–68	No usable data for any review question
de Pedro-Cuesta J, Bleda MJ, Rabano A, Cruz M, Laursen H, Molbak K, Siden A. Classification of surgical procedures for epidemiologic assessment of sporadic Creutzfeldt–Jakob disease transmission by surgery. *Eur J Epidemiol* 2006;**21**:595–604	Wrong outcome
Frontzek K, Moos R, Schaper E, Jann L, Herfs G, Zimmermann DR, *et al.* Iatrogenic and sporadic Creutzfeldt–Jakob disease in 2 sisters without mutation in the prion protein gene. *Prion* 2015;**9**:444–8	No usable data for any review question
Graziano S and Pocchiari M. Management and prevention of human prion diseases. *Curr Neurol Neurosci Rep* 2009;**9**:423–9	Review with no original data
Gregori L, Yang H, Anderson S. Estimation of variant Creutzfeldt–Jakob disease infectivity titres in human blood. *Prion* 2012;**6**:139	No usable data for any review question
Gubbels S, Bacci S, Laursen H, Hogenhaven H, Cowan S, Molbak K, Christiansen M. Description and analysis of 12 years of surveillance for Creutzfeldt–Jakob disease in Denmark, 1997 to 2008. *Euro Surveill* 2012;**17**:12	Superceded data
Hamaguchi T. Clinical manifestations and epidemiology of prion diseases in Japan. *Rinsho Shinkeigaku* 2013;**23:**1246–8	Superceded data
Ironside JW, Head MW, Peden A, Ward H. Asymptomatic vCJD infection detected at autopsy in a UK haemophilic patient. *Haemophilia* 2010;**16**:29	Superceded data
Karhade AV, Vasudeva VS, Dasenbrock HH, Lu Y, Gormley WB, Groff MW, *et al.* Thirty-day readmission and reoperation after surgery for spinal tumours: a National Surgical Quality Improvement Program analysis. *Neurosurg Focus* 2016;**41**(2)	Wrong outcome
Klug GM, Boyd A, Lewis V, McGlade A, Stehmann C, Masters CL, Collins SJ. Surveillance of Creutzfeldt–Jakob disease in Australia: 2009 update. *Commun Dis Intell Q Rep* 2019;**33**:188–91	Superceded data
Kobayashi A, Matsuura Y, Iwaki T, Iwasaki Y, Yoshida M, Takahashi H, *et al.* Sporadic Creutzfeldt–Jakob disease MM1 + 2C and MM1 are identical in transmission properties. *Brain Pathol* 2016;**26**:95–101	Review with no original data
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 Neuropathol* 2015;**130:**159–70	Review with no original data

Reference	Primary reason for exclusion
Kovacs GG, Majtenyi K. Creutzfeldt–Jakob disease in Hungary. *Folia Neuropathol* 2005;**43**:279–85	Superceded data
Maddox RA, Person MK, Minino AM, Blevins JE, Schonberger LB, Belay ED. Unusually young prion disease cases in the United States, 1979–2014. *Prion* 2016;**10**:S98–S99	No usable data for any review question
Maheshwari A, Fischer M, Gambetti P, Parker A, Ram A, Soto C, Hussein HM. Recent us case of variant Creutzfeldt–Jakob disease-global implications. *Emerg Infect Dis* 2015;**21**:750–9	Superceded data
Mei LL, Sin HF, Suk ML, Wai CL. Effectiveness of 2D barcode tracking in recording instrument sterilisation & avoiding spread of infection in operating theatre. *J Microbiol Immunol Infection* 2015;**48**:S68	Wrong outcome
Mikol J, Deslys JP, Zou WQ, Xiao W, Brown P, Budka H, Goutieres F. Creutzfeldt–Jakob disease with unusually extensive neuropathology in a child treated with native human growth hormone. *Clin Neuropathol* 2012;**31**:127–34	Superceded data
Papacostas S, Malikides A, Petsa M, Kyriakides T. Ten-year mortality from Creutzfeldt–Jakob disease in Cyprus. *East Mediterr Health J* 2008;**14**:715–19	Data from pre-2005
Parchi P. Molecular-phenotypic correlation in sporadic and genetic Creutzfeldt–Jakob disease: Insights from recent studies. *Clin Neuropathol* 2009;**28**:235–36	Review with no original data
Ritchie DL, Lowrie S, Le Grice M, Burns K, Ironside JW. Amyloid-beta accumulation in human growth hormone related iatrogenic CJD patients in the UK. *Neuropathol Appl Neurobiol* 2017;**43**:39	Not CJD related
Rohan Z, Rusina R, Maresova M, Matej R. Human prion diseases in the Czech Republic. *Epidemiol Mikrob Im* 2015;**64:**115–20	No usable data for any review question
Saba R, Booth SA. The genetics of susceptibility to variant Creutzfeldt–Jakob disease. *Public Health Genomics* 2013;**16**:17–24	No usable data for any review question
Sawyer EB, Edgeworth JA, Thomas C, Collinge J, Jackson GS. Preclinical detection of infectivity and disease-specific PrP in blood throughout the incubation period of prion disease. *Sci Rep* 2015;**5**:17742	No usable data for any review question
Takeuchi A, Kobayashi A, Ironside JW, Mohri S, Kitamoto T. Characterization of variant Creutzfeldt–Jakob disease prions in prion protein-humanised mice carrying distinct codon 129 genotypes. *J Biol Chem* 2013;**288**:21659–66	No usable data for any review question

Appendix 4 Elicitation exercise relating to epidemiological parameters (conducted 18 January 2018)

List of participants

Participating experts: in alphabetical order of surname

- Dr David Hilton: Consultant Neuropathologist, University Hospitals Plymouth 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 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 E Oakley: Professor of Statistics, University of Sheffield.

Parameters related to misdiagnoses of the cause of death in patients who die as a result of Creutzfeldt–Jakob disease

The quantity of interest is the percentage of patients whose death was due to CJD who were misdiagnosed as having died from another neurodegenerative disease, since 2005.

A separate percentage is considered for each of three age categories:

1. aged < 60 years
2. aged 60–79 years
3. aged ≥ 80 years.

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.

Parameter 1 definition: the percentage of patients, aged less than 60 years, whose death was because of Creutzfeldt–Jakob disease, that are misdiagnosed as having died from another neurodegenerative disease, since 2005

Individual judgements

Without conferring, the experts made the probability judgements for parameter 1 as shown in *Table 31*.

Group discussion and consensus judgements

Expert C argued that correct diagnosis would be dependent on whether or not 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.

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

Expert A was willing to revise their own judgements upwards somewhat, but thought that 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*.

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 blue shaded region indicates that, given this choice of distribution, a probability of about 0.99 has been assumed that the percentage misdiagnosed will be < 40%. Percentiles from the fitted distribution for parameter 1 are shown in *Table 33*.

TABLE 32 Consensus percentiles for parameter 1

Plausible lower limit (%)	25th percentile (%)	Median (%)	75th percentile (%)	Plausible upper limit (%)
0	5	10	20	50

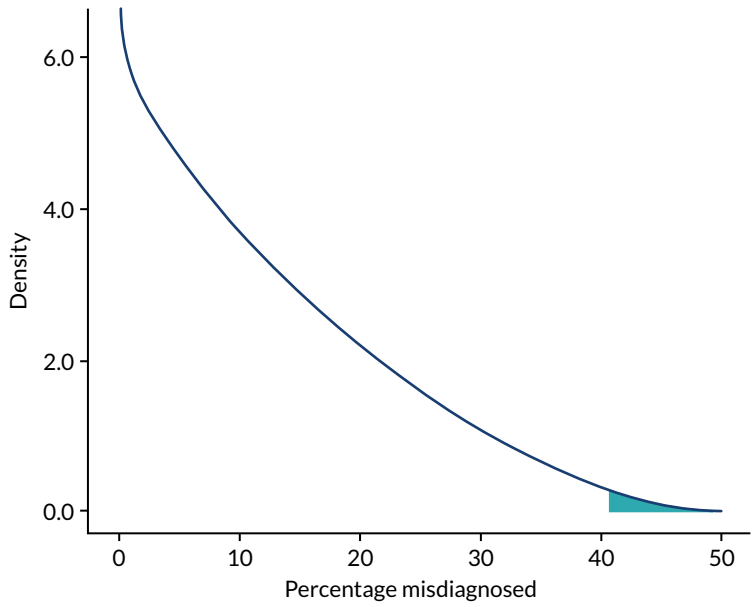

FIGURE 21 The distribution chosen to represent the experts' consensus judgements for parameter 1: the percentage of patients aged < 60 years whose death was due to CJD who are misdiagnosed as having died from another neurodegenerative disease, since 2005.

TABLE 33 Percentiles from the fitted distribution for parameter 1

Percentile	1st	5th	95th	99th
Parameter value	0.1%	0.8%	33.0%	40.6%

Parameter 2 definition: the percentage of patients aged ≥ 80 years whose death was because of Creutzfeldt–Jakob disease who are misdiagnosed as having died from another neurodegenerative disease, since 2005.

Individual judgements

Without conferring, the experts made the probability judgements for parameter 2 as shown in *Table 34*.

Group discussion and consensus judgements

Expert C argued for higher values of parameter 2, 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 sCJD 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. The consensus judgements are given in *Table 35*.

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 blue 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*.

Parameter 3 definition: the percentage of patients aged 60–79 years whose death was because of Creutzfeldt–Jakob disease who 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: aged < 60 years and ≥ 80 years). 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*.

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

TABLE 35 Consensus percentiles for parameter 1

Plausible lower limit	25th percentile	Median	75th percentile	Plausible upper limit
0%	40%	60%	65%	100%

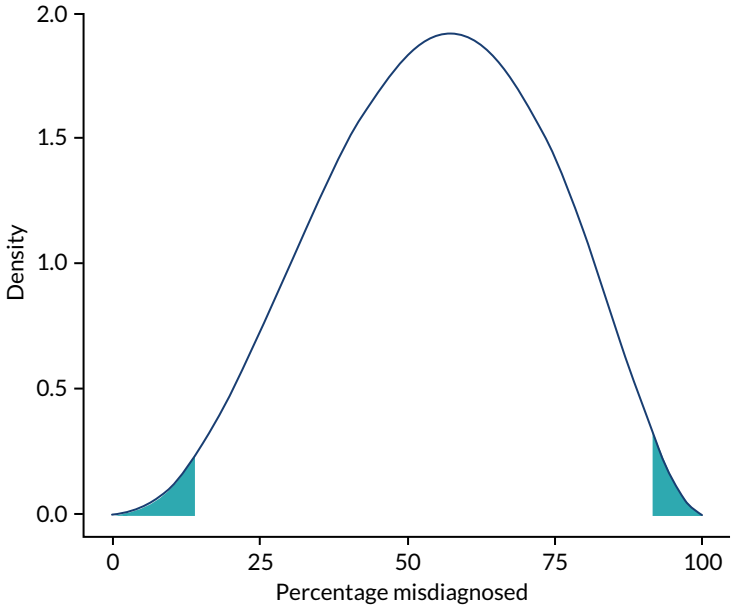

FIGURE 22 The distribution chosen to represent the experts' consensus judgements for parameter 2: the percentage of patients aged ≥ 80 years whose death was due to CJD who are misdiagnosed as having died from another neurodegenerative disease, since 2005.

TABLE 36 Percentiles from the fitted distribution for parameter 2

Percentile	1st	5th	95th	99th
Parameter value	14%	23%	85%	92%

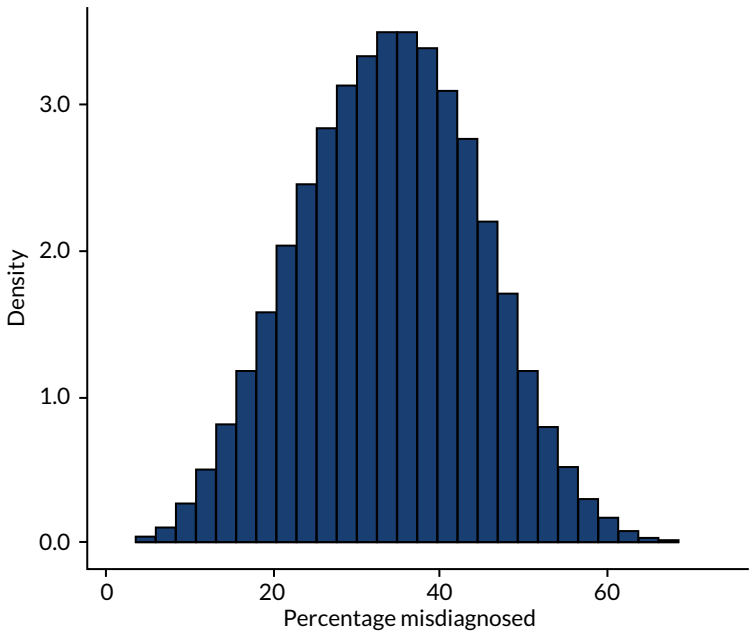

FIGURE 23 The distribution chosen to represent the experts' consensus judgements for parameter 3: the percentage of patients aged 60–79 years, whose death was due to CJD who are misdiagnosed as having died from another neurodegenerative disease, since 2005.

TABLE 37 Simulated percentiles from parameter 3

Percentile	1st	5th	95th	99th
Parameter value	10%	16%	51%	58%

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 the genotypes of both 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.

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 (i.e. posterior eye, brain, neuroendoscopy, and intradural spinal surgery), genotype unknown for each patient.

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*.

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*.

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 blue shaded region indicates that, given this choice of distribution, 98% of incubation periods will lie between 0.32 years and 48.8 years.

To allow for uncertainty in the estimated distribution, it was proposed to allow the percentages in each interval to vary by up to 15% in intervals 1–3 and up to 10% in interval 4. For example, an alternative distribution would be as shown in *Table 40* and *Figure 25*. The blue shaded region indicates that, given this choice of distribution, 98% of incubation periods will lie between 0.37 years and 48 years.

TABLE 38 The probability judgements for each expert related to incubation periods

Expert	Plausible lower limit (years)	25th percentile (years)	Median (years)	75th percentile (years)	Plausible upper limit (years)
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

TABLE 39 Consensus quartile intervals related to incubation periods. As a central estimate, it was assumed that 25% of incubation period would occur within each interval

Interval 1	Interval 2	Interval 3	Interval 4
0.25–2 years	2–10 years	10–20 years	20–50 years

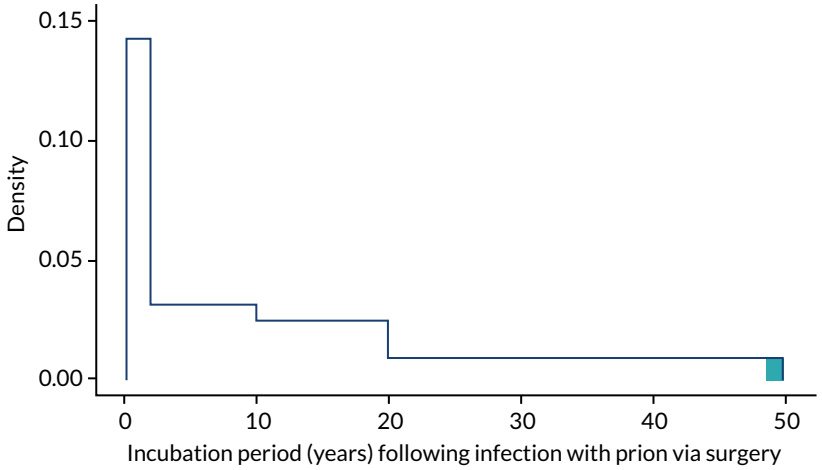

FIGURE 24 An estimate of the distribution of incubation periods for all patients the distribution of incubation period in years, in all patients, following infection with prion via surgery (posterior eye, brain, neuroendoscopy, and intradural spinal surgery), genotype unknown for each patient.

TABLE 40 An illustrative alternative distribution of patients between incubation intervals

	Interval 1	Interval 2	Interval 3	Interval 4
Incubation period	0.25–2 years	2–10 years	10–20 years	20–50 years
Percentage of patients	15%	35%	35%	15%

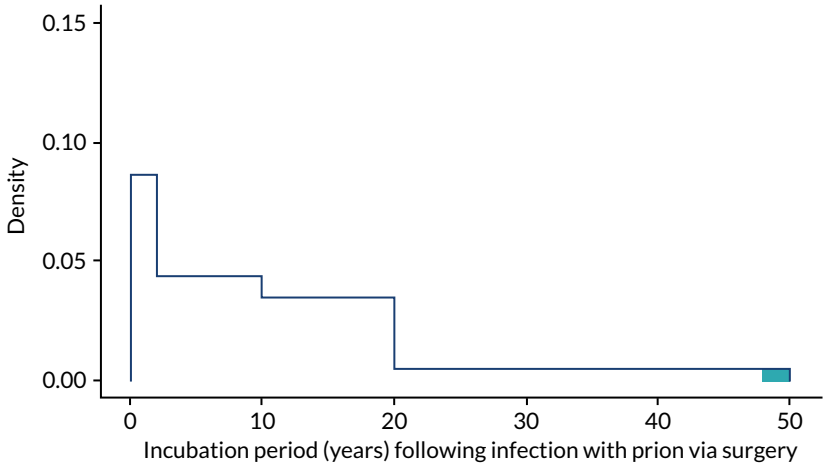

FIGURE 25 Alternative the distribution of incubation periods, constructed by perturbing the proportions of the population in each interval from the central estimates.

Susceptibility of patients to Creutzfeldt–Jakob disease: 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 MV genotype and VV genotype at codon 129 patients were non-susceptible.

The prevalence of Creutzfeldt–Jakob disease 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- to 39-year-old band, was not appropriate. It was commented that because sCJD increases with age but vCJD incubation could be greatest in younger ages, using the same distribution independent of age would be appropriate. The previous distribution used for 16- to 39 year-olds for prevalence per million people was a beta (1.24, 2225.393). This distribution is shown in *Figure 26*. The blue 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 CNS 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.

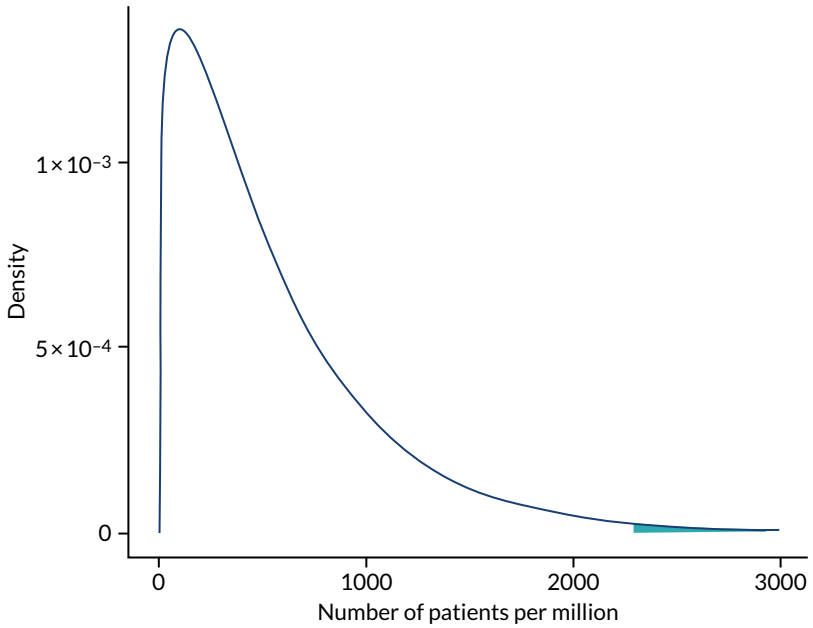

FIGURE 26 The distribution chosen to represent the experts' consensus judgements for the number of patients per million with CJD-prions in central nervous system tissue.

TABLE 41 Percentiles from the fitted distribution for the prevalence of CJD in the central nervous system

Percentile	1st	5th	95th	99th
Prevalence (patients per million)	12	46	1547	2304

Appendix 5 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 *Figures 27–31*.

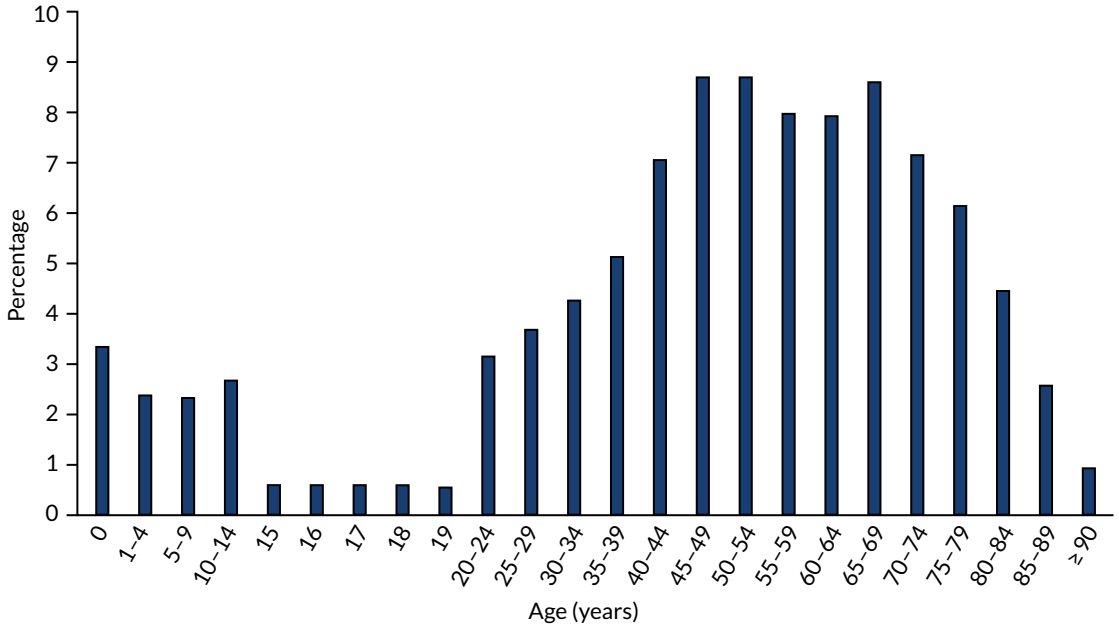

FIGURE 27 The assumed age profile of patients undergoing brain surgery who are assumed to have normal life expectancy.

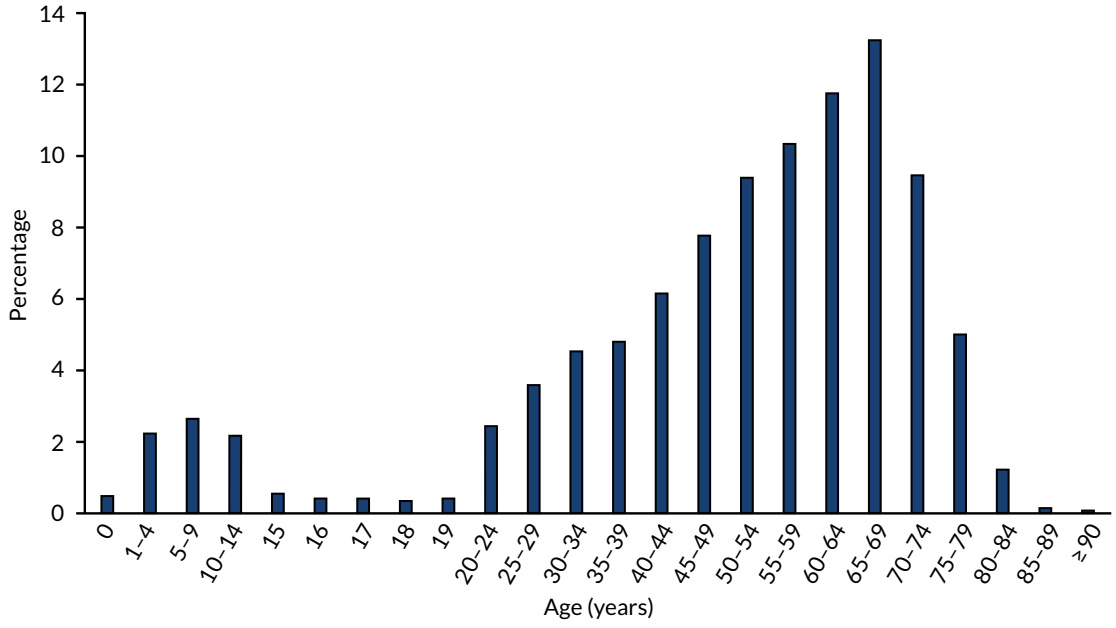

FIGURE 28 The assumed age profile of patients undergoing brain surgery assumed to die at 18 months.

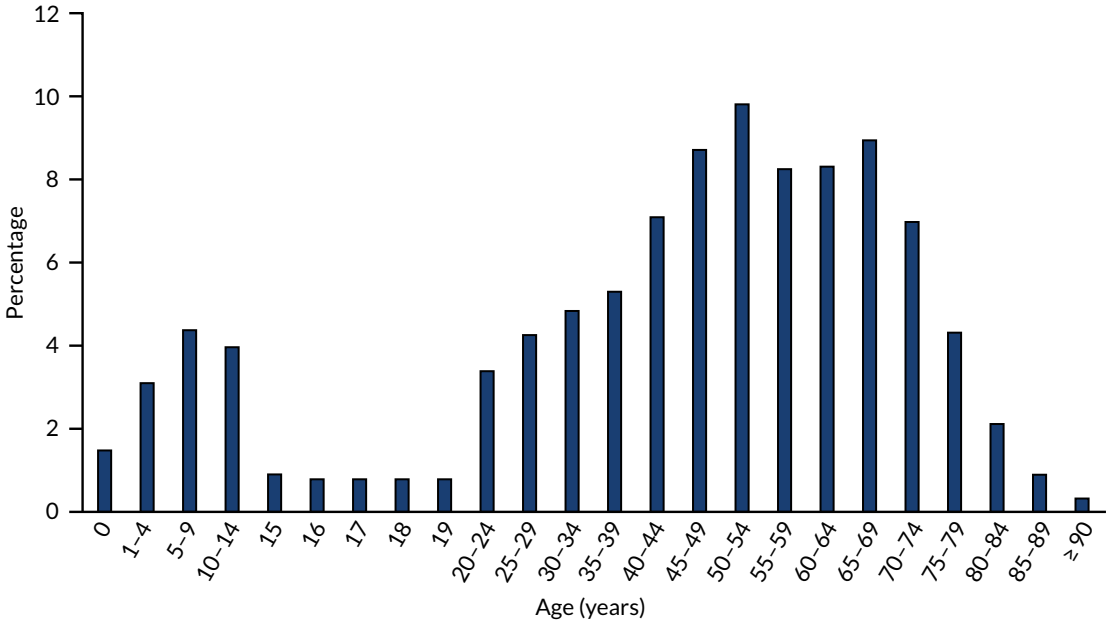

FIGURE 29 The assumed age profile of patients undergoing brain surgery who are assumed to have a 50% chance of death at 18 months otherwise who are assumed to have normal life expectancy.

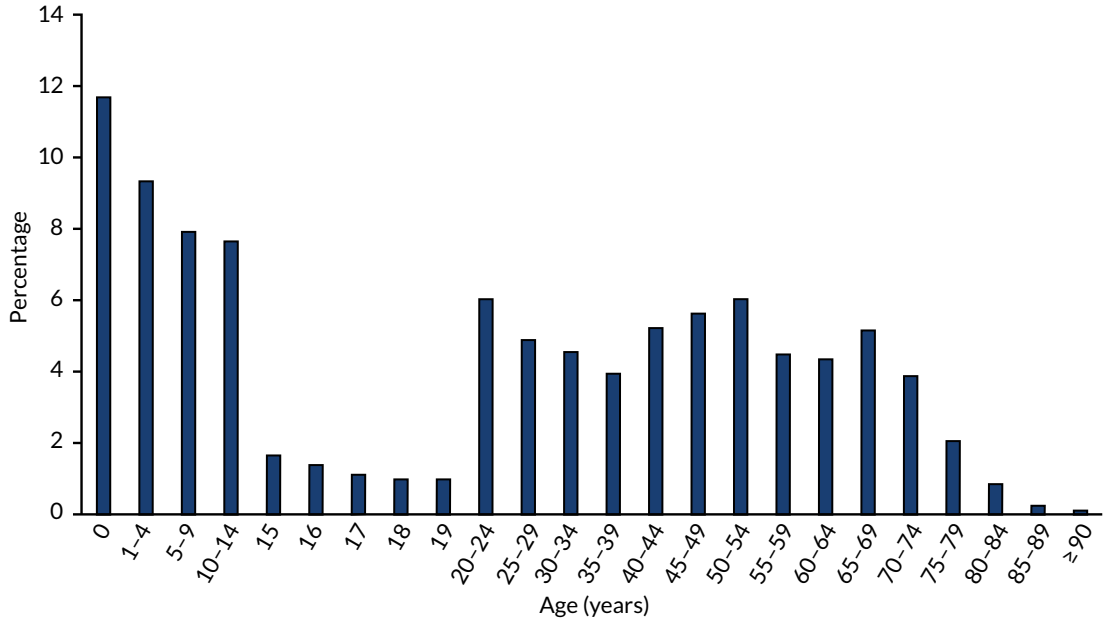

FIGURE 30 The assumed age profile of patients undergoing neuroendoscopy.

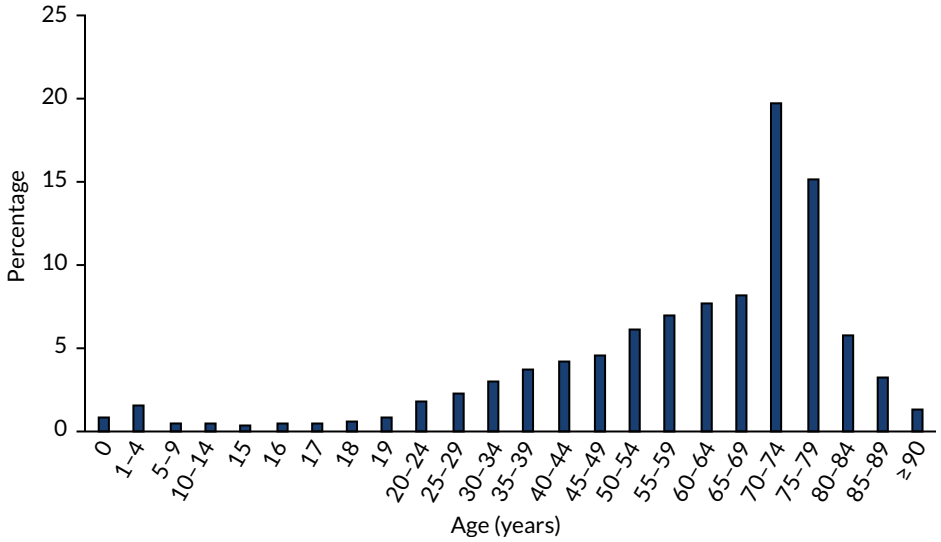

FIGURE 31 The assumed age profile of patients undergoing posterior eye operations.

Appendix 6 The operations considered to be at high risk

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

TABLE 42 Brain operations: patients modelled to die within 12 months

National code	Operation
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

NEC, not elsewhere classified.

TABLE 43 Brain operations: patients modelled to have a 50% chance of death within 12 months, otherwise normal life expectancy

National code	Operation
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

NEC, not elsewhere classified.

TABLE 44 Brain operations: patients modelled to have normal life expectancy

National code	Operation
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

TABLE 44 Brain operations: patients modelled to have normal life expectancy (*continued*)

National code	Operation
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)

continued

TABLE 44 Brain operations: patients modelled to have normal life expectancy (*continued*)

National code	Operation
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

TABLE 44 Brain operations: patients modelled to have normal life expectancy (*continued*)

National code	Operation
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

continued

TABLE 44 Brain operations: patients modelled to have normal life expectancy (*continued*)

National code	Operation
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

NEC, not elsewhere classified.

TABLE 45 Neuroendoscopy operations

National code	Operation
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

National code	Operation
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

NEC, not elsewhere classified.

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 in age category i, over the period 2005–18. The age categories are $i = 1$: ≤ 59 years; $i = 2$: 60–79 years; and $i = 3$: ≥ 80 years. We write $T = [T^{(1)}, T^{(2)}, T^{(3)}]$.
- $R^{(i)}$ – the number of transmissions of CJD via surgery that result in clinical symptoms, in age category i, over the period 2005–18, 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 2005–18, there were 15 recorded deaths from CJD, where the individuals were known to have had surgery. Hence, any number between 0 and 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:

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

- $\phi^{(i)}$ – 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:

$$R^{(i)} \,|\, T^{(i)},\ \phi^{(i)} \sim Binomial[T^{(i)},\ 1 - \phi^{(i)}] \tag{4}$$

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

$$\phi = [\phi^{(1)}, \phi^{(2)}, \phi^{(3)}]. \tag{5}$$

$M^{(i)}$ the maximum number of transmissions of CJD via surgery that result in clinical symptoms, in age category i, over the period 2005–2018, that resulted in deaths recorded as being due to CJD. We have:

$$M^{(1)} + M^{(2)} + M^{(3)} = 15, \tag{6}$$

and that:

$$R^{(i)} \leq M^{(i)}, \tag{7}$$

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

$$M = [M^{(1)}, M^{(2)}, M^{(3)}], \tag{8}$$

we make the assumption that:

$$M|C \sim Multinomial\left(15; \frac{1}{3}, \frac{1}{3}, \frac{1}{3}\right), \quad (9)$$

that is, that each of the 15 potential cases were 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 CJD via surgery that result in clinical symptoms; 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 CJD via surgery that result in clinical symptoms, as more can be undetected.

'*S*' and '*Y*' can be defined as follows:

- $S = (s_1, \ldots s_{27})$ – 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 to 3 inclusive, and in the second, each s_i is coded as an integer from 4 to 6 inclusive. These correspond to the six scenarios S1 to S6 defined in *Chapter 3*, *Categoristation of surgical units*. (The P96 group are infectious from birth in scenarios S1 to S3 only.)
- *Y* – the number of discounted QALYs that would be lost, as a result of transmission of CJD via surgery that result in clinical symptoms, due to surgery that took place between 2019 and 2023.

Estimating the number of quality-adjusted life-years lost owing to surgically transmitted Creutzfeld–Jakob disease caused by an operation between 2019 and 2023

The aim is to draw a sample of values $Y_1, \ldots, Y_N$ 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:

$$p(Y|C) = \int p(Y|C, \theta) p(\theta|C) d\theta. \quad (10)$$

Hence, we can obtain a sample $Y_1, \ldots, Y_N$ by obtaining a sample $\theta_1, \ldots, \theta_N$ from $p(\theta|C)$, and then sampling Y_1 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 or not the event *C* has occurred 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 $\theta_1, \ldots, \theta_N$ from $p(\theta|C)$. For each accepted θ value, the model can be run forward to produce the desired sample $Y_1, \ldots, Y_N$. We refer to this as the 'simple rejection ABC algorithm'.

Implementing the simple rejection approximate Bayesian computation algorithm

The output quantities produced by the simulation model are $T^{(1)}$, $T^{(2)}$, $T^{(3)}$. To determine from these whether or not 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:

$$p(\theta, M, S, \phi|C) = p(M, \phi|C)p(\theta, S|M, \phi, C), \tag{11}$$

and we assume:

$$p(M, \phi|C) = p(M|C)p(\phi|C). \tag{12}$$

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

Note that:

$$p(\theta, S|M, \phi, C) = p(\theta, S|M, \phi), \tag{13}$$

since given:

$$M = [M^{(1)}, M^{(2)}, M^{(3)}], \tag{14}$$

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:

$$p(\theta, S|\phi) = p(\theta|\phi)p(S|\phi) = p(\theta)P(S) \tag{15}$$

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:

$$R^{(i)}|T^{(i)},\ \phi^{(i)} \sim Binomial[T^{(i)},\ 1 - \phi^{(i)}]. \tag{16}$$

5. Observe whether or not, within the simulation model, the event:

$$R^{(i)} \leq M^{(i)}, \tag{17}$$

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

$$\bar{Y} = \frac{1}{M}\sum_{i=1}^{M} Y^{(i)}, \tag{18}$$

and an approximate 95% CI for $E(Y|C)$ can be calculated as:

$$\bar{Y} \pm 2\sqrt{S_Y^2/M}, \tag{19}$$

with:

$$S_Y^2 = \frac{1}{M-1}\sum_{i=1}^{M}[Y^{(i)} - \bar{Y}]^2. \tag{20}$$

We actually use a slightly different estimator for $E(Y|C)$ which has a lower variance, but we retain the CI given above. Note also that there is a computational bottleneck in step 3 of this algorithm; running the model to observe whether or not 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 CJD via surgery that result in clinical symptoms 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 CJD via surgery that result in clinical symptoms in the age < 60 years 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 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 CJD via surgery that result in clinical symptoms 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:

$$\gamma = 10^{\theta_M} \times \theta_R \times \theta_P, \tag{21}$$

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 $\theta_1, \ldots, \theta_{2000}$ were drawn from the appropriate distributions. $Y_1, \ldots, Y_{2000}$ was calculated in each case, and 12 RN streams (corresponding to 12 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 CJD via surgery that result in clinical symptoms 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 CJD via surgery that result in clinical symptoms for six RN streams (six surgical centres).
3. If the total number of transmissions of CJD via surgery that result in clinical symptoms for the first six RN streams for the aged < 60 years category exceeds 36, reject θ^* and return to step 1.
4. Continue simulating RN streams in batches: reject θ^* if in streams 7 to 13 the rejection 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.

A weighted ABC scheme

Instead of using the estimator $\bar{Y}$, 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:

$$\hat{E}(Y|C) = \sum_{i=1}^{509} \tilde{w}_i Y_i, \tag{22}$$

with:

$$\tilde{w}_i = \frac{w_i}{\sum_{i=1}^{509} w_i}. \tag{23}$$

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, the model simulates numbers of transmissions of CJD via surgery that result in clinical symptoms in each age band, under all scenarios for each surgical centre. The transmissions of CJD via surgery that result in clinical symptoms corresponding to the scenarios in S can then be selected.

For $k = 1, \ldots, 100{,}000$:

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 CJD via surgery that result in clinical symptoms in each age band. Denote these by:

$$T^{(i)}_{j,k} \text{ for } i = 1, 2, 3. \tag{24}$$

2. Randomly sample M from its multinomial distribution. Denote the sampled values by:

$$M_k^{(1)}, M_k^{(2)}, M_k^{(3)}. \tag{25}$$

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

$$\phi_k^{(1)}, \phi_k^{(2)}, \phi_k^{(3)}. \tag{26}$$

4. Given the sampled values in step 2, we now have:

$$R^{(i)} \mid T^{(i)}_{j,k},\ \phi^{(i)}_k \sim Binomial[T^{(i)}_{j,k},\ 1-\phi^{(i)}_k]. \tag{27}$$

5. Compute, from the corresponding binomial distributions in step 3:

$$w_{j,k} = \prod_{i=1}^{3} Pr[R^{(i)} \leq M^{(i)}_k]. \tag{28}$$

6. The weight w_i is estimated as:

$$\hat{w}_j = \frac{1}{100{,}000} \sum_{k=1}^{100{,}000} w_{j,k}. \tag{29}$$

Implementation

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

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