

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 Chick³ and
Ruth Wong¹

¹School of Health and Related Research (ScHARR), University of Sheffield, Sheffield, UK

²School of Mathematics and Statistics, University of Sheffield, Sheffield, UK

³INSEAD, Fontainebleau, France

*Corresponding author m.d.stevenson@sheffield.ac.uk

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Scientific summary

Surgically transmitted Creutzfeldt–Jakob disease risk

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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 $\leq 5 \mu\text{g}$ 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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