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The cost-effectiveness of surgical instrument management policies to reduce the risk of vCJD transmission to humans

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Current sterilization techniques may not be completely effective at removing prions from surgical instruments, which can then infect patients on whom these instruments are subsequently used. This risk is increased due to the current level of instrument migration. With wide uncertainty in the numbers of patients that are incubating variant Creutzfeldt–Jakob disease (vCJD) and effectiveness of decontamination, the UK is facing a potentially self-sustaining epidemic, which could be averted with the introduction of single-use instruments. This paper focuses on the cost-effectiveness of management strategies concerning the introduction of single-use instruments and measures to prevent migration. We formulated a discrete event simulation model of the dynamics of infection transmission, surgical instrument contamination and migration, together with the results that were pivotal in shaping Government policy. Field data about vCJD transmission has then been used to update cost-effectiveness assessments as part of a retrospective analysis, which reinforces the initial decision.
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Introduction

This paper describes the modelling and analysis of surgical instrument replacement and management policies for certain operations that may present a risk to human patients for transmitting and contracting variant Creutzfeldt–Jakob disease (vCJD). Current hospital decontamination processes in the UK do not completely de-activate the vCJD prion (Taylor *et al*, 1994), nor do they remove all residual mass that may remain on surgical instruments (Baxter *et al*, 2006). Surgical instruments used on patients that are incubating vCJD could infect subsequent patients. The introduction of single-use instrument sets would eliminate surgical transmission but would require considerable expenditure and could result in higher complication rates (Tomkinson *et al*, 2005).

One aim of this paper is to evaluate whether introducing single-use instruments could be considered cost-effective in certain high-risk interventions: brain and posterior eye surgery. A second aim is to provide a retrospective analysis of the decisions and cost–benefit analysis.

The scope of the model includes the life cycle of surgical instruments (circulation, potential contamination, cleansing and replacement) in a specialized-care surgical setting, and the dynamics of patient demand for brain and posterior eye surgery (age-dependent demand and recurrent demand, the risk of patients to potentially contaminate or be contaminated by instruments). The scenarios that were analysed include a base case that is representative of the UK system, and two alternative policies for high-risk operations: the deployment of single-use instruments for all patients, or more targeted deployment of single-use instruments for high-risk patients.

The 'Methods' section below describes the modelling choices and tools that were used to account for the significant levels of parameter uncertainty, as well as the conceptual and simulation models for assessing important operational and replacement policy issues for surgical instruments.

The 'Results of initial analysis' section below provides expected costs and quality adjusted life year (QALY) gains for the instrument replacement policies. We assess whether each policy satisfies the maximum threshold of £30 000 per QALY gained (NICE, 2004). Given the significant parameter uncertainty that exists, we also provide an uncertainty analysis via cost-effectiveness acceptability curves (CEACs) that describe the probability that policies are cost-effective (Fenwick *et al*, 2001). Costs and benefits were discounted at 3.5% per annum in accordance with current guidelines of the UK National Institute for Health and Clinical

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Effectiveness (NICE, 2004). Costs included instrument procurement and the care of vCJD patients, and were valued using 2006 UK prices.

The initial analysis was commissioned by NICE to provide information to the CJD Advisory Sub-committee (*CJDAS*) *who then provided guidance to NICE regarding the introduction of single-use instruments throughout the UK*. While there never been a reported incidence of iatrogenic vCJD infection due to surgery this may be because patients incubating the disease had not yet reached the ages at which brain and posterior eye surgery are most likely, that the infectious period, defined as when surgical instruments could become contaminated had not yet been reached or a combination of both factors; thus future iatrogenic surgical infections could not be excluded.

The requested scope did not include patients younger than 16 years, who were assumed to be not incubating vCJD, as they were not exposed to the primary source of infection, and use different instrument sets to that used on adult patients. Analyses on younger patients may be useful future research. The CJDAS peer reviewed the analysis and was the source for many of the assumptions and expert recommendations used. A full study report (Stevenson *et al*, 2006, www.nice.org.uk/guidance/IPG196) of that analysis provides fuller details about the methods and analysis, and considers other surgical areas.

This paper extends that report in several ways. The 'Methods' section further discusses modelling choices. The section 'Results of the initial study' gives additional statistical refinement. The 'Results of retrospective analysis' section provides a new *post hoc* view of the cost-effectiveness of the instrument management choices, in light of the fact that no new cases of vCJD transmission via surgical instruments have been observed in the year since the initial report was submitted. This is done by using Bayes rule to combine the initially elicited prior distributions for unknown vCJD transmission parameters, with data on the lack of new cases observed, and estimates of the likelihood of no new cases being observed via stochastic simulation techniques. The retrospective analysis reinforces the evidence for policy decisions that were made one year prior, following the initial analysis. While increased attention has been given in the simulation literature to accounting for parameter uncertainty in simulation experiments (Chick, 2001; Merrick *et al*, 2005), and Currie *et al* (2003) combine prior information and field data with normal-distribution approximation likelihood function techniques, we are not aware of other work in the discrete event simulation and operations management literature that uses simulation output itself to estimate a likelihood function, with the purpose of retrospectively assessing decisions, based on newly available data. This paper therefore extends the set of tools that are currently commonly used by operations researchers that use simulation and applies it to an important policy context.

Q1

Variant Creutzfeldt–Jakob disease

The widespread exposure of the UK population to bovine spongiform encephalopathy (BSE)-infected meat between the late 1980s and early 1990s was followed by the emergence of a new disease. vCJD is a progressive, fatal neurological disease thought to be causally related to the BSE epidemic in the UK (Bruce *et al*, 1997). It was first described in 1996 (Will *et al*, 1996) and has, until January 2008, resulted in an estimated 163 deaths in the UK (NCJDSU, 2007). The potential scale of infection is uncertain. Hilton *et al* (2004) estimate the number of people currently carrying vCJD without clinical symptoms to be 237 per million (95% confidence interval (CI) of 49–692 per million). Ghani *et al* (2003) provided a 95% CI of 10–7000 deaths for future vCJD cases in the UK, based on data up to 2002, which was subsequently revised to a 95% CI of 10–190 deaths due to the continual decline in clinical cases up to the analysis cut-off of 2006 (Clarke and Ghani, 2005).

Once infected, the concentration of vCJD prions varies throughout the body, reaching levels of 10^8 ID50/gram in the brain and posterior eye, with remaining sites having equal or fewer than 10^6 ID50/gram (Bruce *et al*, 2001). One ID50 (infectious dose 50%) is the number of pathogens required to cause infection in half of the exposed hosts, and is a standard unit for infectivity.

The genotype of an individual can affect both the likelihood of contracting clinical CJD and the time before clinical symptoms occur, if at all, following infection (Bishop *et al*, 2006). Three genotypes exist, methionine homozygous (m-m), methionine/valine heterozygous (m-v) and valine homozygous (v-v), which are estimated to be 40, 50 and 10% of the UK population, respectively (Ironside *et al*, 2006). Until 2006, all clinical cases of vCJD from dietary infection have been of the m-m genotype. It is uncertain whether individuals with m-v or v-v genotypes are less susceptible to vCJD, whether the incubation period before clinical symptoms become apparent is of a longer duration in these genotypes, or a combination of both factors. However, in 2004, a case of vCJD was reported in a recipient of blood in whom signs of infection were detected in the spleen but who did not go on to develop clinical symptoms (Peden *et al*, 2004). This person was of m-v genotype, suggesting susceptibility. Additionally, a retrospective analysis of DNA extracted from appendix tissue has shown that patients with v-v genotype are also susceptible to vCJD infection (Ironside *et al*, 2006).

Methods

The analysis is a model-based assessment of the costs and health outcomes of surgical instrument management policies. The analysis accounts for two important types of uncertainty. One type of uncertainty involves disease transmission and instrument decontamination parameters, whose values are poorly known due to lack of data and the difficulty or ethics of collecting data. A panel of experts, who were familiar with published and grey literature, were therefore convened

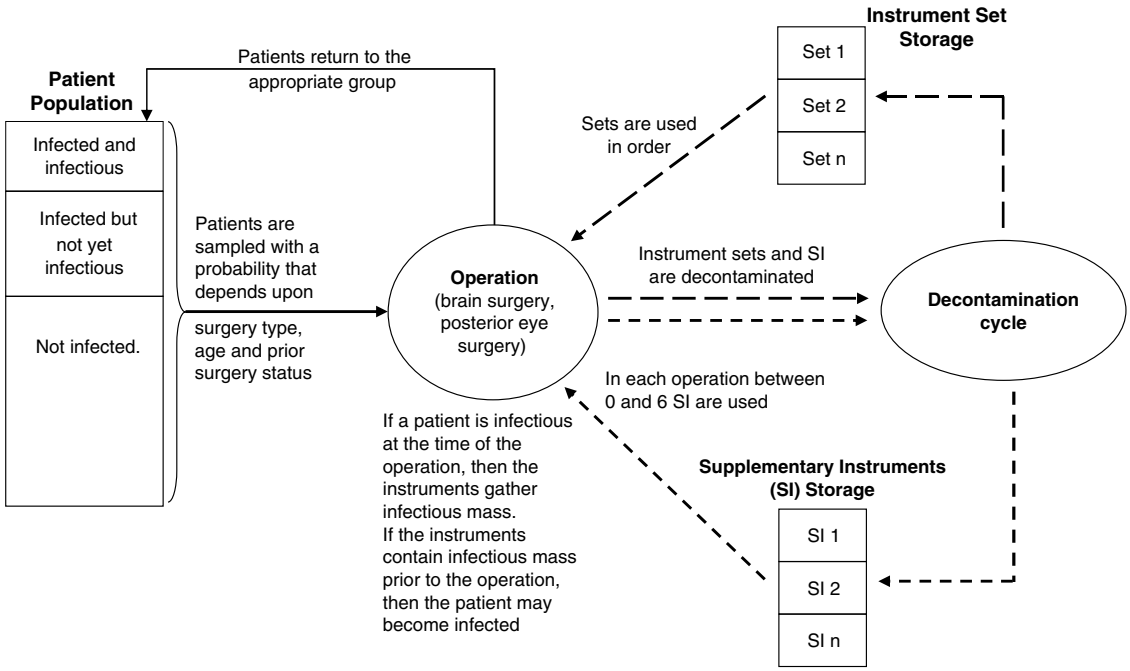

Figure 1 Flows of patients, instrument sets, and supplementary instruments (SI). The decontamination cycle removes mass from the instruments and reduces the infectious titre where applicable. During the operation, in the decontamination process, and in the instrument storing process, instruments may migrate between sets. Additionally, SIs cannot always be identified among similar items from the main set, and migration of SI and set items can occur.

to describe the uncertainties that surround those parameters using probability elicitation techniques (O'Hagan *et al*, 2006).

A second type of uncertainty, stochastic uncertainty, involves the random outcomes associated with stochastic demand for operations, the probability of disease transmission upon exposure, and random events that involve instrument usage.

Figure 1 shows a schematic of the conceptual model that was simulated. The flow of patients that it depicts accounts for the age dependency, risk factors that are associated with prior surgery, and the potential for patients to be infected with vCJD. Instrument sets and supplementary instruments (SI) pass through a decontamination cycle and are stored before reuse. Instruments and SIs may migrate between sets.

The modelled population represented a human population that is 1/27 of the size of England and Wales, based upon the number of neurosurgical centres. As there are a similar number of posterior eye centres, the model contained one brain surgical and one posterior eye centre. There were 12 sets of instruments for each specialty, which were used in rotation. There were six different types of supplementary instruments, which are kept individually and used in addition to a standard set. Each had six instruments that were used in rotation. The probability that a particular type of supplementary instrument was required was 20% per operation.

In order to account for both types of uncertainty (Chick, 2001), the unknown disease transmission and instrument decontamination parameters are sampled from their prior probability distributions, and then input into a dynamic model that accounts for stochastic uncertainty for patient demand, disease transmission, and surgical instrument usage. Deterministic differential equation (DE) models are often useful for epidemic control policy decisions (Jacquez, 1996; Bennett *et al*, 2005; Department of Health, 2006a), and might therefore be considered to approximate the effects of the model in Figure 1. However, Brennan *et al* (2006) note that infection outcomes of stochastic models may differ from deterministic differential equation models when infection transmission can occur in small populations or when disease prevalence may be rare. The reason is that DE models are derived from large population assumptions, and stochastic outcomes for nonlinear infection transmission systems with small subpopulations can lead to biased estimates for costs and benefits. The present decision context requires the modelling of sets of surgical instruments that may migrate and become contaminated in small numbers. Several of the statistical distributions that describe the natural history of vCJD are not exponential distributions, and therefore are not directly amenable to Markov chain analysis. The recommendations of Brennan *et al* (2006) thus suggest that a stochastic model of individual instruments is more appropriate for modelling this second type of uncertainty. We therefore modelled instruments and patients that are currently undergoing surgery with the traditional entity-based discrete-event simulation tools, as

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Q3

Q4 Q5

previously adopted by Davies *et al* (2003) and Rauner *et al* (2005). The number of individuals with a given characteristic (age group, vCJD infection status, history of surgery) was maintained as a count, rather than as individual entities, in order to improve runtimes while still modelling randomness in the outcomes.

Bennett *et al* (2005) and Garske *et al* (2006) model the potential transmission of vCJD via surgical instruments using deterministic DE models. Their sensitivity analysis identified the following key factors that drive uncertainty about the eventual number of iatrogenic (via medical intervention) vCJD cases: the number of times a single instrument is reused, the infectivity of contaminated instruments, and the effectiveness of cleaning. Our modelling approach allows this paper to confirm those factors, and to further assess the importance of instrument migration on the costs and benefits of instrument replacement policies.

The rest of this section describes the operations at risk, the use of data and expert elicitation to describe model parameters, the flow of patients, and summarizes the analysis. Assumptions were reviewed with CJDAS as part of the validation process.

The operations considered to be at risk

Expert advisors identified brain and posterior eye operations that would result in surgical instruments becoming contaminated were the patient incubating vCJD (Stevenson *et al*, 2006). The numbers of such operations undertaken annually were taken from Hospital Episode Statistics (HES) data (2006) and were inflated by 15% to include operations undertaken in the private sector, as assumed in previous work (Department of Health, 2006a). This results in approximately 23 000 brain operations and 42 000 posterior eye operations per year.

The life expectancy for each patient, if they remain uninfected by vCJD, was taken from interim life tables published by the Office for National Statistics (2006). The prognoses of patients undergoing brain operations are poor. One-third of brain operation patients die within a year regardless of whether or not they contracted vCJD (Stevenson *et al*, 2006).

The policies evaluated

In the base case scenario, instrument migration continued at the estimated current rate. Two policy options were analysed. Single-use instruments sets for all patients undergoing brain or posterior eye surgery, and a targeted approach where single-use instruments were used only on those patients who had previously undergone brain or posterior eye surgery. Each policy option was analysed under two scenarios—first with instrument migration continuing at estimated current levels, then with instrument migration prohibited.

Given the number of at-risk operations per year and the costs of re-usable instrument sets (£3500 for brain surgery and £1000 for posterior eye surgery) adopting a single-use policy for all patients in both specialties would cost an estimated £121 million per annum (Stevenson *et al*, 2006).

Eliciting distributions for unknown parameters

In many cases, there was limited or no data regarding key parameters for epidemiological transmission and the decontamination of surgical instruments. The timeline and budget of the project, as well as the ethics of causing CJD transmission in order to collect data about transmission parameters, did not allow for all uncertainty to be resolved with exhaustive scientific studies. Consequently, it was necessary to elicit expert beliefs about these parameters using formal elicitation techniques (O'Hagan *et al*, 2006). The purpose of the elicitation sessions was to obtain suitable probability distributions to represent the experts' uncertainty about the parameters of interest; the experts were not asked to provide single estimates of the parameters at any stage of the process. Where published literature relevant to the decision problem existed these were discussed by the experts and taken into consideration when formulating distributions.

The elicited distributions are reported in Table 1 for epidemiological data and Table 2 for parameters associated with decontamination. For example, the experts believed that the time to clinical onset via the central nervous system would be significantly quicker than that of 6.5 years, which has been observed in contraction of vCJD from blood transfusion (Llewelyn *et al*, 2004). The distributions were presented to other experts for comment, but this did not result in any proposed substantial changes. We pessimistically assume that all patients incubating vCJD at the initiation of the model had reached the infectious period.

The residual mass expected on an instrument set

A review of the published and grey literature was undertaken to estimate the average wet mass equivalent residing on an instrument, which was assumed to be 2.88 mg (Stevenson *et al*, 2006). We assumed that 18 instruments were at risk of contacting infectious tissue during brain surgery and nine during posterior eye surgery, resulting in total wet mass equivalent of 51.84 and 25.92 mg, respectively. We adopted an approach described by the Department of Health (2006a) which assumes that the residue on an instrument is in steady state, and that whatever mass is removed through transference to a patient, or through subsequent decontamination cycles (Table 2), would be replaced by mass harvested from the next operation. The infectious titre of the prion is assumed to decrease on the first three decontamination cycles, following which no further reduction is achieved.

Instrument migration

As the integrity of instrument sets may not be maintained during the use and decontamination process, the simulation model allowed instruments to migrate between sets and also to become exchanged with supplementary ones. Migration is an

Table 1 Summary of elicited epidemiological values

Parameter	*Distribution*	*10th percentile*	*Median*	*90th percentile*
The number of asymptomatic individuals, aged 16–39 years who were incubating vCJD per million in this group in 2005.	Beta (1.24, 2225.39)	84	400	1216
The ratio, in 2005, of the proportion of asymptomatic individuals, aged 0–15 years, who are currently incubating vCJD to the proportion of asymptomatic individuals, aged 16–39 years, that were incubating vCJD.	Beta (0.88, 4.02)	0.02	0.15	0.41
The ratio, in 2005, of the proportion of asymptomatic individuals, aged 40–69 years, who are currently incubating vCJD to the proportion of asymptomatic individuals, aged 16–39 years, who were incubating vCJD.	Beta (1.52, 5.40)	0.05	0.20	0.43
The ratio, in 2005, of the proportion of asymptomatic individuals, aged 70 years and above, who are currently incubating vCJD to the proportion of asymptomatic individuals, aged 16–39 years, who were incubating vCJD.	Beta (2.72, 47.31)	0.02	0.05	0.09
The incubation period for an individual of m-m genotype at codon 129, with secondary infection from central nervous system to central nervous system surgery (years)	Log normal, Mean (on log scale): 0.69, s.d. (on log scale): 0.35	1.27	2	3.15
The incubation period for an individual of m-v genotype at codon 129, with secondary infection from central nervous system to central nervous system surgery (years)	Log normal, Mean (on log scale): 1.95, s.d. (on log scale): 0.35	4.48	7	10.95
The incubation period for an individual of v-v genotype at codon 129, with secondary infection from central nervous system to central nervous system surgery (years)	Log normal, Mean (on log scale): 2.49, s.d. (on log scale): 0.36	7.53	12	19.10
The population median proportion of the incubation period in which the patient is infectious at the central nervous system.	Beta (0.75, 1.63)	0.17	0.20	0.23
The proportion of individuals who are m-m at codon 129 who are susceptible to clinical infection	Point estimate	1.00	1.00	1.00
The proportion of individuals who are m-v at codon 129 who are susceptible to clinical infection	Uniform (0.40–0.60)	0.42	0.50	0.58
The proportion of individuals who are v-v at codon 129 who are susceptible to clinical infection	Uniform (0.00–0.40)	0.04	0.20	0.36

Table 2 Summary of elicited decontamination values for brain and posterior eye surgical instruments

Parameter	*Distribution*	*10th percentile*	*Median*	*90th percentile*
(1) The log reduction in infectivity associated with current autoclaving procedures alone on the first decontamination cycle	Normal: mean 2.50, variance 0.55	1.55	2.50	3.45
The log reduction associated with subsequent autoclaving cycles. Expressed as a proportion of (1)	Beta (3.55, 18.97). mean 0.16, variance 0.01	0.07	0.15	0.26
(2) Current log reduction in infectivity associated with current detergents alone on the first decontamination cycle	Gamma (1.45, 2.26). mean 0.64, variance 0.29	0.12	0.50	1.35
Subsequent levels of reduction in infectivity due to current detergents. Expressed as a proportion of (2)	Beta (1.37, 1.53). mean 0.47, variance 0.060	0.13	0.50	0.83
The proportion of mass that has already been through one complete decontamination process that is removed in the next washing cycle	Beta (0.65, 70.45). mean 0.0090, variance 0.0001	0.0004	0.0050	0.0200
The proportion of mass existing on instruments following previous decontamination cycles that will be transferred to a patient in an operation	Beta (0.75, 1.63). mean 0.32, variance 0.06	0.03	0.25	0.70

important parameter in the transmission of surgical CJD as it can significantly increase the number of secondary infections. For example, suppose there are 10 ID50s on an instrument set. If all mass collected were transferred to the next patient, there would be only one infection were the set to remain intact. However, were this set to become compromised, and

incorporated into five different sets, with each possessing two ID50s, there would be five infections.

As robust empirical data could not be obtained regarding the level of instrument migration occurring currently, and some implementations of tracking systems had difficulties, our advisors estimated this to be equal to a 50% chance that an instrument, along with any infectious tissue it contained, migrated from a set following every operation. Where migration occurs between simulated sets, between 0 and 20% of the infectious mass on each set would be transferred to the other set, with both proportions independently sampled. Where a supplementary instrument became substituted with that from a set, all of the infectious mass on the initial supplementary instrument would be added to the new set, and between 0 and 10% of the infectious mass of the set would reside on the new supplementary instrument. Based on the available anecdotal data, instruments have an approximate life span of 250 uses, with the probability of disposal sampled after each operation for each instrument (geometric distribution, mean 250 uses). When an instrument was disposed of, between 0 and 12% of any infectious mass of a neurosurgical set would be removed, and between 0 and 25% for a posterior eye set; the difference being due to the different number of instruments per set.

Patient risk factors

The probability that an individual in the population would require surgery depends upon the age of the patient, and the prior history of surgery.

The age distribution was estimated from the HES database which classifies patients into the following age bands: 0–14 years, 15–59 years, 60–74 years and 75 years and over, although only the latter three are relevant to our study. The summary figure of mean patient age is also provided by the HES data. The data were also used to characterize the age-dependent demand of patients for brain and posterior eye surgery. The methodology we used to fit a statistical distribution is subjective. Patient ages were randomly assigned within their respective age-band and a statistical distribution was fitted to these while maintaining the mean age. The age of patients requiring brain surgery was fitted by a Beta distribution (1.306, 1.547) scaled from 0 to 94 years, the age of patients requiring posterior eye surgery was fitted by a Beta distribution (3.230, 1.870) scaled from 0 to 95 years.

A prior history of surgery increases the probability of future surgery in that specialty, which can result in patients who were iatrogenically infected in a previous surgical episode contaminating subsequent sets of instruments. The likelihood of a patient with a history of neurosurgery returning for a future operation compared with patients without a history of neurosurgery was calculated based on data obtained from Hospital Episode Statistics and adjusted for the likely number of deaths following neurosurgery. A patient who had undergone a brain operation was a factor of 43 times more likely to have a subsequent brain operation than an age-matched control during a fixed time interval (Stevenson *et al*, 2006). The corresponding 'Return to Surgery' factor for patients who had posterior eye surgery was 60.

We sampled the demand for operations by constructing a multi-dimensional array that tracked the number of individuals by their age, and prior surgery status and additionally their vCJD infection status (non infected, infected but not infectious, infected and infectious). Patient demand for surgery was sampled at a rate that accounts for age and prior surgery status, and the probability that a patient that was sampled was infectious for vCJD was determined accordingly.

Calculating the risk of infection in an operation

The probability that a patient becomes infected following an operation via contaminated instruments is related to the infectious load transferred, which is defined as the wet mass equivalent (in g) transferred multiplied by the infectious titre. For each operation simulated, the wet mass equivalent of infectious matter transferred from the instrument set to the patient was sampled. The infectious titre of any infectious matter is updated in the model as successive decontamination cycles are undertaken and thus the infectious load transferred to a patient can be estimated. The risk of infection was assumed to be half of the infectious load, with loads of two ID50s or greater resulting in certain infection (consistent with Bennett *et al*, 2005. A sensitivity analysis to this assumption, *versus* an assumption of independently infective ID50s, showed no significant differences). Patients who become clinically infected are assumed to cost the health service £40 000 in medical care and, due to the severity of the disease, are assumed to accrue no further QALYs once clinical symptoms become apparent (Stevenson *et al*, 2006). Patients who become sub-clinically infected are assumed to incur neither costs nor QALY losses, with the elicited distribution of patient susceptibility to clinical infection provided in Table 2.

A patient who becomes infected will contaminate instruments used in subsequent operations, if the infectious period has been reached, regardless of whether they are clinically susceptible. This could cause further infections or even risk a self-sustaining epidemic, if current conditions remain prevalent. Simulated patients that die due to poor prognoses were assumed not to display clinical CJD even if they were infected. These patients were still modelled, as they could remove some of the infectious material on an instrument set.

The time horizon of the model

From commercial-in-confidence data, CJDAS decided that an intervention would be in widespread use that would deactivate or remove all prions from surgical equipment within 5 years. The model was thus run for a 5-year period of statistical output, following a 2-year simulation warm-up period.

Analyses undertaken

For each intervention, 1000 sets of input parameters, denoted θ_i (for $i = 1, 2, \ldots, 1000$), were sampled using Monte Carlo techniques using the distributions in Tables 1 and 2. For each θ_i, 50 simulations were run using different random numbers, resulting in cost and benefits estimates c_{ij} and b_{ij}, for each parameter input and each independent simulation run $j = 1, 2, \ldots, 50$. The output for a given intervention can be summarized by the mean cost per QALY $\sum_{i=1}^{1000}\sum_{j=1}^{50} c_{ij} / \sum_{i=1}^{1000}\sum_{j=1}^{50} b_{ij}$, and by the distribution of the cost per QALY that is due to parameter uncertainty, which is estimated with $CPQ_i = \sum_{j=1}^{50} c_{ij} / \sum_{j=1}^{50} b_{ij}$, $i = 1, 2, \ldots, 1000$. Those values can be used to plot a CEAC to compare interventions. The *post hoc* analysis is described in 'Results of retrospective analysis' section.

Results of initial analysis

Cost per QALY values

Table 3 presents classical incremental cost per QALY ratios, calculated as the sum of the increased costs from each simulation run divided by the sum of the increased QALYs from each simulation run, relative to no single-use instruments, and the mean and median deaths estimated to occur, assuming that instrument migration continues. Table 3 also presents the probability that costs are saved due to a reduced number of vCJD cases, the probability that the incremental cost per QALY is cost-effective at the £30 000/QALY threshold, and the probability that the intervention saves no QALYs at all. Those probabilities reflect both the random outcomes for a given set of parameters, and the parameter uncertainty as described by the expert panel. The 95% probability range for the mean incremental cost per QALY ratio, due primarily to parameter uncertainty, were computed using jackknife techniques in order to reduce statistical bias that comes from classical estimates of a nonlinear function like cost per QALY (Inglehart, 1975; we examined the mean and variance of the 1000 estimators that result from dropping out the 50 replications for each individual θ_i). The jackknife means differ somewhat from the classical means previously reported, but are consistent with the uncorrected estimates, in the sense that they remain on the same side of the £30 000/QALY threshold. Table 4 presents the same information, but assumes that instrument migration can be completely prohibited.

Instrument migration significantly increases the expected number of deaths from an infectious operation and the cost per QALY ratios. If instrument migration can be effectively prohibited, then single-use instrument sets are not cost-effective in either surgery using mean cost per QALY values. If migration cannot be prohibited, then targeted sets for patients in brain and posterior eye surgery are cost-effective policies. The incremental cost per QALY of moving from targeted sets in posterior eye surgery to single-use for all was £16 399 (additional data, not shown in table), thus taking this further step was also estimated to be cost-effective.

Table 3 Cost-effectiveness results and expected deaths for brain and posterior eye operations when instrument migration continues

Surgery specialty	*Single-use instruments for*	*Mean cost per QALY (£) compared with single-use instruments for no patients*	*Mean cost per QALY (£) from jackknife estimator (95% CI)*	*Probability that costs are saved due to reduced number of cases*	*Probability that the cost per QALY ratio is below £30 000*	*Probability that no QALYs are saved*	*Mean number of secondary deaths caused by infection during the 5-year period in England and Wales*	*Median number of secondary deaths caused by infection during the 5-year period in England and Wales*
Brain	No patients	N/A	N/A	N/A	N/A	N/A	485	127
	Targeted patients	18 666	11 493 (4219–18 767)	2%	26%	19%	348	89
	All patients	39 079	38 718 (31 002–46 433)	1%	18%	2%	0	0
Posterior Eye	No patients	N/A	N/A	N/A	N/A	N/A	1224	213
	Targeted patients	3819	882 (Dominating – 4248)	8%	33%	17%	510	157
	All patients	9189	9002 (5879–12 125)	5%	34%	4%	0	0

Dominating means that QALYs are gained and costs are saved.

Table 4 Cost-effectiveness results and expected deaths for brain and posterior eye operations when instrument migration is prohibited

Surgery specialty	*Single-use instruments for*	*Mean cost per QALY (£) compared with single-use instruments for no patients*	*Mean cost per QALY (£) from jackknife estimator (95% CI)*	*Probability that costs are saved due to reduced number of cases*	*Probability that the cost per QALY ratio is below £30 000*	*Probability that no QALYs are saved*	*Mean number of secondary deaths caused by infection during the 5-year period in England and Wales*	*Median number of secondary deaths caused by infection during the 5-year period in England and Wales*
Brain	No patients	N/A	N/A	N/A	N/A	N/A	134	51
	Targeted patients	99 481	98 228 (75 552–120 904)	0%	6%	19%	108	38
	All patients	145 931	145 183 (124 332–166 034)	0%	4%	2%	0	0
Posterior Eye	No patients	N/A	N/A	N/A	N/A	N/A	281	81
	Targeted patients	45 181	43 206 (22 932–63 481)	1%	11%	25%	162	63
	All patients	53 326	52 627 (39 964–65 291)	0%	13%	4%	0	0

These results were subject to large uncertainty. Even in scenarios where the average cost per QALY gain is cost-effective at the £30 000 level, there are many plausible values of the uncertain epidemiological and decontamination parameters for which single-use instruments are not cost-effective. For example, in Table 3 where single-use instruments are used for all patients undergoing posterior eye surgery, the expected cost per QALY is £9189. However, due to the uncertainty about the various epidemiological and decontamination parameters, there is a 66% probability that single-use instruments would not be cost-effective at the £30 000 threshold. There is a 5% probability that the introduction of single-use instruments is associated with net cost savings due to the large number of infections avoided and a 4% probability that this policy will result in no QALY gain.

The effect of uncertainty in the input parameters in relation to cost-effectiveness can be viewed with a CEAC. The CEAC describes the probability that an intervention is cost-effective at specified cost/QALY levels, given the uncertainty in the input parameters, and is estimated by the empirical cumulative distribution function of the 1000 cost/QALY estimates for each input parameter. Figure 2(a) and (b) display CEACs for single-use instruments for all brain surgeries, when instrument migration continues (2a) or is prohibited (2b). CEACs for other scenarios are presented elsewhere (Stevenson *et al*, 2006). The higher curve in Figure 2(a), relative to the curve in Figure 2(b) indicates that single use instruments for all undergoing brain surgery is more likely to be cost-effective when instrument migration continues than when instrument migration is prohibited.

The distributions of simulated deaths from vCJD infection are shown graphically in Figure 3 for both brain and posterior eye surgery. Both indicate that there is a high probability for fewer than 50 deaths, but also indicate a reasonable potential, given the elicited uncertainty of the experts, for up to several thousands of deaths. The high probability of fewer deaths, explains why the CEACs curves in Figure 2 indicate a high probability that instrument replacement policies will not be cost-effective even at the £200K/QALY level, as large costs are incurred with a significant chance that few deaths are averted.

The cost analysis assumed that the prices of single-use sets are the same as their re-usable counterparts. At the time of this work, few single use instruments were available for the operations considered; therefore, using the cost of re-usable sets was thought to be realistic. It is likely that the costs would fall were single-use instruments to become mass-produced which would make their introduction more cost-effective.

The analysis also assumed that all single-use instruments are quality controlled and that appropriate procurement and surveillance protocols are in place to ensure that single-use instruments are of the same quality as re-usable ones. This approach was demonstrated to result in equivalence in performance between single use and re-usable instruments, when implemented in Wales for tonsillectomy

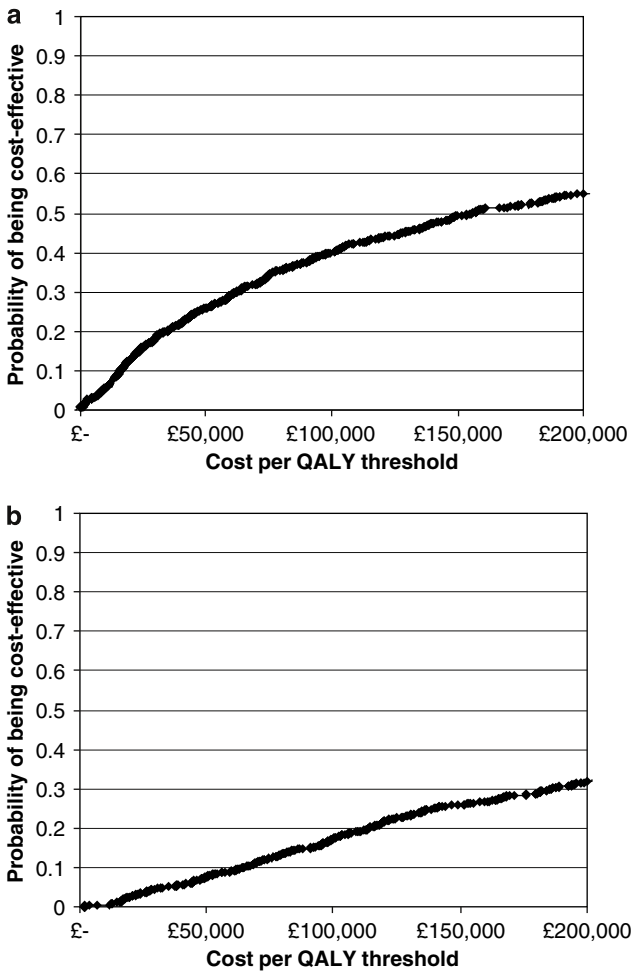

Figure 2 CEACs for employing single-use instruments for all patients undergoing brain surgery, based on the elicited prior distributions for unknown parameters, (a) With instrument migration continuing at the present rate. (b) When instrument migration is prohibited.

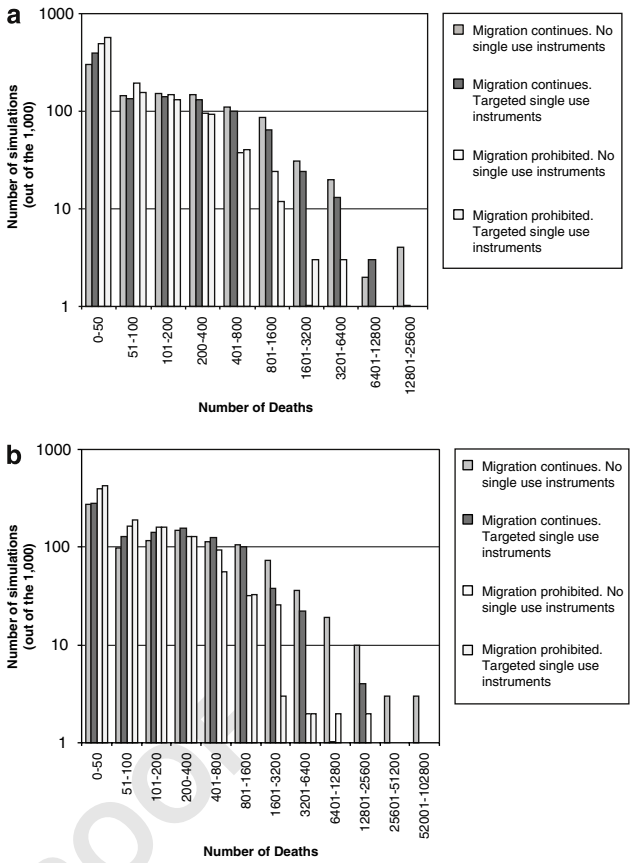

Figure 3 The number of vCJD deaths in England and Wales caused by contaminated instruments over the 5-year period, based on the elicited prior distributions, in (a) brain surgery and (b) posterior eye surgery.

operations (Tomkinson *et al*, 2005). If mass-produced single-use instruments resulted in increased complication rates, as has occurred in England and Wales (Tomkinson *et al*, 2005; Royal College of Surgeons, 2006), their introduction could become markedly less cost-effective and even be dominated, that is cost more and provide fewer QALYs than re-usable sets. The analyses also assumed that single-use instruments could be introduced without disruption to service. If this were to occur, then the cost-effectiveness of this policy would be reduced. The risks of increased complications and logistical problems were borne in mind by CJDAS, alongside the cost-effectiveness data, when arriving at the decision to maintain re-useable instruments.

The cost-effectiveness of preventing instrument migration

A threshold analysis was conducted to determine the maximum expenditures in England and Wales to ensure that instrument migration was prohibited, while remaining under a £30 000 per QALY threshold. These were calculated to be £159 million in brain surgery, and £294 million in posterior eye surgery. A number of methods could be employed for ensuring that instruments do not migrate, which include tracking systems and the purchase of additional instruments to abolish supplementary instruments. Furthermore, maintaining the integrity of the set constitutes good practice across the NHS and was highlighted as such in HSC 2000/032 (Department of Health, 2006b). While the costs needed to prohibit migration could not be reliably estimated, it is unlikely to be greater than the thresholds and thus it would appear that prohibiting migration would be a cost-effective policy.

Results of retrospective analysis

During the year that has elapsed since the report was published, there have been no additional observed cases of iatrogenic surgical transmission of vCJD in the UK. While some iatrogenic cases may be misclassified as detection is only possible via linking cases, which require multiple clinical onset and robust investigation, the numbers of reported vCJD cases in 2007 was low with only one diagnosis of

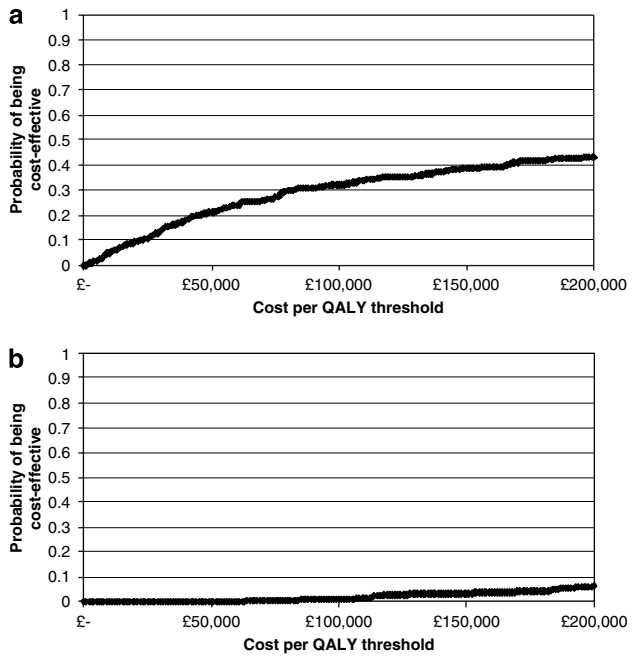

Figure 4 CEACs for employing single-use instruments for all patients undergoing brain surgery, based on the retrospective posterior distributions for unknown parameters, (a) With instrument migration continuing at the present rate. (b) When instrument migration is prohibited.

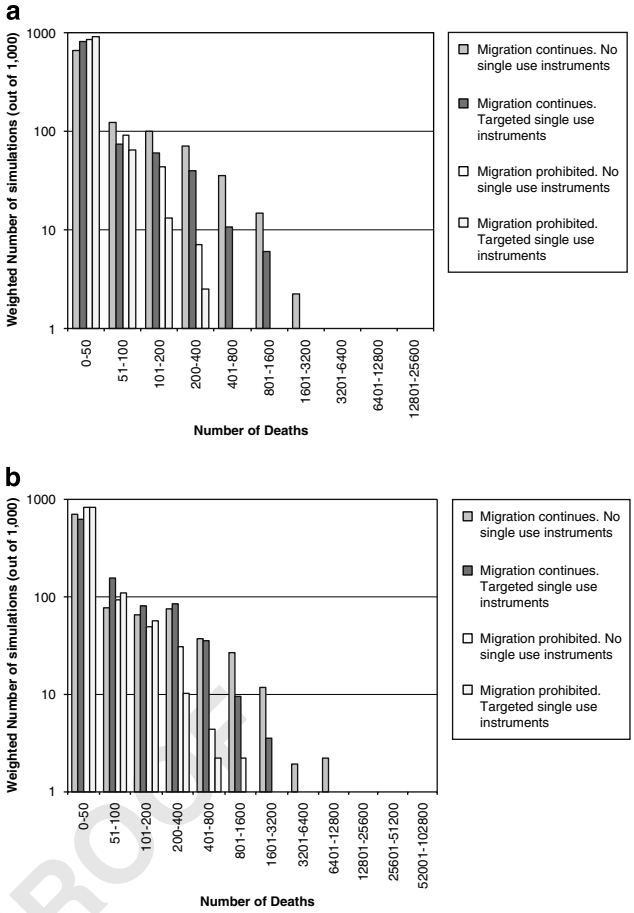

Figure 5 The number of vCJD deaths in England and Wales caused by contaminated instruments over the 5-year period, based on the retrospective posterior distributions, in (a) brain surgery and (b) posterior eye surgery.

vCJD (Andrews, 2007). We have assumed that this was not caused by a surgical procedure. This information can be used to update the probabilistic assessments that were initially reported to allow more weight to be given to a configuration of parameters (eg low prevalence of vCJD and high decontamination efficacy) that rarely produced one or more simulated infections than for a configuration that frequently produced one or more simulated infections (eg with high prevalence of vCJD and poor decontamination). This is similar in spirit to the process where, due to the relatively low numbers of observed clinical cases, the numbers of predicted deaths from vCJD have been downwardly revised (Ghani *et al*, 2003; Clarke and Ghani, 2005).

That analysis is implemented by applying Bayes rule to the prior distributions for the unknown parameters that were elicited from the experts, and the likelihood function for observing no new cases. The likelihood function was estimated by using the simulation output to estimate both the probability of at least one vCJD transmission via brain or posterior eye surgery during the given year, and the distribution of the number of vCJD transmissions via surgical instruments given that instruments were contaminated during a brain surgery or a posterior eye surgery (for a given parameter set θ_i, the likelihood of 0 was estimated with a binomial probability that 27 regions each had no detected transmissions, based on the 50 runs with θ_i as input, and that any transmission could be detected with a given probability: 40% for posterior eye, and 26% for brain. These probabilities were calculated on the assumption that only m-m cases would become clinically apparent within the first year of the simulation, and that for brain operations 1/3 of patients would die before clinical symptoms could become apparent). Standard likelihood ratio and importance sampling ideas (Geweke, 1989) are then used to re-weight the outputs from the initial analysis in order to assess the posterior distribution for the cost/QALY that is induced by the resulting posterior distribution for the unknown input parameters, given that no iatrogenic surgical cases have been detected for one year, which corresponded to the first year of the simulation. In principle, further updating of the prevalence parameter distribution would be possible in the light of the small observed numbers of non-iatrogenic cases. Such an analysis is an area of future work.

The CEACs in Figure 2 based upon the prior distribution for the unknown parameters in Figure 2 are updated to the CEACs in Figure 4. The prior distribution for the number of deaths that is described in Figure 3 is similarly updated to become the posterior distribution for the

Table 5 Cost-effectiveness results and expected deaths for brain and posterior eye operations using the retrospective posterior distribution for unknown parameters

		Instrument migration continues at current level				*Instrument migration prohibited*			
Surgery specialty	*Single-use instruments for*	*Prior mean cost per QALY (£) compared with single-use instruments for no patients*	*Posterior mean cost per QALY (£) compared with single-use instruments for no patients*	*Prior mean number of secondary deaths caused by infection during the 5-year period in England and Wales*	*Posterior mean number of secondary deaths caused by infection during the 5-year period in England and Wales*	*Prior mean cost per QALY (£) compared with single-use instruments for no patients*	*Posterior mean cost per QALY (£) compared with single-use instruments for no patients*	*Prior mean number of secondary deaths caused by infection during the 5-year period in England and Wales*	*Posterior mean number of secondary deaths caused by infection during the 5-year period in England and Wales*
Brian	No patients	N/A	N/A	485	89	N/A	N/A	134	25
	Targeted patients	18 666	60 514	348	44	99 481	231 486	108	14
	All patients	39 079	220 518	0	0	145 931	760 909	0	0
Posterior Eye	No patients	N/A	N/A	1224	152	N/A	N/A	281	34
	Targeted patients	3819	85 278	510	89	45 181	1 432 721	162	29
	All patients	9189	100 869	0	0	53 326	464 668	0	0

number of deaths in Figure 5. Costs per QALYs and the expected number of deaths following the posterior analyses are given in Table 5.

The retrospective analysis indicates that the introduction of single-use instruments are markedly less cost-effective, and that the expected number of deaths prevented has greatly decreased. In each scenario where interventions had an *a priori* mean cost per QALY below the £30 000 cost-effectiveness threshold the posterior mean cost per QALY was raised distinctly above that threshold. The posterior distribution for the number of deaths is also clearly reduced. While there remains a possibility that single-use instruments are cost-effective even after instrument migration is prohibited (Table 4), NICE use the mean cost per QALY to assess cost-effectiveness and these values are greater than £30 000 indicating that the purchasing of single-use instruments would not represent an efficient use of resources.

A sensitivity analysis with respect to the probability of detecting cases of vCJD infection due to surgical instruments showed that the decision to focus on prohibiting instrument migration is relatively robust with respect to uncertainty in that parameter.

Discussion

General

The cost-effectiveness of single-use instruments and the number of expected deaths through secondary infection appear firmly dependent on whether instrument migration can be successfully prohibited. If so, then single-use sets are not a cost-effective option using mean cost per QALY values. However, if instrument migration continues at current rates then single-use instruments may have to be introduced for all posterior eye operations and targeted at those patients who have a repeat brain operation. The lack of observed cases in the year since the analyses may indicate that single-use instruments are not cost-effective even if instrument migration were to continue.

Given the remaining level of uncertainty about unknown parameters and the high likelihood of more effective deactivation methods becoming available in the near future, NICE made minimal changes to surgical instrument policy, with reinforcement for the policy of preventing instrument migration, and recommended urgent further research and evaluation of technologies. More significant policy changes would have resulted in the acquisition of many single-use instruments, at high cost, along with a significant probability of little improvement, or even deterioration, in patient safety.

The guidance provided by CJDAS to the health service was predicated on the belief that instrument migration could be prohibited, and thus that single-use instrument sets for brain and posterior eye surgery should not be recommended (NICE, 2006). It suggested that migration between instrument sets be audited and if it cannot be shown to have been prohibited then

a re-evaluation of the introduction of single-use instrument sets be made.

The retrospective analysis indicates a significantly decreased probability that single-use instruments will be cost-effective at the £30 000 per QALY threshold. The new data therefore supports, in hindsight, the decision to focus on prohibiting instrument migration, rather than implementing single-use instruments on a wide scale.

Limitations

There are a number of simplifying assumptions in all models. This model was developed with input from CJDAS and other experts, along with literature (eg Bennett *et al*, 2004, others listed in Stevenson *et al*, 2006), in order to provide reasonable estimates of costs and benefits without being overly complex. Parameter uncertainty is a limitation for the state of knowledge.

An example of research in progress that could provide valuable information about the epidemiology of the disease is the analysis of 100 000 fresh tonsil samples from routine tonsillectomies (Anonymous, 2004). Such information is urgently needed and would remove the need for some of the elicited distributions that were central to our work and which were subject to a good deal of uncertainty. While these were fed back to experts to ensure that beliefs were captured faithfully, correlation between pairs of elicited distributions was not considered, allowing potential errors to be introduced.

When formulating models it is common practice to validate them against empirical data (Weinstein *et al*, 2003). The lack of an observed iatrogenic case from surgery could be used to try and exclude combinations of values for the uncertain parameters that are likely to have produced a relatively large number of cases, for example where prevalence is high and decontamination efficacy low (Garske *et al*, 2006). Alternatively, this paper used expert opinion to provide prior probability distributions for the unknown parameters and a retrospective analysis with Bayes rule in order to update the distributions for parameter uncertainty. The two approaches, which use different modelling approaches, lead to qualitatively similar predictions for the number of vCJD deaths caused by iatrogenic surgical transmission to occur in the coming years and both highlight the importance of decontamination and instrument re-use. This paper also highlights the importance of instrument migration, and the cost–benefit trade-offs for various instrument replacement policies.

New and more effective decontamination methods are likely to become available for routine use in the NHS within the next 5 years, thus curtailing a self-sustaining epidemic. However, if the 5-year time period were to be extended indefinitely, there is a possibility that significant secondary infections could occur, if deleterious values of the unknown parameters were realized. Introducing single-use sets might still become cost-effective if that technology does not appear in the coming several years.

Techniques such as those by Zouaoui and Wilson (2003) might be used to provide further efficiencies for estimating mean values, as would analytical results for estimating the distribution functions of conditional expectations (of which the CEAC is a special case). Because the conclusions that are suggested by the analysis (regarding instrument migration) are relatively clear, more sophisticated techniques than those applied here were not needed. Research for simulation analysis for efficient estimation of CEAC curves, when both parameter and stochastic uncertainty are to be modelled, is an area of future research.

Conclusion

This work has influenced Government policy on the introduction of single-use instrument. While the mean cost per QALY values indicate that the introduction of single-use instruments are not cost-effective, there is great uncertainty in these results and the modelling and/or policy may need to be revised if pertinent data become available. Even an additional year passing without an observed iatrogenic surgical case does not rule out the possibility of a large number of such cases in the future although further supports the decision that single-use instruments are unlikely to be cost-effective. Better data on decontamination, the prevalence of vCJD and when those infected will reach the infectious period are urgently needed and would improve the accuracy of the results. The level of success of methods introduced to prohibit instrument migration must also be validated to ensure that the conditions on which the results were predicated are achieved.

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