Survival and Re-Operation Rates after Neurosurgical Procedures in Scotland: Implications for Targeted Surveillance of Sub-Clinical Variant Creutzfeldt-Jakob Disease

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Key Words

Neurosurgical procedure • Five-year survivorship • Re-operation rate • Variant Creutzfeldt-Jakob disease • Transmission risk • Autopsy surveillance

Abstract

Background/Aim: To assess the feasibility of post-mortem surveillance for subclinical variant Creutzfeldt-Jakob disease (vCJD) at least 5 years after neurosurgical procedures. **Methods:** Using Scottish record linkage, we estimated 5-year survival and re-operation rates after 4 neurosurgical procedures performed during 1993–2001 and identified as high or medium risk for transmitting vCJD: [B] *drainage of extra- or subdural haematoma*, [E] *primary or revisional decompression operations* and [H] *creation of other ventricular shunts* were classified as high risk; [C] *operations on cerebral aneurysm (clipping)* were classified as medium risk. **Results:** Fatality rate at 1 year depended strongly on procedure, weakly or not at all on sex and era, and increased with age. Procedure rates differed by sex. The rate of subsequent neurosurgical operations was highest for procedure [H] (sole: 21%; multiple: 28%). **Conclusion:** Each year, the UK has a new cohort of some 5,000 5-year survivors after a high- or medium-risk neurosurgical procedure, whose subsequent annual mortality is at least 3%. Even if half the surviving 5-year survivors of

neurosurgery since 1996 gave consent-in-life for vCJD-informative testing at post-mortem, there would be too few relevant post-mortems in 2008–2010 (around 1,600) for 'nil detections' to exclude a 1 in 1,000 subclinical vCJD rate. Autopsy surveillance beyond 2010, or among 5-year survivors of non-neurosurgical at-risk operations, would be needed.

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Introduction

The primary route of vCJD exposure in the UK was bovine to human through dietary consumption of BSE-contaminated meat products in 1980–1995 [1–12]. Secondary transmission between humans has occurred via transfusion of non-leucodepleted blood [13–21]. Blood products, transplantation of organs or tissues, and transmission from mother to baby may also confer risk, despite the absence (to date) of relevant clinical cases and, until 2009 for blood products, of subclinical vCJD. Moreover, because the infectious agent is resistant to normal methods of sterilisation, there is concern that the re-use of surgical instruments in neurosurgical and other high (and medium) risk procedures confers a transmission risk [22]. Individuals infected by the abnormal prion protein (PrP^{Sc}) may be asymptomatic for a period of years

before developing (if at all) clinical symptoms of vCJD [23–28]. Whether or not clinical symptoms develop depends on exposure route, age [7, 8] and genotype [26–28], as well as on the individual's post-exposure expected natural lifetime. All vCJD cases to date have been methionine homozygous at codon 129 of the prion protein, whereas only 40% of the UK population is, and about 70% of the UK's sporadic CJD cases in 1990–2001 were.

Well before the UK's first case of human-to-human vCJD transmission in December 2003 [15], a scientific case for the surveillance of subclinical vCJD at forensic autopsies had been made at the Medical Research Council/Department of Health Steering Group for Studies of Detectable PrP^{Sc}. The Steering Group oversaw both retrospective testing for detectable PrP^{Sc} of appendiceal tissue (mainly) [24] and tonsil tissue [23] from operations in 1995–1999 [25, 28] and the establishment of the UK's tonsil archive. Prior to being disbanded in October 2004, it impressed on the UK's Chief Medical Officer the need for both additional human surveillance in forensic post-mortem tissues and for all recipients of blood from vCJD donors to be autopsied [21, 18–19, 29–30]. The reasons were to estimate the rate of subclinical carriage of vCJD by genotype and birth cohort, and for better understanding of human-to-human transmission of subclinical vCJD (by blood, blood products, tissue or in operating theatres). At the behest of the UK's Spongiform Encephalopathy Advisory Committee (SEAC), work began in autumn 2006 on a surveillance protocol for forensic autopsies [29–30].

In 2007, ethical approval was granted for anonymised testing in the UK – over 3 years and starting in 2008 – of spleen (and, as available, brain) tissue from at least 100,000 adult forensic post-mortems. Surveillance can only proceed by consent from the deceased's next of kin. Testing will be unattributable, unless or until results – including by genotype – add to the scientific arguments for attribution [18]. Currently, UK coroners face a range of political and resource pressures, which threaten further delay [30]. Therefore, other designs for surveillance of subclinical carriage of vCJD need to be re-assessed.

Post-mortems and epidemiological foresight in flagging individuals potentially at risk of vCJD have been crucial to our understanding of secondary transmission of vCJD. The UK's first case of probable blood-borne vCJD transmission [15] was diagnosed only at post-mortem, and because an astute clinician had persuaded the deceased's family to agree to an autopsy. The patient's death had also been flagged by the National CJD Surveillance Unit [14], which then completed the diagnostic cir-

cle. Following this case, recipients of vCJD-contaminated blood were alerted and asked to inform their doctor, dentist and surgeon ahead of any invasive procedures. There were 3 further blood-borne transmissions up to 31 December 2007, 1 of them subclinical [26] in a patient who was heterozygous at codon 129 of the prion protein. This lady, in her eighties, had died from abdominal aortic aneurysm and her subclinical carriage in spleen was detected at medico-legal post-mortem. The youngest was a male recipient in his thirties [20]. In 2009, subclinical carriage was detected at post-mortem in a 70-year-old man with haemophilia who had received vCJD-contaminated blood products more than a decade previously, and whose cause of death was not related to vCJD.

Prior to SEAC's endorsement of the need for additional surveillance of detectable PrP^{Sc} in humans, especially at autopsy, the National Institute for Health and Clinical Excellence (NICE) was asked to produce guidance on cost-effective measures to reduce the risk of vCJD transmission by interventional procedures (www.nice.org.uk/guidance/IPG196). Unsurprisingly, NICE's first recommendation was that research is urgently needed to establish the prevalence of vCJD infectivity in the UK population. Without knowing prevalence, uncertainty about the potential for a self-sustaining secondary epidemic cannot be reduced, nor appropriate counter measures assessed (including single-use or quarantine of surgical instruments).

NICE's guidance made the uncoded presumption that migration of neurosurgical and posterior eye instruments between operation sets was prohibited. NICE asked for this prohibition to be audited because without it iatrogenic vCJD cases could double (25th percentile) or treble (75th percentile), and migration had not been effectively prevented hitherto.

We therefore set out to document the potential for vCJD transmission through contaminated neurosurgical instruments in 1993–2001, and to assess the feasibility of post-mortem surveillance for subclinical vCJD in those who have survived for 5 or more years after selected neurosurgical procedures.

Methods

Data Acquisition

Scotland has excellent records on patients' surgical morbidity and mortality. A data extraction protocol was agreed with the Information Statistics Division (ISD) of National Services Scotland and implemented in 2006. Data extraction was complete up to 31 December 2005. It provided us with multi-way contingency tables

Table 1. Interval death rates, 5-year survival rates and subsequent event rates for 10 invasive neurological procedure groups in Scotland, 1993–2001

Neurological procedure	Totals				Sole subsequent event (crude rate)	More than 1 subsequent event (crude rate)	Proportion of individuals with subsequent events that underwent >1 subsequent event
	1-year hazard	deaths in years 2+3 for 1-year survivors	deaths in years 4+5 for 3-year survivors	5-year survival rate (survivors)			
Primary/revisional excision of lumbar disc [A]	41/5,486 (0.7)	43/5,445 (0.8)	58/5,402 (1.1)	5,344/5,486 (97.4)	712/5,486 (13.1)	177/5,486 (3.2)	177/889 (19.9)
Drainage of extra- and sub-dural haematoma [B]	546/2,654 (20.6)	221/2,108 (10.5)	195/1,887 (10.3)	1,692/2,654 (63.8)	221/2,654 (8.3)	63/2,654 (2.4)	63/284 (22.2)
Operations on cerebral aneurysm (clipping) [C]	122/1,782 (6.8)	58/1,660 (3.5)	43/1,602 (2.7)	1,559/1,782 (87.5)	264/1,782 (14.8)	127/1,782 (7.1)	127/391 (32.5)
Primary/revisional excision of cervical intervertebrae [D]	55/1,424 (3.9)	56/1,369 (4.1)	42/1,313 (3.2)	1,271/1,424 (89.3)	196/1,424 (13.8)	53/1,424 (3.7)	53/249 (21.3)
Primary/revisional decompression operations [E]	43/1,222 (3.5)	56/1,179 (4.7)	39/1,123 (3.5)	1,084/1,222 (88.7)	188/1,222 (15.4)	55/1,222 (4.5)	55/243 (22.6)
Decompression of lumbar spine [F]	29/1,162 (2.5)	47/1,133 (4.1)	50/1,086 (4.6)	1,036/1,162 (89.2)	155/1,162 (13.3)	40/1,162 (3.4)	40/195 (20.5)
Carpal/tarsal tunnel release [G]	3/952 (0.3)	26/949 (2.7)	28/923 (3.0)	895/952 (94.0)	257/952 (27.0)	41/952 (4.3)	41/298 (13.8)
Creation of other ventricular shunts [H]	108/900 (12.0)	47/792 (5.9)	30/745 (4.0)	715/900 (79.4)	191/900 (21.2)	255/900 (28.3)	255/446 (57.2)
Excision of brain – unspecified [I]	376/911 (41.3)	132/535 (24.7)	25/403 (6.2)	378/911 (41.5)	110/911 (12.1)	63/911 (6.9)	63/173 (36.4)
Excision of brain lesion – frontal/etc. [J]	469/1,072 (43.8)	234/603 (38.8)	49/369 (13.3)	320/1,072 (29.9)	139/1,072 (13.0)	60/1,072 (5.6)	60/199 (30.2)
Other, includes non-invasive [K]	2,573/17,789 (14.7)	856/15,216 (5.6)	559/14,360 (3.9)	13,801/17,789 (77.6)	2,515/17,789 (14.1)	1,672/17,789 (9.7)	1,672/4,187 (39.9)

Rates are expressed as percentages in parentheses.

by calendar era (1993–1995, 1996–1998, 1999–2001), sex, birth cohort, index neurosurgical procedure and outcome (at 1, 3 and 5 years after index procedure). The statistical information respected patient confidentiality, but, for Scotland's 10 most frequent neurosurgical operations, was also sufficient to map the 'journey' of patients in terms of subsequent survival and neurosurgical re-operation.

NICE's guidance classified certain neurosurgical operations as potentially high risk for operative transmission of vCJD. Along broadly similar lines, 3 of the ISD's top 10 neurosurgical procedures were identified by H.W. and R.G.W. as conferring a high potential risk for transmission of vCJD and 1 as presenting a medium risk: [B] *drainage of extra- or subdural haematoma*, [E] *primary or revisional decompression operations* and [H] *creation of other ventricular shunts* (high risk); [C] *operations on cerebral aneurysm (clipping)* (medium risk).

We focus on these 4 procedures in terms of the number of operations performed in Scotland, neurosurgical re-operation rates, 5-year survival rates and the hazard rate for operated patients who died within 4–5 years post-operatively.

Statistical Analysis

Recall that linked neurosurgical operations and mortality data for Scotland for the period 1993–2001 were made available summarily as a series of multi-way contingency tables according to a pre-specified protocol. Patients feature once only per index procedure per era, but may undergo more than 1 index procedure within an era, or between eras, and so would then be counted multiply.

Interval death rates in table 1 are for the first post-operative year; for 1-year survivors, in years 2 and 3 after index procedure; and for 3-year survivors, in years 4 and 5 after index procedure. Because the extracted data were complete only to 31 December 2005, surviving patients of a procedure in 2001 contributed less than 5 person-years of follow-up. Taking this into account (by assuming that one third of operations in 1999–2001 occurred in 2001, and so contributed 1.5 person-years of follow-up during years 4 and 5) and halving the person-years contribution for deaths made only small differences (typically under 1%) to the estimated 5-year survival rates, unless death rates were high (Appendix 1).

We briefly analysed operation frequency, post-operative survival and re-operation rates for Scotland's top 10 neurosurgical procedures and for all others combined.

Next, for the 4 procedures of key interest, we used Poisson regression to quantify demographic influences on 1-year fatality rate (and 5-year fatality rate: available from authors) for patients who underwent a single procedure in any calendar era. Our selection accounts for about 79% of the key procedures: it was chosen to avoid double-counting within era, but involves some loss of generality as different neurosurgical re-operation rates apply per procedure.

Mid-year population estimates from the General Register Office for Scotland (Appendix 2) were used in the evaluation of the operation rates per 100,000 of population per annum. For each birth cohort and sex combination, mid-year population estimates corresponded to years 1994, 1997 and 2000 and, hence, were multiplied by 3 to give era-specific approximations of operation rates per 100,000 of population per annum.

χ^2 Tests were used to test for homogeneity. If a key comparison, such as by sex, could potentially be confounded by changes that had occurred, say across eras, confounding was controlled for in the reported χ^2 tests by computing expected values per sex within era (or other relevant stratum), and then summing expectations across eras.

Minimum Neurosurgical Re-Operation Rates

Because individuals were classified as undergoing a single 'index event', 'sole subsequent event' or 'more than 1 subsequent event', the true rate of neurosurgical re-operations could not be evaluated. However, a minimum value could be calculated by considering that each individual with 'more than 1 subsequent event' had at least 2 neurosurgical re-operations. This rate was evaluated over the number of operable years to account for the impact of age-related mortality across different cohorts. Re-operation rates are also minimal because patients operated on in 2001 lacked a full 5 years' follow-up, and further re-operations may have occurred. χ^2 Tests were used to compare re-operation risks and rates between procedures, cohorts, sexes and eras.

Results

Initial Exploration of Survival and Re-Operation Rates

In order of 5-year survivors, table 1 summarises the interval death rates, approximate 5-year survivorship, and subsequent neurosurgical procedure rates for each of the top 10 neurosurgical procedure groups. Properly adjusted 5-year survivorships and hazard rates are shown in Appendix 1.

Survivorship varied considerably across procedures with [A] *primary/revisional excision of lumbar disc* exhibiting the highest overall 5-year survival rate of 97% (5,344 survivors to the end of data extraction) and [J] *excision of brain lesion – frontal/etc.* the lowest at around 30% (320 survivors to the end of data extraction).

The high- and medium-risk procedures had overall 5-year survival rates (survivors) as follows: high risk: [B] *drainage of extradural and subdural haematoma* – 64%

(1,692 survivors); [E] *primary/revisional decompression operations* – 89% (1,084 survivors); [H] *creation of other ventricular shunts* – 79% (715 survivors); medium risk: [C] *operations on cerebral aneurysm (clipping)* – 88% (1,559 survivors).

Scotland's 5-year survivors from high-risk neurosurgical procedures in 1993–2001 are a rough guide to the number of 5-year survivors from a single year of operations in the UK, approximately 3,500 (approx. 1,692 + 1,084 + 715).

For specific procedures, including those of high [B] and medium risk [C], the 1-year death rate was substantially greater than death rates over the 2 subsequent 2-year intervals (for properly adjusted 1-year hazard rates, see Appendix 1):

[B] *drainage of extradural and subdural haematoma* (21 vs. 11 and 10%; adjusted 1-year hazard rates of 23 vs. 6 vs. 6%);

[C] *operations on cerebral aneurysm (clipping)* (7 vs. 4 and 3%; adjusted 1-year hazard rates of 7 vs. 2 vs. 2%);

[D] *creation of other ventricular shunts* (12 vs. 6 and 4%; adjusted 1-year hazard rates of 13 vs. 3 vs. 2%);

[I] *excision of brain – unspecified* (41 vs. 25 and 6%; adjusted 1-year hazard rates of 52 vs. 14 vs. 4%);

[J] *excision of brain lesion – frontal/etc.* (44 vs. 39 and 13%; adjusted 1-year hazard rates of 56 vs. 24 vs. 8%).

The rate of subsequent neurosurgical operation (sole or multiple) was highest for high-risk procedure [H] *creation of other ventricular shunts*, at 21% sole and 28% multiple. Moreover, of all procedures, procedure [H] had the highest proportion at 57% (255/446) of patients undergoing subsequent neurosurgery who underwent 2 or more procedures.

Low-risk operation [G] *carpal/tarsal tunnel release* had the highest sole subsequent procedure rate within 5 years at 27% (95% CI: 24–30%).

For patients whose index procedure was their single neurosurgical operation within a 5-year horizon, table 2 compares the index procedural incidence (and 1-year death rate) by sex and era. Per procedure, 1-year fatality rates were broadly comparable by sex and era.

However, neurosurgical procedures were strikingly more frequent in males, except for high-risk procedure [C] *operations on cerebral aneurysm (clipping)* and low-risk procedure [G] *carpal/tarsal tunnel release*, both predominant for females, and high-risk [H] *creation of other*

Table 2. For single procedures: operation frequency (see denominators) and 1-year death rates in Scotland's neurosurgical procedure groups for males versus females and for 1993–1995 versus 1999–2001

Sex or era	Males	Females	1993–1995	1999–2001
Primary/revisional excision of lumbar disc [A]	21/2,600 (0.8)	17/1,988 (0.9)	16/1,514 (1.1)	10/1,527 (0.7)
Drainage of extradural and subdural haematoma [B]	369/1,739 (21.2)	147/631 (23.3)	157/701 (22.4)	169/874 (19.3)
Operations on cerebral aneurysm (clipping) [C]	35/461 (7.6)	81/930 (8.7)	53/566 (9.4)	29/324 (9.0)
Primary/revisional excision of cervical intervertebrae [D]	33/695 (4.7)	16/480 (3.3)	13/379 (3.4)	21/442 (4.8)
Primary/revisional decompression operations [E]	20/607 (3.3)	14/372 (3.8)	11/237 (4.6)	5/358 (1.4)
Decompression of lumbar spine [F]	22/528 (4.2)	5/439 (1.1)	4/279 (1.4)	8/321 (2.5)
Carpal/tarsal tunnel release [G]	1/234 (0.4)	2/420 (0.5)	1/164 (0.6)	1/258 (0.4)
Creation of other ventricular shunts [H]	48/229 (21.0)	39/225 (17.3)	39/156 (25.0)	21/145 (14.5)
Excision of brain – unspecified [I]	181/370 (48.9)	165/360 (45.8)	92/218 (42.2)	122/242 (50.4)
Excision of brain lesion – frontal/etc. [J]	245/468 (52.4)	180/405 (44.4)	122/266 (45.9)	180/348 (51.7)
Other, includes non-invasive [K]	1,299/7,229 (18.0)	1092/6,464 (16.9)	825/4,457 (18.5)	803/4,435 (18.1)
One-year death rates given as percentage values in parentheses.				

ventricular shunt and [I] *excision of brain – unspecified*, both equally common in males and females.

There was a marked increase between eras in operations for high-risk [B] *drainage of extradural and subdural haematoma*, [F] *primary/revisional decompression operations*, [J] *excision of brain lesion – frontal/etc.* and [G] *carpal/tarsal tunnel release*, but a sharp decrease in high-risk procedure [C] *operations on cerebral aneurysm (clipping)*.

High- and Medium-Risk Single Neurosurgical Procedures: Covariate Influences

On 1-Year Fatality Rate. Table 3 presents a Poisson regression analysis of 1-year death rates for the 5,194 patients (3,036 male and 2,158 female) who underwent, as their sole procedure in 1993–2001, 1 of the 4 neurosurgical operations of key interest. Their modal birth cohort was 1940–1959 [1,837 patients: 1,036 (56%) male and 801 female] followed by pre-1930 [1,266 patients: 725 (57%) male and 541 female] with only 634 patients born in 1970

or later [423 (67%) male and 211 female]. Fatality rate at 1 year depended strongly on procedure, weakly or not at all on sex and era, and increased with age.

On Operation Rates. Table 4 shows how the annual operation rate varied by sex within each birth cohort. The youngest birth cohort was too sparse for analysis. With that caveat, table 4 confirms that the sex which dominated a high- or medium-risk procedure did so in almost every birth cohort.

Table 4 also shows how procedure rates varied per 100,000 of population by birth cohort. For high-risk procedure [B] *drainage of extradural and subdural haematoma*, the operation rate in males decreased sharply from 25, 13 and 7 per 100,000 per annum for those born before 1930, in 1930–1939 and in 1940–1959 to 5 per 100,000 for the 1960–1969 birth cohort. The female operation rate was about one third of the male rate for those born before 1960, but even lower at younger ages.

For high-risk procedure [E] *primary/revisional decompression operations*, the single operation rate in males was

Table 3. Poisson regressions for 1-year fatality rate for individuals who underwent a single high- or medium-risk neurosurgical procedure in 1993–2001, Scotland

	Parameter estimate	Standard error	z-score n.a.
Constant	–1.71	0.10	
<i>Neurological procedure</i>			
[B] (M: 1,739, F: 631)	–	–	–
[C] (M: 461, F: 930)	–0.87	0.11	–7.69
[H] (M: 229, F: 225)	0.26	0.12	2.17
[E] (M: 607, F: 372)	–1.81	0.18	–10.09
<i>Era</i>			
1993–1995 (M: 952, F: 708)	0.18	0.09	1.94
1996–1998 (M: 1,044, F: 789)	0.16	0.09	1.79
1999–2001 (M: 1,040, F: 661)	–	–	–
<i>Birth cohort</i>			
Pre-1930 (M: 725, F: 541)	0.45	0.09	4.85
1930–1939 (M: 503, F: 405)	0.12	0.11	1.03
1940–1959 (M: 1,036, F: 801)	–	–	–
1960–1969 (M: 349, F: 200)	–0.58	0.17	–3.43
1970–1990+ (M: 423, F: 211)	–1.10	0.17	–6.29
<i>Sex</i> (M: 3,036, F: 2,158)	–0.05	0.08	–0.58
Deviance = 115.4 on 109 degrees of freedom.			

around 5 per 100,000 per annum for those born before 1960, but considerably lower for the younger birth cohorts. The female rate was about half the male rate per birth cohort.

For high-risk procedure [H] *creation of other ventricular shunts*, the annual rate was independent of sex and birth cohort, and in the order of 1 per 100,000 of population.

Finally, for medium-risk procedure [C] *operation on cerebral aneurysm (clipping)*, the annual rate in females was highest, at around 8 per 100,000, in the 1930–1939 and 1940–1959 birth cohorts, and decreased sharply to around 3 per 100,000 for those born before 1930 or in 1960–69, and lower still at younger ages. Other than at young ages, the male rate was typically about half the female rate by birth cohort.

On Minimum Neurosurgical Re-Operation Rates within 5 Years. By birth cohort and sex, table 5 reports the minimum neurosurgical re-operation rate within 5 years (or to end of data extraction) per 100 person-years. Re-operation rates were procedure-specific. In general, they showed little variation by sex or birth cohort.

Re-operation rates were similar at 3.5, 5 and 3.5 per 100 person-years for high-risk [B] *drainage of extradural and subdural haematoma*, medium-risk [C] *operation on cerebral aneurysm (clipping)* and high-risk [E] *primary/revisional decompression operations*, but considerably higher at around 20 per 100 person-years for [H] *creation of other ventricular shunts*, albeit somewhat lower in the oldest birth cohort.

Summary

Our record linkage findings for high- or medium-risk neurosurgical procedures were:

- Significant variation in 1-year fatality rate by procedure and birth cohort, with increasing fatality rates in older age.
- Significant variation in procedure rate by birth cohort and sex.
- Re-operation rate dependent upon the procedure undergone, rather than on birth cohort, sex or era.
- Some differences in operation rates and 1-year fatality rates by era.
- Over 6,500 high- or medium-risk index procedures in 1993–2001 in Scotland, over 5,000 of them without neurosurgical re-operation within 5 years.

Discussion

UK recipients of blood or blood products from donors who subsequently developed vCJD were initially flagged for mortality, but not informed about their vCJD risk until the first probable case of blood-borne vCJD transmission was confirmed in December 2003. Surviving recipients from all donors who had subsequently developed vCJD were then informed through their family practitioners.

Other ‘at-vCJD-risk’ networks include: (1) blood donors to a patient who subsequently developed vCJD, (2) other recipients of blood donors to a patient who subsequently developed vCJD, (3) surgical ‘contacts’, through instruments used in invasive procedures, of ultimately diagnosed vCJD cases, and (4) recipients of multiple blood transfusions. Persons in ‘at-vCJD-risk’ networks have to take precautions against surgical transmission, but there is uncertainty about how elevated their own vCJD risk is.

For example, about 1% of transfusion recipients have more than 80 donor exposures in a single year. Given an estimated 1 in 4,000 subclinical prevalence of vCJD in UK blood donors and presumed 50% blood-borne risk of vCJD

Table 4. Sex- and cohort-specific operation rates per 100,000 of population for individuals who had a single neurosurgical procedure of high or medium potential risk for vCJD transmission

Birth cohort	Pre-1930	1930–1939	1940–1959	1960–1969	1970–1989	1990+
Drainage of extra-dural and subdural haematoma [B]	248.6 (0.00) [M: 25.0, F: 8.7] {M: 557, F: 310}	112.7 (0.00) [M: 13.5, F: 4.4] {M: 295, F: 107}	177.6 (0.00) [M: 7.2, F: 2.0] {M: 424, F: 121}	104.6 (0.00) [M: 5.0, F: 0.9] {M: 178, F: 34}	131.7 (0.00) [M: 3.9, F: 0.7] {M: 232, F: 41}	15.7 (0.00) [M: 2.3, F: 0.8] {M: 53, F: 18}
Operations on cerebral aneurysm (clipping) [C]	13.4 (0.00) [M: 1.6, F: 3.1] {M: 35, F: 111}	54.7 (0.00) [M: 3.3, F: 8.6] {M: 71, F: 211}	54.1 (0.00) [M: 4.4, F: 7.7] {M: 257, F: 465}	4.98 (0.03) [M: 2.0, F: 2.8] {M: 70, F: 103}	2.65 (0.10) [M: 0.5, F: 0.7] {M: 27, F: 40}	sparse
Primary/revisional decompression operations [E]	22.4 (0.00) [M: 4.6, F: 2.3] {M: 102, F: 83}	28.5 (0.00) [M: 5.6, F: 2.5] {M: 122, F: 61}	37.9 (0.00) [M: 5.2, F: 2.9] {M: 305, F: 177}	10.04 (0.00) [M: 1.9, F: 1.0] {M: 68, F: 38}	0.78 (0.38) [M: 0.2, F: 0.2] {M: 9, F: 13}	sparse
Creation of other ventricular shunts [H]	1.47 (0.23) [M: 1.4, F: 1.0] {M: 31, F: 37}	1.77 (0.18) [M: 0.7, F: 1.1] {M: 15, F: 26}	2.00 (0.16) [M: 0.9, F: 0.6] {M: 50, F: 38}	1.48 (0.22) [M: 0.9, F: 0.7] {M: 33, F: 25}	0.10 (0.75) [M: 1.2, F: 1.3] {M: 73, F: 76}	0.16 (0.69) [M: 1.2, F: 1.1] {M: 27, F: 23}

Values show results of χ^2 analysis on 1 degree of freedom for male versus female difference in operation rates, with p values given in parentheses. Square brackets contain the annual sole operation rates per 100,000 of population. Curley brackets contain numbers of sole operations in 1993–2001 by sex per birth cohort.

Table 5. Sex and cohort-specific minimum re-operation rates (within 5 years) per 100 person-years for individuals who had a single neurological procedure of high or medium potential risk for vCJD transmission

Birth-cohort		Pre-1930	1930–1939	1940–1959	1960–1969	1970–1989	1990+
Drainage of extradural and subdural haematoma [B]	χ^2	7.96 (0.01)	0.27 (0.61)	3.86 (0.05)	1.88 (0.17)	1.58 (0.21)	10.15 (0.00)
	RR	3.5	3.5	3.9	3.5	2.7	3.5
	M	82/1,960	42/1,256	64/1,832	28/874	30/1,192	5/281
	F	23/1,058	18/474	30/556	9/179	8/209	8/88
Operations on cerebral aneurysm (clipping) [C]	χ^2	0.02 (0.89)	0.12 (0.73)	7.79 (0.01)	0.70 (0.40)	0.01 (0.94)	sparse
	RR	5.1	5.2	7.2	6.3	4.4	
	M	8/163	18/380	84/1,487	30/435	7/165	
	F	29/557	58/1,117	236/2,967	38/646	10/224	
Primary/revisional decompression operations [E]	χ^2	1.53 (0.22)	0.53 (0.47)	0.01 (0.94)	3.31 (0.07)	0.00 (0.96)	sparse
	RR	4.1	5.8	5.4	3.7	9.0	
	M	23/454	40/726	104/1,934	10/378	5/62	
	F	12/391	23/354	60/1,085	13/240	8/82	
Creation of other ventricular shunts [H]	χ^2	0.50 (0.48)	1.37 (0.24)	0.17 (0.68)	3.25 (0.07)	0.86 (0.35)	2.50 (0.11)
	RR	7.8	15.2	16.0	19.4	18.5	22.3
	M	4/69	15/78	49/318	39/251	154/785	99/402
	F	11/123	15/119	43/257	80/361	147/838	45/245

χ^2 Values refer to male vs. female differences in minimum re-operation rate by birth cohort, with p values in parentheses. RR = minimum re-operation rate within 5 years per 100 person-years for both sexes combined. Minimum re-operations/approximate person-years within 5 years of index operation in 1993–2001 are broken down into males (M) and females (F).

Table 6. Conservatively estimated expected autopsies in 2008–2010 if 20–50% of UK patients who survived at least 5 years after a high- or medium-risk neurosurgical procedure gave consent-in-life for vCJD-informative testing in the event of their death.

Year of neurosurgical procedure with high or medium potential risk for vCJD transmission	2008		2009		2010	
	surviving 5-year survivors	expected deaths	surviving 5-year survivors	expected deaths	surviving 5-year survivors	expected deaths
1996	4,164	125 (62; 25)	4,039	121 (60; 24)	3,918	118 (59; 24)
1997	4,293	129 (64; 26)	4,164	125 (62; 25)	4,039	121 (60; 24)
1998	4,426	133 (66; 27)	4,293	129 (64; 26)	4,164	125 (62; 25)
1999	4,563	137 (68; 27)	4,426	133 (66; 27)	4,293	129 (64; 26)
2000	4,704	141 (71; 28)	4,563	137 (68; 27)	4,426	133 (66; 27)
2001	4,850	146 (73; 29)	4,704	141 (71; 28)	4,563	137 (68; 27)
2002	5,000	150 (75; 30)	4,850	146 (73; 29)	4,704	141 (71; 28)
2003			5,000	150 (75; 30)	4,850	146 (73; 29)
2004					5,000	150 (75; 30)
2005						
Post-mortem totals		(479; 192)		(539; 216)		(598; 240)
Survivors of 1996–2000 operations	22,150		21,485		20,840	
(and born in 1960–1989: at least 20% of total)	4,430		4,297		4,168	

Figures in parentheses show post-mortem rates if 50% and 20% of people consented, respectively. The 3% annual death rate has not been actuarially enhanced for 10-year vs. 5-year survivors.

from such donors, there is an estimated 1% vCJD risk for recipients with more than 80 donor exposures. Multiply transfused recipients' 5-year survivorship may be as low as 25%, but the UK has in excess of 32,000 such survivors. Even if their annual death rate were as low as 5 per 1,000, there could be 160 deaths per annum which, if subject to autopsy, would be informative about whether those who survived 5 years or more after being multiply transfused have at least a 1% risk of subclinical carriage of vCJD. Specifically, vCJD testing at autopsy of 500 5-year survivors of multiple (80+) transfusions could challenge the assumption of 1% blood-borne vCJD transmission risk.

We now consider whether autopsy surveillance should target those who, 5 years or more prior to death, underwent a neurosurgical (or other) operation with a high or medium potential risk for vCJD transmission, in whom we may wish to exclude a modestly elevated risk of subclinical vCJD, such as from 1/4,000 to 1/1,000. Specifically, the objective of autopsy surveillance after selected neurosurgery would be to exclude an elevated vCJD carriage risk of 1/1,000 among those who underwent high- or medium-risk neurosurgical procedures 5 or more years previously.

Scotland has a population of around 5 million, about one tenth that of England and Wales, and so – making allowance for some over-counting – it is reasonable to read our 9-year neurosurgical data for Scotland as the plausible outturn for England and Wales in a single year. Each year, therefore, the UK has a new cohort of some 5,000 5-year survivors after a high- or medium-risk neurosurgical procedure, at least 20% of them born in 1960–89 (table 4; 1,060/5,194 were born in 1960–1989). Their subsequent annual mortality is at least 3% per annum (see deaths of 3-year survivors in table 1 and Appendix 1).

In table 6, we set out what might be achievable from targeted autopsy surveillance if, from 2008, 20–50% of eligible surviving 5-year survivors after selected neurosurgery were consented-in-life for vCJD-informative tests to be done at post-mortem. Death rates have been conservatively estimated at 3% per annum.

Table 6 shows that even if half the surviving 5-years survivors of high- or medium-risk neurosurgical procedures gave consent-in-life vCJD informative tests at autopsy, there would be too few relevant post-mortems in 2008–2010 for 'nil detections' to confidently exclude a 1 in 1,000 subclinical vCJD carriage rate [31].

Moreover, the last row of table 6 suggests that, in any year of 2008–2010, the UK may have some 4,000 individuals, born in 1960–1989, who have survived for 10 years after a high- or medium-risk neurosurgical procedure performed in 1996–2000. At operation, their rate of primary vCJD carriage rate (if between 1 in 3,000 and 1 in 4,000 [25, 28]) could find later clinical expression as vCJD – at least in the 40% who are methionine homozygotes at codon 129 of the prion protein. One or two such clinical cases during 2008–2010 would be roughly consistent with such an expectation, and should not trigger any undue alert.

Equally, if any neurosurgical transmission risk applied essentially to the next 2 patients on whom contaminated instruments were used and was maximally 1 in 4,000 from the fifth of operated subjects in 1996–2000 who were born in 1960–1989, then that ‘neurosurgical operation risk’ would only be of the order of 1 in 10,000.

It could, in any year, find clinical expression via some 17,000 surgical cases in 1996–2000 who survived at least 5 years after a high- or medium-risk neurological operation and were, mainly, born before 1960. Continued absence of clinical vCJD cases in 2008–2010 with this surgical history [32] should be relatively reassuring to neurosurgeons.

In conclusion, record linkage can help to determine the feasibility of targeting autopsy surveillance for sub-clinical vCJD on 5-year survivors of surgical procedures, be they neurosurgical, as here, or gastrointestinal.

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Appendix 1

Summary of overall hazards, survival rates and subsequent event rates for the top 10 invasive (and other) neurological procedure-groups in order of 5-year survivors, 1993–2001 in Scotland

Neurological procedure	Totals				Sole subsequent event (crude rate)	More than 1 subsequent event (crude rate)	Proportion of individuals with subsequent events that underwent >1 subsequent event
	deaths in year 1/ person-years at risk (hazard rate)	deaths in years 2+3/person- years at risk (hazard rate)	deaths in years 4+5/person- years at risk (hazard rate)	5-year survival rate [survivors] (excludes individuals from triad 1999–2001)			
Primary/revisional excision of lumbar disc [A]	41/5,466 (0.8)	43/10,847 (0.4)	58/9,036 (0.6)	3,588/3,695 (97.1)	712/5,486 (13.1)	177/5,477 (3.2)	177/889 (19.9)
Drainage of extra- and sub-dural haematoma [B]	546/2,381 (22.9)	221/3,995 (5.5)	195/3,082 (6.3)	1,065/1,686 (63.2)	221/2,654 (8.3)	63/2,654 (2.4)	63/284 (22.2)
Operations on cerebral aneurysm clipping [C]	122/1,721 (7.1)	58/3,262 (1.8)	43/2,832 (1.5)	1,194/1,363 (87.6)	264/1,782 (14.8)	127/1,782 (7.1)	127/391 (32.5)
Primary/revisional excision of cervical intervertebrae [D]	55/1,397 (3.9)	56/2,682 (4.1)	42/2,148 (2.0)	806/908 (88.8)	196/1,424 (13.8)	53/1,424 (3.7)	53/249 (21.3)
Primary/revisional decompression operations [E]	43/1,201 (3.6)	56/2,302 (2.4)	39/1,843 (2.1)	691/790 (87.5)	188/1,222 (15.4)	55/1,222 (4.5)	55/243 (22.6)
Decompression of lumbar spine [F]	29/1,148 (2.5)	47/2,219 (2.1)	50/1,822 (2.7)	699/782 (89.4)	155/1,162 (13.3)	40/1,162 (3.4)	40/195 (20.5)
Carpal/tarsal tunnel release [G]	3/951 (0.3)	26/1,872 (1.4)	28/1,480 (1.9)	535/577 (92.7)	257/952 (27.0)	41/952 (4.3)	41/298 (13.8)
Creation of other ventricular shunts [H]	108/846 (12.8)	47/1,537 (3.1)	30/1,263 (2.4)	496/626 (79.2)	191/900 (21.2)	255/900 (28.3)	255/446 (57.2)
Excision of brain lesion – frontal/etc. [I]	469/838 (56.0)	234/972 (24.1)	49/619 (7.9)	219/646 (33.9)	139/1,072 (13.0)	60/1,072 (5.6)	60/199 (30.2)
Excision of brain – unspecified [J]	376/723 (52.0)	132/938 (14.1)	25/678 (3.7)	259/615 (42.1)	110/911 (12.1)	63/911 (6.9)	63/173 (36.4)
Other, includes non-invasive [K]	2,573/16,503 (15.6)	856/29,576 (2.9)	559/23,932 (2.3)	9,183/11,835 (77.6)	2,515/17,789 (14.1)	1,672/17,789 (9.7)	1,672/4,187 (39.9)

Appendix 2

Mid-year population estimates for Scotland by sex and birth cohort (years 1994, 1997, 2000) from the General Register Office, Scotland

Birth cohort	Sex	1994	1997	2000
Pre-1930	M	304,776	245,141	192,634
	F	472,516	395,590	323,354
1930–1939	M	254,821	242,594	228,713
	F	280,971	273,267	264,135
1940–1959	M	656,979	650,705	644,089
	F	673,504	669,948	666,364
1960–1969	M	400,200	391,029	384,626
	F	410,741	409,083	408,751
1970–1989	M	672,140	658,523	643,649
	F	653,345	650,315	646,538
1990+	M	164,426	254,330	338,215
	F	157,791	242,815	321,872
Total		5,102,210	5,083,340	5,062,940

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