Expert judgement and re-elicitation for prion disease risk uncertainties

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Abstract: Much uncertainty surrounds transmission of transmissible spongiform encephalopathies (TSEs) through blood and blood derived products. A first expert elicitation with 14 experts was conducted in March 2008, and a second re-elicitation involving 11 experts was held a year later in March 2009. Both expert groups were calibrated using a series of seed questions for which values are known, and then were asked to provide their individual judgements on a set of seven target questions for which values are not known or have not been determined through conventional research. Questions dealing with uncertainty of TSE prevalence, genotype effects, susceptibility, and infectivity were answered by the experts. Elicitation can be used to obtain quantitative values for parameters affecting prion uncertainty gaps. We show that the method is amenable to re-elicitation over time allowing refinement of expert opinion as new knowledge becomes available for improved risk assessments where data gaps continue to exist.

Keywords: expert elicitation; bovine spongiform encephalopathy; variant Creutzfeldt-Jakob disease; blood safety; risk assessment; iatrogenic transmission.

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1 Introduction

Expert opinion to inform decision making is used extensively in several areas including economics, finance, insurance, medicine, law and public policy. Very little information exists in the current literature detailing a formalised approach that uses quantitative expert opinion for its application in decision making. In addition, a dearth of information is available on evaluating expert opinion for its precision and validity. Currently, expert panels such as the Royal Society and the Council of Canadian Academies are routinely used as a way to provide expert recommendations on various public health risk issues. Formal expert panels can take extensive amounts of time to convene meetings, review data, verify risk models, complete risk assessments and reach consensus answers. For example, the first expert panel convened at the beginning of the UK's bovine spongiform encephalopathy (BSE) outbreak, the Southwood Working Party, required nearly one year to reach consensus conclusions regarding the safety of milk, meat, and animal health (BSE Inquiry, 2000a). Solicited expert opinions and expert panel recommendations can greatly influence policy decisions and are almost invariably sought when technical uncertainty impacts on an important decision process. Because uncertainty in scientific knowledge is ubiquitous and occurs frequently in research there are often gaps in expert knowledge. As a result, without an established evidence base, experts cannot be absolutely certain about the answer. It is extremely unlikely that experts will ever be in total agreement with one another when answering questions where such uncertainty is substantial, or where the consequences of the decision are particularly catastrophic or onerous.

In circumstances where scientific uncertainty impinges on the determination of an issue, soliciting expert advice is not new. Under such conditions an expert group is usually asked to reach a consensus opinion. Generally, this has been pursued on an informal basis, and such an unstructured approach is rarely, if ever, found entirely satisfying to all parties obliged to reach a collective compromise. Deliberations over answers may be influenced or dominated by experts who are seemingly more forceful, entrenched or appear more certain in their answers. The approach can result in bias and the loss of other opinions that may possess greater value for reliable decision support. To offset these shortcomings a structured expert judgement elicitation can be used. This subjects the entire procedure to transparent methodological rules with the goal of treating expert judgements as scientific data in a formal decision process which then can be statistically quantified.

Various methods for assessing and combining expert uncertainty for research are documented in the literature including simple averaging, committee consensus, the Delphi method, decision conferencing and expert self-weighting. While many of these approaches work for eliciting consensus opinions they are susceptible to bias or may not weight experts appropriately. Part of the motivation for the present study was to use the EXCALIBUR structured expert judgement procedure, formulated by Cooke (1991) or the 'Classical Model', to avoid the weaknesses inherent in other approaches.

The classical model has been used previously in a number of scientific and industrial domains to quantify levels of uncertainty. The method has been used in: space engineering (propulsion system reliability, strength of composites); aeronautics risk management (space debris impact); industrial uses (flange connection failures, fuelling crane failure); hydrology (predicting groundwater contamination; reservoir erosion modelling); meteorology (flood forecasting); seismology (earthquake hazards);

volcanology (volcano hazards); and most recently in health and medicine (personal protective equipment failure). Cooke and Goossens (2008) reported that the method has been used in more than 45 studies, in many different scientific disciplines, and that it is found to produce good results for problems where expert opinion is the most comprehensive, and sometimes only, source of information.

Several areas of prion disease that are relevant to secondary variant Creutzfeldt-Jakob disease (vCJD) transmission risks require expert evaluation. For example, the accuracy of estimates of transmissible spongiform encephalopathy (TSE) incidence/prevalence as well as the effects of prion gene codon 129 amino acid genotype on human TSE susceptibility remains highly uncertain (Cancellotti et al., 2007). Secondly, prion strains can exhibit very different biochemical and biological properties in the same host species (Legname et al., 2005) and when interspecies transmission of prions occurs it frequently gives rise to new strains that can adapt and become more virulent in the new host over time (Bartz et al., 1998, 2000). Third, both atypical BSE (Yamakawa et al., 2003; Casalone et al., 2004) and atypical scrapie forms (Benestad et al., 2003; Buschmann et al., 2004) may have augmented tropism for humans (Kong et al., 2005). Fourth, chronic wasting disease (CWD) transmission to humans from exposure to infected wild game remains another poorly quantified threat (Kong et al., 2008). Fifth, products previously considered safe such as milk (Ligios et al., 2005) and muscle (Thomzig et al., 2007; Angers et al., 2006) may carry some risk of prion infectivity during periods of comorbid viral infection and inflammation or may have their risk profile altered by strain and species differences. Sixth, further challenging conventional knowledge of these disease etiologies is the discovery of 'spontaneous generation' of infectious prions generated *de novo* during *in vitro* experiments (Supattapone, 2004; Castilla et al., 2006). Aggregated prion protein with partial protease resistance was detected in normal human and cattle brains which can act as a template for protein misfolding cyclic amplification (PMCA) (Yuan et al., 2006). The behaviour of aggregated prion in propagating disease is another area of uncertainty.

Secondary transmission of vCJD (e.g., iatrogenic transmission through blood, blood products, cells, tissues or organs) is a risk issue that requires timely responses and options with foresight to help mitigate the consequences. Risk assessments which are the main tool used to estimate the hazard by experts can take lengthy periods of time to complete as an input for formal decision making. Moreover, risk management decisions are required in the absence of a strong evidence base. For secondary, vCJD transmission the World Health Organization (WHO) (2006) concluded that there is insufficient research investigating the efficacy of manufacturing processes in reducing TSE infectivity in blood, blood components and plasma-derived products and in other cells, tissues and organs. Currently, no validated tests can rapidly and specifically detect TSE infectivity in such materials from sources potentially infected with BSE or vCJD agents.

Of particular interest is the uncertainty of prion disease transmission and the transmission of other infectious diseases through blood and blood derived products. Globalisation has had significant impacts on blood safety and blood supplies in several ways. For example, air travel can result in rapid spread of blood-borne pathogens before management measures to reduce transmission can be implemented. The impacts of West Nile Virus in North America were greatly enhanced by ecological factors that allowed the spread of this zoonotic disease in a naïve ecosystem (Brown et al., 2008). Plasma products from new outbreak areas are traded internationally and can transmit pathogens to blood product recipients (Farrugia, 2008). Recent evidence shows vCJD transmission

has occurred to a patient with hemophilia in the UK, likely through contaminated blood products (Canadian Hemophilia Society, 2009; Peden et al., 2010).

The intrinsic uncertainty, changing nature of prion strains and variable infectivity require an available group of experts to evaluate these threats. The expert elicitation process can provide expert estimates for uncertainty gaps as well as provide response to risk issues as the available evidence base changes over time. Any risk model used in this area must address information gaps in order to support improved public health policies, to guide regulatory decision making, and to facilitate more effective risk communication to the public.

Recognising the obstacles which need to be overcome to obtain such data quickly, a formalised expert elicitation approach can help provide a more objective evaluation of existing information and gaps in knowledge, and can assist in the development of more adequate risk analysis, assessment and communication for evidence-based regulation and decision support. A formalised expert elicitation approach provides rational, and auditable, best current estimate parameter inputs for risk assessments given limited existing evidence and can also provide justifiable estimates of uncertainty derived from credible intervals obtained through the elicitation process (Cooke and Goossens, 2008).

A first elicitation of experts was conducted in March 2008 (Expert elicitation group 1), and a second re-elicitation (Expert elicitation group 2) was completed in March 2009. Experts from both groups were asked the same 14 seed or calibration questions and both groups were then asked the same seven Target Item questions for which answers are not known but quantification is desired for risk assessment purposes. Questions related to TSEs focused on areas of uncertainty, genotype effects on susceptibility, disease prevalence in the UK, and the latency time of those who are infected and subsequently donate blood. A comparison of the results for seven target item questions is presented herein. Interpretations of the answers and their relevance for policy and decision making regarding blood, blood products, cells, tissues and organs are discussed.

2 Methods

Expert elicitations were analysed using the Cooke method of weighting expert opinion, as it is the only one currently available that has the attribute of genuine empirical control on the resulting individual scores, through the use of calibration seed questions for which the answers are known *a priori* (Cooke, 1991).

The first expert elicitation workshop using the Cooke Classical Model and the EXCALIBUR software package (© TU Delft, Delft, the Netherlands; available freely from http://www.dutiosc.twi.tudelft.nl/~risk/) was held on March 28, 2008 in Ottawa, Ontario Canada. Dr. Susie ElSaadany from the Blood Safety Surveillance and Healthcare Acquired Infections Division of the Public Health Agency of Canada assumed the role of 'problem owner'. Dr. Willy Aspinall, who has extensive experience in eliciting expert opinion on a wide range of topics acted as facilitator (Aspinall, 2010). More than 20 people attended the elicitation workshop, and 14 participated actively in the elicitation exercise. For reporting the findings of the elicitation exercise, experts' answers were anonymised: experts were identified only by number, and not by name. The experts invited to participate in this exercise were chosen for their knowledge of prion diseases based on their contributions to the peer reviewed scientific literature in this area and through referrals by other experts consulted during the expert selection process. All

14 experts provided responses to the full set of seed items used for calibration and performance weighting. In total, 14 seed questions for which answers were known were asked of the group (data not shown). For the target questions, 13 experts provided responses to target items 1 to 4; 11 experts provided responses to target item 5, and seven provided responses to target items 6 and 7. Because of the variable number of responses to the target questions, it was necessary to re-compute the optimal weighted solutions in EXCALIBUR to take account of the fact that not all of the top four weighted experts completed all seven target items.

The second expert elicitation workshop was held one year later on March 17, 2009 in Ottawa, Ontario, Canada. Dr. Susie ElSaadany again served as the problem owner, and Dr. Willy Aspinall again acted as facilitator. All 11 participating experts provided responses to the full set of seed items for calibration and weighting. The second expert group answered 12 of the 14 seed questions; two of the seed questions were discarded by the expert group after discussion. For the target item questions ten experts answered all seven questions. No re-calculations of the optimal weighted solutions in EXCALIBUR were needed for the second elicitation group as the top three weighted experts completed all of the target questions. The second elicitation involved an additional 15 questions regarding vCJD prevalence, infectivity, and transmissibility for a total of 22 target item questions. Results for the additional 15 questions that were answered by the second elicitation group are reported in Tyshenko et al. (2011).

Seven of the experts participated in both elicitation exercises, each answering and later re-answering the same seven target questions about TSE risks for which there exists considerable uncertainty. Five experts who participated in the first elicitation were not available to participate in the second; and three new experts participated in the second exercise.

For each target item, five points (the minimum, 5th percentile, median, 95th percentile, and maximum) on the empirical distribution of results across experts are used to represent the uncertainty distribution as a non-parametric smoothed cumulative distribution that can be used in a probabilistic risk assessment. The 90% uncertainty interval spanning the 5th to 95th percentiles will be referred to here as the ‘credible range’. A detailed description of the elicitation mathematical weighting is provided in Cooke (1991) and summarised in Tyshenko et al. (2011).

A final aim of the study was to compare the results of the seven target items of both expert elicitations. The purpose of this comparison is not to examine discrepancies between the two elicitations, but rather to evaluate the differences in re-elicitation over time. New information that reduces or increases uncertainty may affect expert judgements of risk.

Re-elicitation between the first and second expert groups was evaluated qualitatively by analysis of the cumulative distribution of the least informative density function with respect to a uniform prior distribution. Further analysis using statistical tests, such as the Kolmogorov-Smirnov (KS) test, which would assess the similarity between the two probability distributions that resulted from the elicitation exercises was not conducted. For each question, the resulting probability distributions from the two elicitation exercises were found using two overlapping groups of experts; this overlap violates the data independence requirement to carry out the KS (or similar) statistical tests.

Table 1 Summary elicitation exercise details of (a) Expert group 1 (EG1) versus (b) Expert group 2 (EG2) with values for seven target questions

(a) Expert elicitation 1 (March, 2008)		
Target question (units)	*Median (90% credible interval)*	
	Equal weights	*Performance weights*
Q1 (MM to MV susceptibility percentage)	44% (0.06 to 100%)	36% (5.1 to 100%)
Q2 (MM to VV susceptibility percentage)	33% (0.003 to 99.3%)	18% (0.0065 to 90.5%)
Q3 (size of bovine to human species barrier -integer range)	1,453 (2.0 to 1.5×10^5)	4,923 (2.1 to 8.4×10^5)
Q4 (probability of new TSE, percentage)	69% (0.007 to 100%)	83% (1.7 to 99.7%)
Q5 (ratio 1996 to 2008; incidence relative to 1)	59 (3 to 4×10^6)	6.25 (2.5 to 4.1×10^3)
Q6 (current UK vCJD prevalence, value as 1 in xxxx)	1 in 14,000 (1 in 857 to 1 in 5.5×10^5)	1 in 164,000 (1 in 2,127 to 1 in 5×10^5)
Q7 (time for blood to transmit after vCJD infection, time in months)	35 mo (0.18 to 338 mo)	107 mo (2.2 to 480 mo)
(b) Expert elicitation 2 (March, 2009)		
Target question (units)	*Median (90% credible interval)*	
	Equal weights	*Performance weights*
Q1* (MV to MM susceptibility percentage)	53.48% (0.39 to 99.62%)	70.72% (4.29 to 99.94%)
Q2* (VV to MM susceptibility percentage)	41.08% (0.00 to 99.54%)	70.87% (8.07 to 99.94%)
Q3 (size of bovine to human species barrier-integer range)	672.1 (1.47 to 4.8×10^5)	1,420 (16.92 to 4.68×10^5)
Q4 (probability of new TSE percentage)	64.14% (5.18 to 99.87%)	98.42% (30.62 to 100%)
Q5 (ratio 1996 to 2009;incidence relative to 1)	0.91 (0.19 to 3.49)	1.55 (0.13 to 4.49)
Q6 (current UK vCJD prevalence, value as 1 in xxxx)	1 in 4,980 (1 in 196.80 to 1 in 7.48×10^5)	1 in 6,140 (1 in 1,040 to 1 in 5.91×10^5)
Q7 (time for blood to transmit after vCJD infection, time in months)	43.42 mo (3.25 to 551.90 mo)	38.49 mo (2.32 to 142.2 mo)

Notes: Performance weighted (best value), equal group weighted (average value), and Median (90% credible interval) for questions 1 to 7 (Q1 to Q7) are shown. For complete question wording see the results section. Question 1 and 2 were reworded during elicitation 2 by the expert group inverting the original MM to MV and MM to VV susceptibility comparisons (see results).

3 Results

Expert responses to the seven target items are shown in Figures 1 to 7, where panel A represents the first expert elicitation held in March, 2008 and panels B represent the second expert elicitation held in March, 2009. For individual expert responses, the central value of the range of opinions shown for that expert represent the median of the uncertainty distribution for that expert, corresponding to the expert's 'best estimate'. The upper and lower limits of the ranges shown correspond to the 5th and 95th percentiles of the uncertainty distribution for that expert. Similar results are given for the opinions of all experts combined, using both the EXCALIBUR performance weights (perf. wts) and equal weights (eq. wts). The 'range graph' plots, which show individual experts' 50 percentile values and their 90% credible intervals as indicated by their 5th and to 95th percentile values for each target item question, are given in the seven figures provided (Figures 1 to 7). These results are also summarised in tabular form for the first [Table 1(a)] and second [Table 1(b)] expert elicitations.

3.1 Comparative analysis of target questions 1 to 7

3.1.1 Target question 1

EG1 What is the relative susceptibility of MM compared to MV to become infected after equal oral classical BSE agent exposure (0 to 100%)?

EG2 What is the relative likelihood of infection of individuals with MV genotype compared to MM genotype after equal oral classical BSE agent exposure (0 to 100%)?

Target question 1 asked the experts about the relative likelihood of infection of individuals with the methionine/methionine (MM) genotype of amino acid position 129 of the prion (PRNP) gene compared to the methionine/valine (MV) genotype at PRNP amino acid position 129 after equal oral classical BSE agent exposure. Responses were given as percentages.

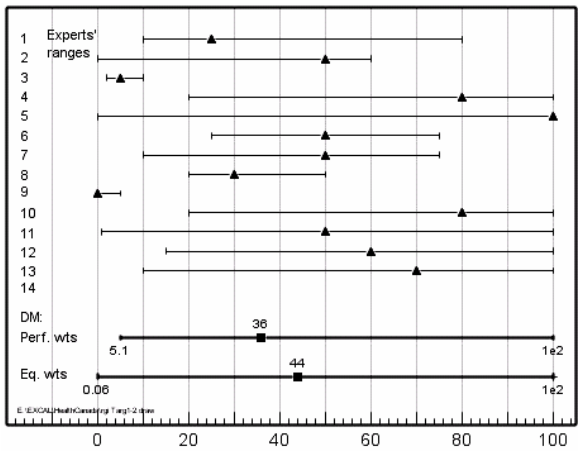
A total of 13 experts in EG1 gave responses to target question 1. The performance weights solution was based on four positively-scored experts' views. The overall uncertainty interval based on performance weights is slightly narrower than that based on equal weights. The experts believed that MM genotypes are more likely to become infected by the BSE agent compared to MV genotypes. It must be emphasised that the experts' opinions on relative genetic susceptibility were subject to substantial uncertainty, with a credible range of 5.1% to 100% [Figure 1(a)].

After some discussion, the second elicitation expert group 2 (EG2), elected to reword the target question, to ask about the relative susceptibility of MV to MM. With this inverse restating of the question, the experts responded that individuals with the MV genotype were 71% less likely to be infected with the BSE agent after oral exposure compared to individuals with MM genotype. As with EG1, the responses for EG2 are subject to considerable uncertainty in the credible range [Figure 1(b)].

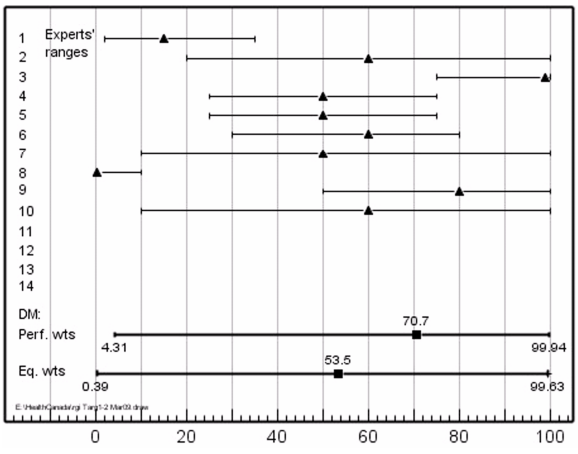
Interpretation

The genotype at codon 129 of the *PRNP* gene is a known risk factor for vCJD (Bishop et al., 2006). The polymorphic *PRNP* gene codon (M129V) may affect the susceptibility to prion diseases (Alperovitch et al., 1999), the incubation time of acquired prion diseases (Brandel et al., 2003) and the clinical pathology of the disease in humans (Goldfarb et al., 1992).

Figure 1 Target question 1, (a) EG1 results: what is the relative susceptibility of MM compared to MV to become infected after equal oral classical BSE agent exposure (0 to 100%)? (b) EG2 results: what is the relative likelihood of infection of individuals with MV genotype compared to MM genotype after equal oral classical BSE agent exposure (0 to 100%)?



(a)



(b)

Notes: Performance weights solution (perf. wts) and equal weights solution (eq. wts) are indicated below the individual, anonymised expert responses. Question 1 was reworded by EG2 to compare MV to MM susceptibility.

Both expert groups perceived differential susceptibility to vCJD following oral exposure to the BSE agent based on prion gene genotype at position 129. The EG1 performance weighted answer MM to MV susceptibility was 36% while the EG2 performance weighted answer of MM to MV susceptibility was 29%.

Despite the rewording by the experts between the first and second exercises both groups gave similar answers of reduced MV genotype susceptibility compared to MM. Both groups were in agreement regarding the relative susceptibility between MM and MV individuals. The MM genotype at position 129 was most susceptible compared, relatively, to the MV genotype. The experts were asked to consider a single polymorphism but it was well known by the experts that in addition to PRNP gene M129V polymorphism other genetic factors are involved in susceptibility (Jackson et al., 2001; Mead et al., 2009).

3.1.2 Target question 2

EG1 What is the relative susceptibility of MM compared to VV genotypes to become infected after equal oral BSE agent exposure (0 to 100%)?

EG2 What is the relative likelihood of infection of individuals with VV genotype compared to MM genotype after equal oral classical BSE agent exposure (0 to 100%)?

Target item question 2 asked the experts to evaluate the relative likelihood of infection of individuals with the MM genotype compared to VV genotype at *PRNP* amino acid position 129 after equal oral classical BSE agent exposure. Responses were given as percentages.

A total of 13 experts in EG1 responded, with the performance weights solution based on four scored experts' views. The performance weights credible interval was slightly narrower than the equal weights credible interval. EG1 believed that VV individuals were less susceptible to the BSE agent than were MM individuals, with VV individuals judged to be approximately 5.5 times (or 18%) less susceptible as MM individuals [Figure 2(a)].

Ten experts from EG2 answered the second target item question, with the performance weights solution based on three scored experts' views. Individuals with VV genotype were thought to be about one third (29%) less likely to be infected with the BSE agent after oral exposure than individuals with the MM genotype; again there was high uncertainty about the relative difference in susceptibility given by the credible range values [Figure 2(b)].

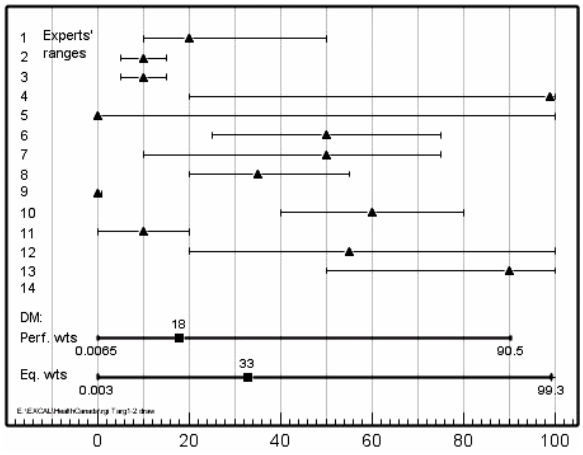
Interpretation

Ingestion of prion contaminated meat from cattle infected with the BSE agent is believed to be the cause of primary vCJD in humans. Approximately 218 cases of vCJD have been recognised since the disease was first reported in 1996.

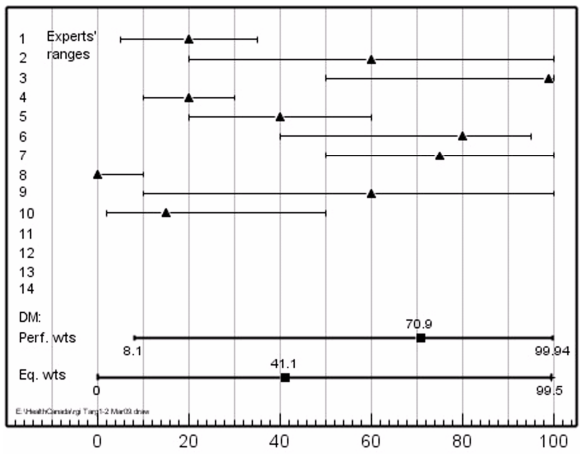
During the second elicitation exercise, EG2 had elected to compare VV to MM genotypes, whereas EG1 compared MM to VV genotypes. EG1 performance weighted answer judged MM to VV susceptibility to be 18% (and conversely VV to MM susceptibility at 82%) while the EG2 performance weighted answer VV to MM susceptibility was 71% (and inversely MM to VV at 29%). Despite the rewording by the experts between exercises one and two both groups gave similar answers for relative MM

to VV susceptibility. Questions 1 and 2 taken together indicate that the experts believe both MV and VV genotypes are less susceptible to this prion disease than MM genotypes after oral challenge of BSE agent. The answers for genotype susceptibility are not surprising given the knowledge that all of the orally exposed cases in the UK have been genotyped as M129M at position 129 of the *PRNP* gene (National Creutzfeldt-Jakob Disease Surveillance Unit, 2010).

Figure 2 Target question 2, (a) EG1 results: what is the relative susceptibility of MM compared to VV genotypes to become infected after equal oral BSE agent exposure (0 to 100%)? (b) EG2 results: what is the relative likelihood of infection of individuals with VV genotype compared to MM genotype after equal oral classical BSE agent exposure (0 to 100%)?



(a)



(b)

Notes: Performance weights solution (perf. wts) and equal weights solution (eq. wts) are indicated below the individual, anonymised expert responses. Question 2 was reworded by EG2 to compare VV to MM susceptibility.

3.1.3 Target question 3

- What is the size of the bovine to human species barrier in the MM genotype for oral exposure to the classical BSE agent?

Target item question 3 asked the experts to estimate the species barrier that exists for infectious transmission of the BSE agent from cattle to humans with the MM genotype via oral exposure to the classical BSE strain.

A total of 13 experts in EG1 responded to the third question. The performance weights solution was based on four scored experts' views. The performance weights solution credible interval is slightly wider than the equal weights solution, and the median value for the performance weights solution (4,923) being over 3-fold greater than the median value (1,453) for the equal weights solution. Although EG1 estimated a species barrier of 4,923 (performance weighted), some experts (#4, 5 and 6) gave values two orders of magnitude lower than this value [Figure 3(a)].

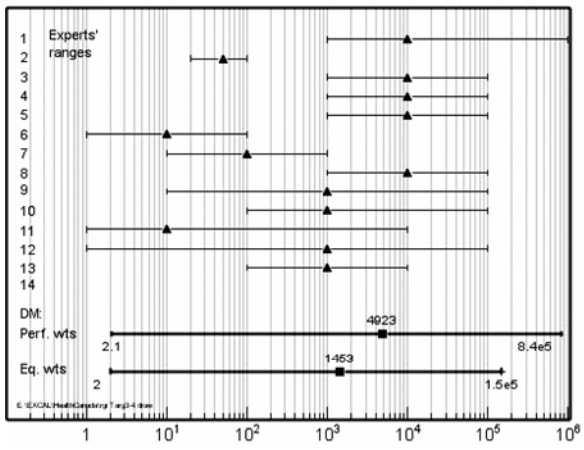
All ten experts in EG2 responded to target item question 3. The performance weights solution was based on three scored experts' views. The performance weights solution credible interval was slightly less than that of the equal weights solution. The median responses were quite similar, with the entire group giving a wider species barrier range. EG2 estimated the cattle to human species barrier at a performance weighted value of 1,420 [Figure 3(b)].

Interpretation

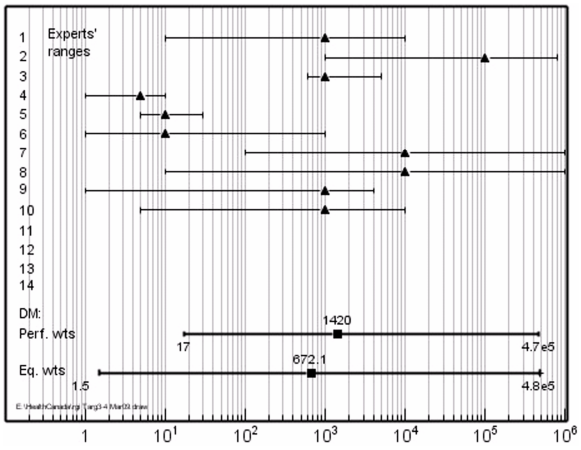
Both expert groups considered the bovine to human species barrier to be appreciable, with humans considered about three orders of magnitude more difficult to infect than bovines when orally challenged with the BSE agent. The best expert judgements from the two elicitations suggested that humans were 1,420 to 4,923 times more resistant to infection with the classical BSE agent than bovines, for exposure via the oral route.

Current estimates in the literature show a range from a factor of 1 (no species barrier) to a factor of 10,000 (meaning that 10,000 times more BSE contaminated bovine material would be needed to infect a human, compared with that needed for infection of a bovine) are plausible values for the species barrier. Although the actual magnitude of the species barrier for the BSE agent between bovines and humans is unknown, the Scientific Steering Committee recommended that in assessing the risk of human exposure to BSE contaminated products, a species barrier of about 1 should be considered as a 'worst case scenario', and that a range of values ranging from 1 to 10,000 should be considered (Scientific Steering Committee, 2000). It is known that almost all (99%) of infectivity is resident in specified risk materials: the brain, spinal cord, trigeminal root ganglia, dorsal root ganglia, distal ileum, spleen, and eyes, collectively (Scientific Steering Committee, 2000). Assuming that 0.1 g of infected brain tissue or spinal cord would make up one cattle oral ID_{50} ($CoID_{50}$) (Scientific Steering Committee, 2000), and using the species barrier values from the two elicitations (1,420 from EG2 and 4,923 from EG1) as a range, this would correspond to human consumption of between 142 g to 492 g of high risk material for an equivalent oral dose. The SSC employed a lower species barrier value of 1,000 and assumed that the effect of cumulative exposure was synergistic if multiple oral exposures occurred within a relatively short period of time; they also indicated a degree of uncertainty by stating that smaller amounts of ingested contaminated material may also result in infection (Scientific Steering Committee, 2000).

Figure 3 Target question 3, what is the size of the bovine to human species barrier in the MM genotype for oral exposure to the classical BSE agent given that the Scientific Steering Committee recommends a range from 10^1 to 10^3?, (a) EG1 results (b) EG2 results for target item 3



(a)



(b)

Note: Performance weights solution (perf. wts) and equal weights solution (eq. wts) are indicated below the individual, anonymised expert responses.

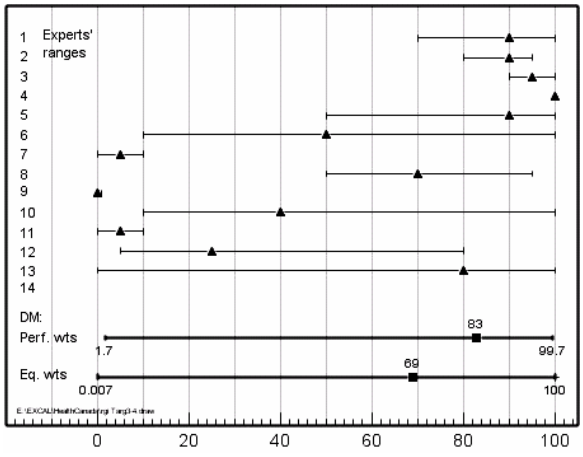
3.1.4 Target question 4

- What is the likelihood of the existence of an undiscovered, human pathogenic TSE strain other than classical BSE (0 to 100%)?

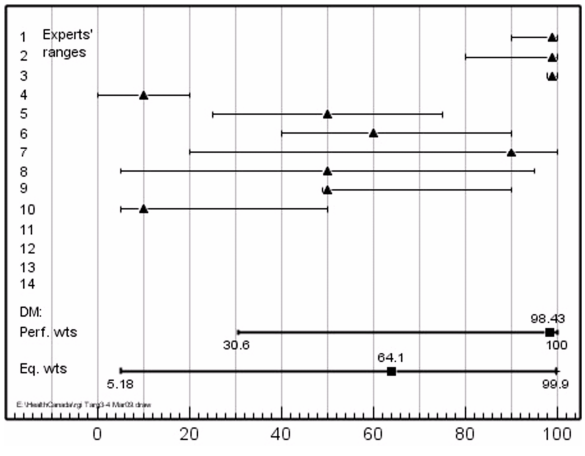
Target question 4 asked the experts to estimate the likelihood of the existence of another zoonotic TSE strain other than classical BSE. Responses were given as a percentage, with 0% and 100% representing the impossibility and certainty, respectively that another such strain exists.

For the 13 experts who responded in EG1, the performance weights solution was based on four scored experts' views. The performance weights solution credible interval is similar to the equal weights solution, while the median value is slightly higher (83% versus 69%). Clearly, a wide range of views are held, which collectively represent a situation in which there is substantial uncertainty, as reflected by the 5th and 95th percentiles of 1.7 to 99.7%, respectively. Despite the wide uncertainty, the performance weights solution indicated an 83% chance of an as yet undiscovered pathogenic TSE strain [Figure 4(a)].

Figure 4 Target question 4: what is the likelihood of the existence of an undiscovered, human pathogenic TSE strain other than classical BSE? (0 to 100%), (a) EG1 results (b) EG2 results



(a)



(b)

Note: Performance weights solution (perf. wts) and equal weights solution (eq. wts) are indicated below the individual, anonymised expert responses.

All ten experts in EG2 answered question 4. EG2 was in reasonable agreement with EG1, but more certain that an undiscovered TSE strain existed; they considered it highly likely

that there exists other animal diseases (other than the classical BSE strain) that may affect humans, indicating that the likelihood for this was over 98%. EG2 also gave a narrower credible interval, ranging from 31% to 100%, indicating greater confidence in their views [Figure 4(b)].

Interpretation

All experts thought that the likelihood of finding new TSEs was very high. This is not a surprising given the long history of discovery of new TSEs affecting an ever-increasing number of species, including: sheep (McGowan, 1922); cattle (Wells et al., 1987); mink (Marsh, 1991); domestic cats (Wyatt et al., 1991); exotic ruminant species (greater kudu, nyala, Arabian oryx, scimitar horned oryx, eland, gemsbok, bison and ankole) (BSE Inquiry, 2000b); zoo cats (tiger, cheetah, ocelot, puma and lion) (Bruce et al., 1994; Jeffrey and Wells, 1988; Kirkwood et al., 1990); white tailed deer; mule deer and elk (Williams and Young, 1980); and lemurs (Bons et al., 1999). Similarly prion diseases in humans include several different forms: CJD, vCJD, sporadic Creutzfeldt-Jakob disease (sCJD), iatrogenic CJD, familial CJD, Gerstmann-Sträussler-Scheinker (GSS) syndrome, fatal insomnia (both sporadic and familial, FFI), kuru and proteinase-sensitive prionopathy (PSPr) [as reviewed by Hope (1999) and Collins et al. (2001)]. In addition, experimental transmission of TSEs has been demonstrated in the laboratory using mice, hamsters, European red deer, voles and primates (squirrel monkey) (Gibbs and Gajdusek, 1973; Marsh et al., 2005; Dagleish et al., 2008).

3.1.5 Target question 5

EG1 What is the ratio of present day vCJD infection incidence in the UK (2008) to infection incidence in 1996?

EG2 What is the prevalence of vCJD infection in the UK in 2009 compared to 1996 (ratio relative to 1)?

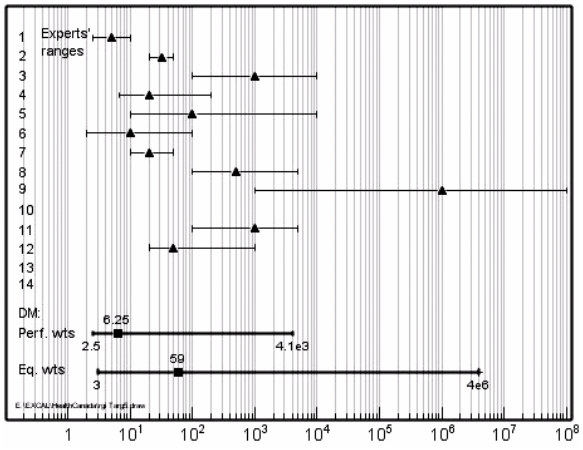
Target question 5 asked experts in EG1 to estimate the prevalence of vCJD in the UK in 2008 (and similarly for EG2 up to the year 2009) compared to prevalence in 1996. Responses were given as a ratio of the prevalence of this disease in 2008 (EG1) or 2009 (EG2) relative to prevalence in 1996.

Eleven experts in EG1 responded; the performance weights solution is based on three scored experts' views. The performance weighted credible interval is notably narrower than equal weights credible interval. Using performance weights, the rate of vCJD infection in the UK in 2008 was judged to be over 6-fold greater than that in 1996, with the corresponding 90% credible interval ranging from about 2 to over 4,000-fold.

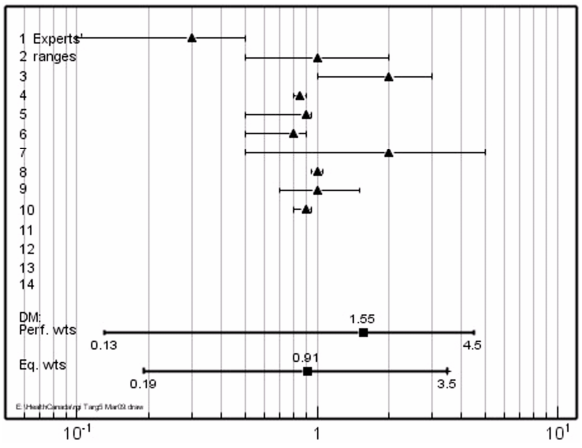
The responses to this target question appear to be particularly informative, in that the elicitation procedure has produced a different central value with narrower credible interval using performance weights as compared to equal weights [Figure 5(a)].

Ten experts in EG2 responded; the performance weights solution is based on three scored experts' views. The experts thought the prevalence of vCJD in the UK increased between 1996 and 2009, but only by about 1.5-fold (range 0.1 to 4.5-fold), according to best expert judgement [Figure 5(b)].

Figure 5 Target question 5, (a) EG1 results: what is the ratio of present day vCJD infection incidence in the UK (2008) to infection incidence in 1996? For example, if it is believed that the current rate is one, one-hundredth of what it used to be, enter the value: 1/100 or 0.01 (b) EG2 results: what is the prevalence of vCJD infection in the UK in 2009 compared to 1996 (ratio relative to 1)?



(a)



(b)

Notes: Performance weights solution (perf. wts) and equal weights solution (eq. wts) are indicated below the individual, anonymised expert responses. Question 5 was reworded from 2008 to 2009 between the two elicitations.

Interpretation

There was agreement between the two elicitations that the prevalence of vCJD infection in the UK was higher in 2009 than in 1996. However, the first elicitation group suggested a larger increase in the prevalence of infection than did the second expert group. The experts likely considered both oral and secondary transmission in providing their responses. An important consideration in estimating the prevalence of infection is the level of exposure to high risk materials by both oral and iatrogenic routes. Even though

only a relatively small number of vCJD cases have been reported in the UK to date (218), there were large numbers of the UK population that had consumed contaminated bovine tissues (Will et al., 1996). The retrospective appendix and tonsil study by Hilton et al., (2004) suggested that the prevalence of prion disease in the UK population was about 1 in 4,000. In 1996, the possibility of blood borne transmission of vCJD was considered to be highly uncertain, but later it was confirmed that secondary vCJD can occur through blood transfusion (Llewelyn et al., 2004) and blood products (Canadian Hemophilia Society, 2009). Over time, experts have revised their estimates of vCJD prevalence as more information has become available and the uncertainty surrounding the risk of vCJD in the UK population has been reduced through the accumulation of new scientific data.

3.1.6 Target question 6

- Given that Hilton et al. (2004) gives a value of 1 in 4,225 and that Clarke and Ghani (2005) give a value of 1 in 550,000 – What are the range and median values to use to represent the prevalence of vCJD in the UK population in a risk model (1 in XXX)?

Target question 6 asked experts to estimate the prevalence of vCJD infection was in the UK population in the current year (2008 and 2009 for EG1 and EG2, respectively). Prevalence estimates were expressed in the form of 1 case in xxx population, where the experts determined the population size in the denominator of the prevalence estimate.

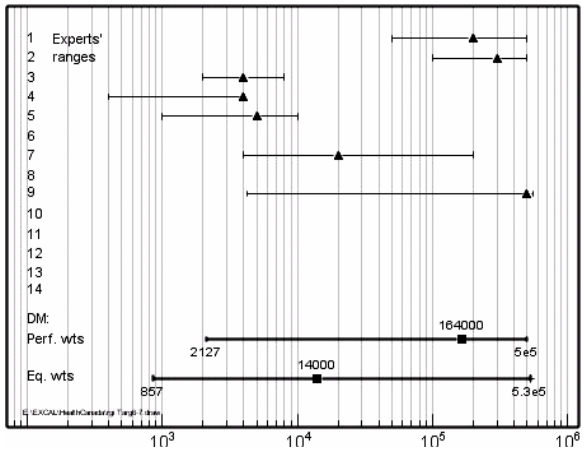
Only seven experts from EG1 responded to this target question. The performance weights solution is based on two scored experts' views. The median performance weighted estimate of the prevalence of vCJD infection in the UK in 2008 was estimated at 1 in 164,000, with a credible interval of about 1 in 2,000 to 1 in 500,000 (the credible interval for the equal weights solution is only slightly wider, ranging from about 1 in 900 to 1 in 530,000) [Figure 6(a)]. Ten experts in EG2 responded. The performance weights solution is dominated by three scored experts' views. The best expert judgement indicated that the current prevalence of vCJD in the UK is about 1 in 6,000; although this is notably lower than the judgement of EG1; the performance weighted credible intervals for EG1 and EG2 are similar [Figure 6(b)].

Interpretation

The appendix and tonsil studies conducted in the UK (Hilton et al., 2004) estimated the prevalence of vCJD infection in the UK to be 1 in 4,225 (model output for higher vCJD infection prevalence); in contrast, Clarke and Ghani (2005) gave a value of 1 in 550,000 (model output for lower vCJD case prevalence). The retrospective study by Hilton et al. (2004) examined tonsillectomy (1,739) and appendectomy (14,964) samples taken between 1995 to 1999, several years after the peak human exposure to BSE, which is likely to have occurred between 1988 and 1992, in order to maximise the chances of identifying vCJD infected individuals.

The expert results for target question 6 appear to be consistent with these findings, and internally consistent with the results for target question 3. The performance weights solution to question 3 showed that EG1 perceived a high species barrier (4,923) between bovines and humans, and a concomitantly low prevalence of vCJD infection of 1 in 164,000. EG2 thought that the species barrier would be somewhat less at a value of 1,420 with a correspondingly higher prevalence of 1 in 6,140. The prevalence estimates from both expert groups fell within the values reported in the literature.

Figure 6 Target question 6: given that Hilton et al. (2004) gives a value of 1 in 4,225 and that Clarke and Ghani (2005) give a value of 1 in 550,000 – what are the range and median values to use to represent the prevalence of vCJD in the UK population in a risk model (give your answer as 1 in XXXXX)?, (a) expert elicitation group 1 results (b) expert elicitation group 2 results



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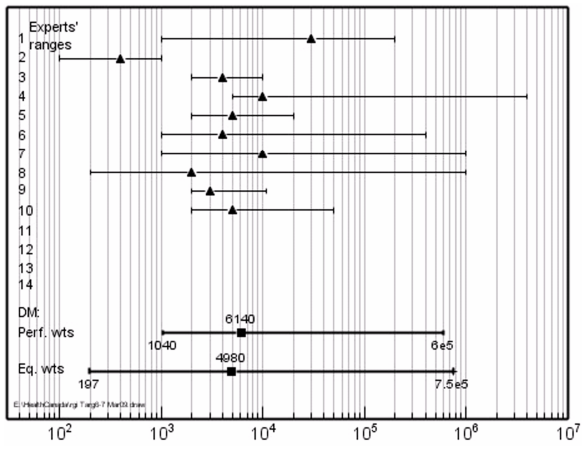


(b)

Notes: Performance weights solution (perf. wts) and equal weights solution (eq. wts) are indicated below the individual, anonymised expert responses. Experts considered the current prevalence for question 6 (EG1 in 2008 and EG2 in 2009).

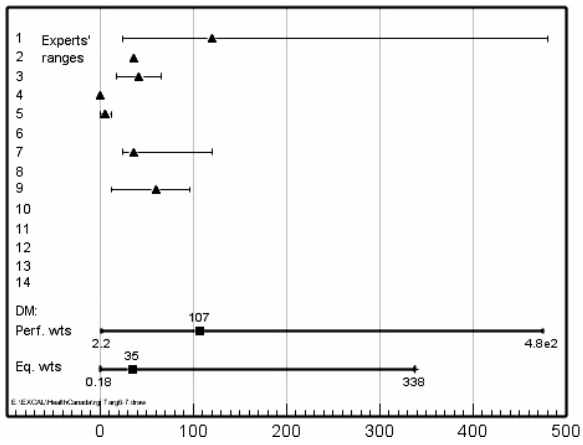
On February 17, 2009, just prior to the second elicitation exercise the UK Health Protection Agency reported that a man with hemophilia was found at post mortem examination to have evidence of vCJD infection in his spleen. The man, who was asymptomatic, died of unrelated causes. This was the first report that a person with hemophilia who was treated with plasma blood products showed evidence of vCJD infection (Canadian Hemophilia Society, 2009). Question 6 made no distinction between primary (oral) and secondary (iatrogenic) routes of transmission. It is likely that the second expert group was influenced by this new information, and considered iatrogenic

routes of exposure with more emphasis when formulating their judgements during the second elicitation exercise.

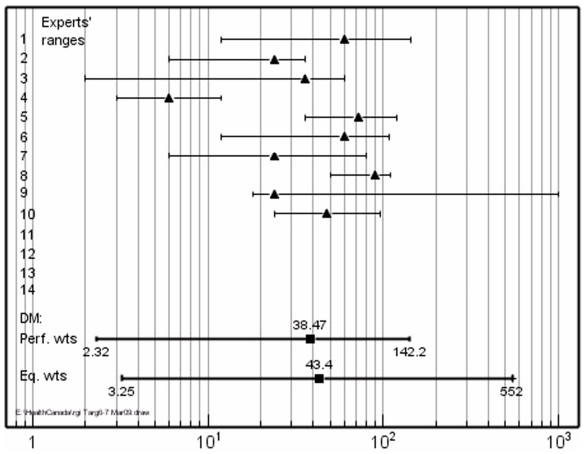
3.1.7 Target question 7

- What is the length of time in months between when a human is infected with vCJD and when 1 unit of their blood is capable of transmitting infection to a recipient (answer given in months)?

Figure 7 Comparison of target item question 7: what is the length of time in months between when a human is infected with vCJD and when 1 unit of their blood is capable of transmitting infection to a recipient?, (a) expert elicitation group 1 results (b) expert elicitation group 2 results



(a)



(b)

Note: Performance weights solution (perf. wts) and equal weights solution (eq. wts) are indicated below the individual, anonymised expert responses.

Seven experts in EG1 responded to question 7. The performance weights solution is based on two scored experts' views. The performance weights solution credible interval is notably greater than the equal weights solution, in this case primarily due to the influence of the views of expert 1. The median value from the performance weights solution was 107 months, with a range from 2.2 months to 480 months [Figure 7(a)].

Ten experts responded in EG2; the performance weights solution was based on three experts' views. The median values of equal (43 months) and performance (39 months) weighted responses were in close agreement. All experts agreed that blood of vCJD infected individuals could be infectious after three years. As in the first elicitation group, a single individual, Expert 9, introduced a high degree of uncertainty to the equal weights solution [Figure 7(b)].

Interpretation

EG2's best judgement of the time from transfusion of infected blood until the recipient becomes infectious (about three years) only one-third of the time (nine years) suggested by EG1. Both groups indicated that infected individuals could transmit the infectious agent within months as indicated, by the 5th percentiles of the credible ranges.

Infection latency was thought by some experts to be lengthy, up to almost 12 years by EG1 and 40 years by EG2. Experts were possibly modulating their answers based on knowledge of kuru disease etiology, another orally acquired human TSE with long incubation periods that has been documented in the scientific literature (Collinge et al., 2008). The large ranges in infection latency times given by the two expert groups may be based on the interpretation of available animal model data known to the experts. For example, prion detection studies in hamsters showed that prions were detectable by PMCA in blood after initial infection, but prions became undetectable in the peripheral blood system during the remainder of the pre-symptomatic phase. Prions were again detectable when the animals neared clinical disease and began displaying symptoms (Saá et al., 2006). The uncertainty distributions expressed by both expert groups demonstrated positive skewness (to the right side), indicating most of the experts are less certain about the upper limit on the latency period for iatrogenic blood transmission of prion disease.

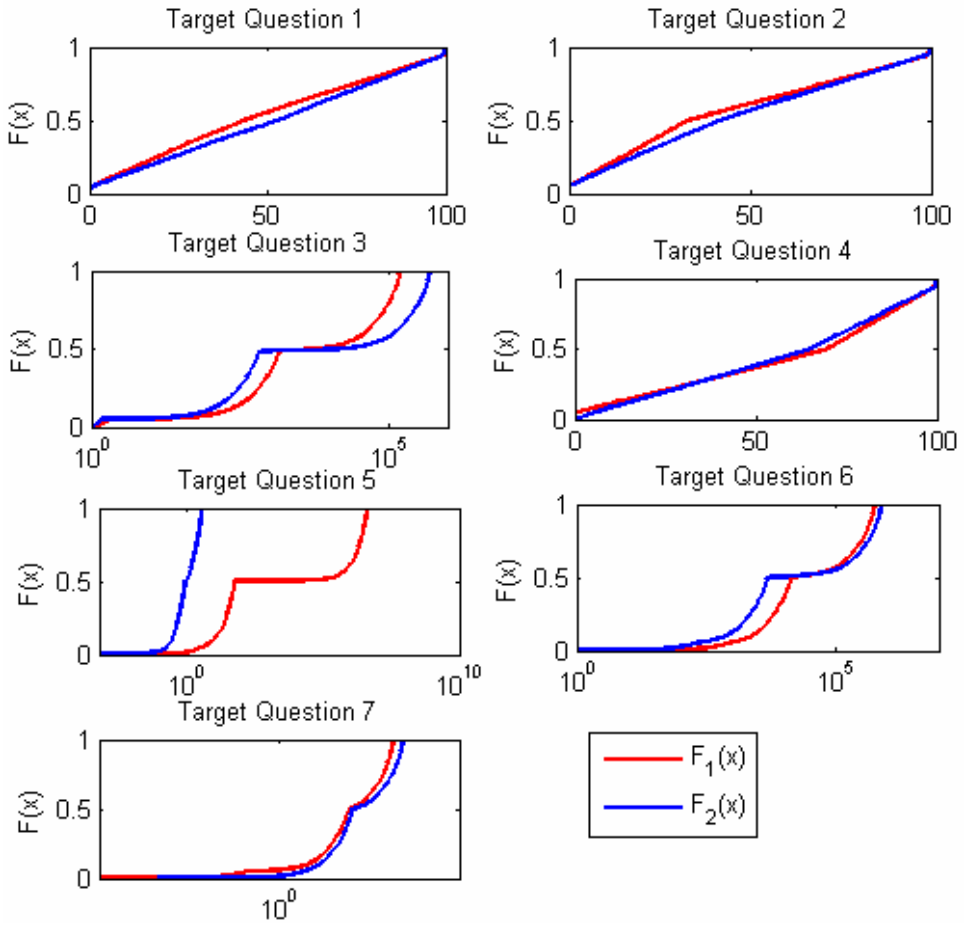
3.2 Qualitative probability distribution comparisons between the seven target questions of the two elicitation groups

A qualitative comparison between the probability distributions resulting from each of the seven target questions in both cases of equal weights (Figure 8) and performance weights (Figure 9) was completed.

From the seven questions, it appears that the risk of contracting vCJD in a population comprised of the MM, MV and VV genotypes is monotonically decreasing in the quantities elicited in questions 1 and 2. Thus using the second elicitation group answers for those two questions in a probabilistic risk assessment would result in a higher risk.

Similarly, the risk of contracting vCJD via the oral route is decreasing in the species barrier quantity (elicited in question 3) and so using the second elicitation group's performance weighted answer in a risk assessment would result in higher risk estimation.

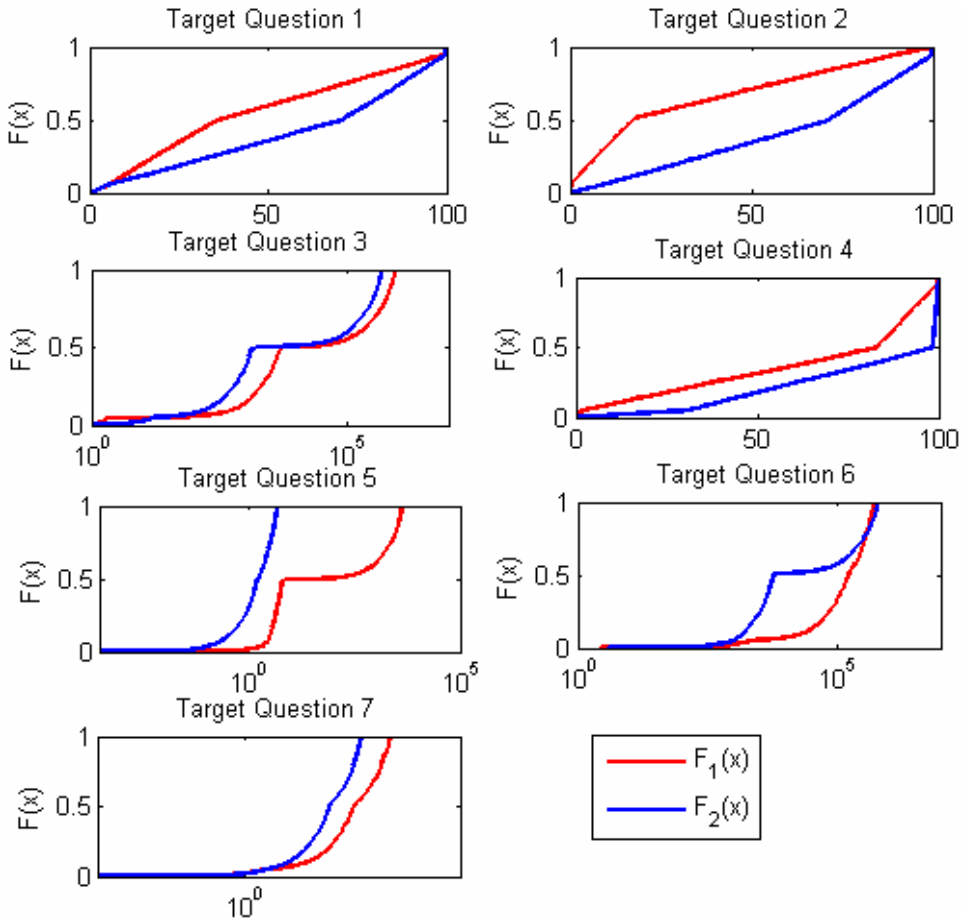
Figure 8 Distribution functions representing the answers of the seven target questions estimated assuming *equal weights* with $F_1(x)$ depicting the answer of the first elicitation group shown in red colour and $F_2(x)$ depicting the answer of the second elicitation group shown in blue colour (see online version for colours)



Note: The x-scale for the target questions 1, 2 and 4 is percentage and a logarithmic scale for the rest of them.

The same follows for the likelihood of a novel TSE strain when using the second elicitation group's performance weighted answer which would result in a higher risk (question 4). Whereas, the risk of transmission of vCJD via blood will depend on choosing either of elicitation group's equal or performance weighted answers (question 7). It is difficult to derive similar conclusions for questions 5 and 6, since the prevalence given in their answers are for different years (2008 and 2009).

Figure 9 Distribution functions representing the answers of the seven target questions estimated assuming *performance weights* with $F_1(x)$ depicting the answer of the first elicitation group shown in red colour and $F_2(x)$ depicting the answer of the second elicitation group shown in blue colour (see online version for colours)



Note: The x-scale for the target questions 1, 2 and 4 is percentage and a logarithmic scale for the rest of them.

4 Conclusions

The theoretical basis for the rational pooling of expert opinion has been well-established by Cooke (1991), and has enjoyed a large number of successful applications involving diverse issues (Aspinall, 2010; Cooke and Goossens, 2008). Within the Bayesian paradigm, when expert opinion is expressed in a quantitative form it can be considered to be prior information, in just the same way as empirical data because both represent an expression of belief about the values of a particular variable, and both incorporate a statement of the associated uncertainty.

TSE research, like many other scientific domains, is an area where experts can, and will, hold different views about the same issues – if not about the central normative

tendencies, then almost invariably about the quantification of uncertainties surrounding those normative tendencies. Prion diseases have exemplified this uncertainty, from its beginning with initial debates as to whether they are caused by infectious protein particles that 'reproduced' in a protein only, template-directed manner, without the involvement of genetic material (Prusiner, 1982; Bastian and Fermin, 2005; Manuelidis, 2007). Issues regarding prevalence, susceptibility and secondary transmission for vCJD through blood, blood products, cells, organs and tissues remain subject to substantial uncertainty. In the absence of clear scientific evidence these and other prion disease risk issues, the considered opinions of experts can provide interim guidance for risk management decision making, until such evidence becomes available.

Various approaches for obtaining a rational consensus from a range of diverse expert opinions are available. The classical expert elicitation approach developed by Cooke (1991), and employed here provides a structured approach to expert elicitation, weighting the opinions of individual experts based on their calibration using seed questions to which the answers are known. The classical approach also provides a quantitative measure of the uncertainty associated with the responses of the experts to the target questions, to which the answers are unknown.

In both elicitation exercises, expert responses to the target questions were generally characterised by substantial uncertainty, suggesting that many of the experts see the risks issues under consideration as possessing a high degree of ambiguity. Nonetheless, the average response of the experts provides a useful indication of the best scientific opinion among the participating experts; the inclusion of a 'credible interval' surrounding this overall average response provides a measure of uncertainty across experts. The consolidation of opinion across experts was done using both performance weights (based on the experts' responses to the seed questions) and equal weights (treating each expert opinion as equally valid.) The uncertainty ranges surrounding the overall average based on the performance weights were narrower than the uncertainty intervals for the overall average based on equal weights. The average response based on the performance weights, which effectively represents the opinions of the subset of experts that scored well on the seed questions, provides the best available scientific opinion about the risk issue reflected in the target question at this time.

The re-elicitation established that while some of the uncertainties related to prion risks had not changed appreciably (question 1, 2 and 4), some had elicited values with decreased uncertainty since the initial elicitation (question 3 and 5), and others had increased (question 6 and 7). Some of these changes are likely related to new information that became available between the first and second elicitations.

For example, the experts appear to have responded to new information that reduces uncertainty concerning vCJD prevalence, as indicated by their responses to target question 5. The prevalence of silent vCJD infections in the UK population was previously very poorly determined. Initially, prion transmission studies in model animal systems established that the same prion strain causes vCJD and BSE (Bruce et al., 1997; Herzog et al., 2005). This led to different models and discussions of the uncertainty about the future size of the vCJD epidemic in the UK (Porta and Morabia, 2004; Sneath, 2004). However, later estimates of population studies of lymphoidal human tissues (tonsils and appendices) (Ghani et al., 2000; Hilton et al., 2004; Clarke and Ghani, 2005; Clewley et al., 2009) provided evidence for experts to refine their opinions of human vCJD prevalence. The completion of additional research over time has helped to provide more evidence for this issue regarding prevalence.

In contrast, the experts have responded to new information that has increased the uncertainty surrounding the likelihood of vCJD transmission. At the beginning of the UK BSE outbreak, transmission to humans was thought to be a low risk [as reviewed by Collee (1990)]. Later, the occurrence of both primary and secondary transmission of disease led to large uncertainty over the eventual size, distribution and persistence of vCJD. Previous risk assessments used expert opinion for several key assumptions and variables (Garske and Ghani, 2010; Dobra and Bennett, 2006; Turner and Ludlam, 2009).

Expert elicitation (unstructured) has been used increasingly in risk management situations to provide quantitative estimates of parameters that cannot be fully determined through direct measurement, by collecting new data, or by other sampling techniques (Budnitz et al., 1995, 1998). In Canada, blood safety regulations to prevent the transmission of TSEs and other communicable diseases through blood and blood products has involved expert judgement since the publication of the Krever Commission report in 1997 (Krever, 1997). Recommended reforms for Canada's blood system, stressed the need for adherence to precautionary principles through clarification of how evidence should be used to formulate policy.

Canada Blood Services (CBS) continues to use expert opinion to ensure safety of the blood supply, through international consensus conferences to develop new risk management policies and strategies in this area (Blajchman et al., 2004). Expert consultation for vCJD and blood safety has been used to guide decision-making on the risks of therapeutic products as scientific evidence from randomised trials could not be generated in a timely manner (Wilson, 2007). Since 1999, Health Canada and the Public Health Agency of Canada have used a growing expert network to evaluate TSE risks from reuse of medical devices such as laparoscopes and plastic surgery tools, as well as the use of dental tissue and islet cells from donors.

The results of the structured expert elicitation performed here can help to formulate specific research questions that need to be answered in order to fill important scientific data gaps, and strengthen the evidence base on which risk management policy is developed. In particular, research needs concerning the further development and validation of modified or novel decontamination processes and tests to identify TSE infectivity in blood and other cells, tissues and organs will be guided by the expert values and uncertainty ranges associated with those values. While the scientific uncertainties involved in characterising the determinants of vCJD risks are likely to remain large, and difficult to quantify precisely, formalised expert elicitation can be used to provide rational constraints and plausible ranges for the parameters of interest.

The results of the two elicitation exercises reported here will inform of the characterisation of vCJD in different ways. For example, a risk assessment model for primary vCJD risks could incorporate the bovine to human species barrier as one of its parameters, as well as the relative susceptibility of individuals with different genotypes. The most recent dose-response function describing oral exposure to BSE agent and the risk of BSE in cattle is derived from a bioassay done by Wells et al. (2007), which shows an approximately linear function at low doses; adjusting the dose by the species barrier will give an estimate for the dose-response function for oral exposure to the BSE agent and the risk of vCJD in humans.

The results of the two elicitations show that it is feasible to conduct structured elicitations over time with weighted pooling of expert opinions for vCJD and other TSE disease risk uncertainties. The findings can provide estimates of the values of key parameters involved in the determination of risk and the uncertainty ranges, and can be

used in the characterisation of TSE uncertainties in the absence of adequate supporting scientific data. Such estimates can be used as proxies until the true values become known. The classical structured elicitation approach developed by Cooke (1991) offers a rational basis for selecting the contributing experts, and for ascribing values and uncertainty distributions to key parameters that affect risk for which current data are sparse, or even non-existent. The elicitation and re-elicitation results can also be used to guide future research to fill important data gaps as they change over time, leading to refined risk characterisations.

This method has been applied successfully to estimating vCJD uncertainty; however, the methodology could also be applied to other emerging real-time public health threats such as pandemic influenza and other emerging blood-borne threats.

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References

Alperovitch, A., Zerr, I., Pocchiari, M., Mitrova, E., de Pedro Cuesta, J.,` Hegyi, I., Collins, S., Kretzschmar, H., van Duijn, C. and Will, R.G. (1999) 'Codon 129 prion protein genotype and sporadic Creutzfeldt-Jakob disease', *Lancet*, Vol. 353, No. 9165, pp.1673–1674.

Angers, R.C., Browning, S.R., Seward, T.S., Sigurdson, C.J., Miller, M.W., Hoover, E.A. and Telling, G.C. (2006) 'Prions in skeletal muscles of deer with chronic wasting disease', *Science*, Vol. 311, No. 5764, p.1117.

Aspinall, W. (2010) 'A route to more tractable expert advice', *Nature*, Vol. 463, No. 7279, pp.294–295.

Bartz, J.C., Bessen, R.A., McKenzie, D., Marsh, R.F. and Aiken, J.M. (2000) 'Adaptation and selection of prion protein strain conformations following interspecies transmission of transmissible mink encephalopathy', *J. Virol.*, Vol. 74, No. 12, pp.5542–5547.

Bartz, J.C., Marsh, R.F., McKenzie, D.I. and Aiken, J.M. (1998) 'The host range of chronic wasting disease is altered on passage in ferrets', *Virology*, Vol. 251, No. 2, pp.297–301.

Bastian, F.O. and Fermin, C.D. (2005) 'Slow virus disease: deciphering conflicting data on the transmissible spongiform encephalopathies (TSE) also called prion diseases', *Microsc. Res. Tech.*, Vol. 68, Nos. 3/4, pp.239–246.

Benestad, S.L., Sarradin, P., Thu, B., Schönheit, J., Tranulis, M.A. and Bratberg, B. (2003) 'Cases of scrapie with unusual features in Norway and designation of a new type, Nor98', *Vet. Rec.*, Vol. 153, No. 7, pp.202–208.

Bishop, M.T., Hart, P., Aitchison, L., Baybutt, H.N., Plinston, C., Thomson, V., Tuzi, N.L., Head, M.W., Ironside, J.W., Will, R.G. and Manson, J.C. (2006) 'Predicting susceptibility and incubation time of human-to-human transmission of vCJD', *Lancet Neurol.*, Vol. 5, No. 5, pp.393–398.

Blajchman, M.A., Goldman, M., Webert, K.E., Vamvakas, E.C., Hannon, J. and Delage, G. (2004) 'Proceedings of a consensus conference: the screening of blood donors for variant CJD', *Transfus. Med. Rev.*, Vol. 18, No. 2, pp.73–92.

Bons, N., Mestre-Frances, N., Belli, P., Cathala, F., Gajdusek, D. and Brown, P. (1999) 'Natural and experimental oral infection of non-human primates by bovine spongiform encephalopathy agents', *Proc. Natl. Acad. Sci.*, Vol. 96, pp.4046–4051, USA.

Brandel, J.P., Preece, M., Brown, P., Croes, E., Laplanche, J.L., Agid, Y., Will, R. and Alpérovitch, A. (2003) 'Distribution of codon 129 genotype in human growth hormone-treated CJD patients in France and the UK', *Lancet*, Vol. 362, No. 9378, pp.128–130.

Brown, H.E., Childs, J.E., Diuk-Wasser, M.A. and Fish, D. (2008) 'Ecological factors associated with West Nile virus transmission, Northeastern United States', *Emerg. Infect. Dis.*, Vol. 14, No. 10, pp.1539–1545.

Bruce, M., Chree, A., McConnell, I., Foster, J., Pearson, G. and Fraser, H. (1994) 'Transmission of bovine spongiform encephalopathy and scrapie to mice: strain variation and the species barrier', *Philos. Trans. R. Soc. London Ser. B.*, Vol. 343, No. 1306, pp.405–411.

Bruce, M.E., Will, R.G., Ironside, J.W., McConnell, I., Drummond, D., Suttie, A., McCardle, L., Chree, A., Hope, J., Birkett, C., Cousens, S., Fraser, H. and Bostock, C.J. (1997) 'Transmissions to mice indicate that 'new variant' CJD is caused by the BSE agent', *Nature*, Vol. 389, No. 6650, pp.498–501.

BSE Inquiry (2000a) *Volume 1: Findings and Conclusions*, 4, The Southwood Working Party and Other Scientific Advisory Committees, available at http://collections.europarchive.org/tna/20090505194948/ and http://bseinquiry.gov.uk/report/volume1/chapter4.htm (accessed on 23 January 2012).

BSE Inquiry (2000b) *Volume 2: Science*, 3, The Nature and Cause of BSE, Section 3.52 Table 3.1, Host Range of BSE, available at http://collections.europarchive.org/tna/20090505194948/ and http://bseinquiry.gov.uk/report/volume3/toc.htm (accessed on 23 January 2012).

Budnitz, R.J., Apostolakis, G., Boore, D.M., Cluff, L.S., Coppersmith, K.J., Cornell, C.A. and Morris, P.A. (1998) 'Use of technical expert panels: applications to probabilistic seismic hazard analysis', *Risk Anal.*, Vol. 18, No. 4, pp.463–1469.

Budnitz, R.J., Boore, D.M., Apostolakis, G., Cluff, L.S., Coppersmith, K.J., Cornell, C.A. and Morris, P.A. (1995) 'Recommendations for probabilistic seismic hazard analysis: guidance on uncertainty and use of experts, NUREG CR-6372', *US Nuclear Regulatory Commission*, Vol. 1, pp.1–278, available at http://www.osti.gov/bridge/servlets/purl/479072-krGkYU/webviewable/479072.pdf (accessed on 23 January 2012).

Buschmann, A., Biacabe, A.G., Ziegler, U., Bencsik, A., Madec, J.Y., Erhardt, G., Lühken, G., Baron, T. and Groschup, M.H. (2004) 'Atypical scrapie cases in Germany and France are identified by discrepant reaction patterns in BSE rapid tests', *J. Virol. Methods*, Vol. 117, No. 1, pp.27–36.

Canadian Hemophilia Society (2009) *vCJD Infection Reported in a Person with Hemophilia in UK: FVIII Concentrates Considered Most Likely Cause*, 19 February, available at http://www.ahcdc.ca/documents/2009-02-19%20CHS%20and%20AHCDC%20vCJD%20infection%20-%20EN.pdf (accessed on 23 January 2012).

Cancellotti, E., Barron, R.M., Bishop, M.T., Hart, P., Wiseman, F. and Manson, J.C. (2007) 'The role of host PrP in transmissible spongiform encephalopathies', *Biochim. Biophys. Acta.*, Vol. 1772, No. 6, pp.673–680.

Casalone, C., Zanusso, G., Acutis, P., Ferrari, S., Capucci, L., Tagliavini, F., Monaco, S. and Caramelli, M. (2004) 'Identification of a second bovine amyloidotic spongiform encephalopathy: molecular similarities with sporadic Creutzfeldt-Jakob disease', *Proc. Natl. Acad. Sci.*, Vol. 101, No. 9, pp.3065–3070, USA.

Castilla, J., Saá, P., Morales, R., Abid, K., Maundrell, K. and Soto, C. (2006) 'Protein misfolding cyclic amplification for diagnosis and prion propagation studies', *Methods Enzymol*., Vol. 412, pp.3–21.

Clarke, P. and Ghani, A.C. (2005) 'Projections of the future course of the primary vCJD epidemic in the UK: inclusion of subclinical infection and the possibility of wider genetic susceptibility', *J.R. Soc. Interface*, Vol. 2, No. 2, pp.19–31.

Clewley, J.P., Kelly, C.M., Andrews, N., Vogliqi, K., Mallinson, G., Kaisar, M., Hilton, D.A., Ironside, J.W., Edwards, P., McCardle, L.M., Ritchie, D.L., Dabaghian, R., Ambrose, H.E. and Gill, O.N. (2009) 'Prevalence of disease related prion protein in anonymous tonsil specimens in Britain: cross sectional opportunistic survey', *BMJ*, May, Vol. 338, p.b1442.

Collee, J.G. (1990) 'Bovine spongiform encephalopathy', *Lancet*, Vol. 336, No. 8726, pp.1300–1303.

Collinge, J., Whitfield, J., McKintosh, E., Frosh, A., Mead, S., Hill, A.F., Brandner, S., Thomas, D. and Alpers, M.P. (2008) 'A clinical study of kuru patients with long incubation periods at the end of the epidemic in Papua New Guinea', *Philos. Trans. R. Soc. Lond. B Biol. Sci.*, Vol. 363, No. 1510, pp.3725–3739.

Collins, S., McLean, C.A. and Masters, C.L. (2001) 'Gerstmann-Sträussler-Scheinker syndrome, fatal familial insomnia, and kuru: a review of these less common human transmissible spongiform encephalopathies', *J. Clin. Neurosci*., Vol. 8, No. 5, pp.387–397.

Cooke, R.M. (1991) *Experts in Uncertainty – Opinion and Subjective Probability in Science*, p.321, ISBN 0195064658, Environmental Ethics and Science Policy Series, Oxford University Press, New York.

Cooke, R.M. and Goossens, L.H.J. (2008) 'TU Delft expert judgment data base', *Reliability Engineering & System Safety*, Vol. 93, No. 5, pp.657–674.

Dagleish, M.P., Martin, S., Steele, P., Finlayson, J., Sisó, S., Hamilton, S., Chianini, F., Reid, H.W., González, L. and Jeffrey, M. (2008) 'Experimental transmission of bovine spongiform encephalopathy to European red deer (*Cervus elaphus elaphus*)', *BMC Vet. Res.*, Vol. 4, No. 1, p.17.

Dobra, S.A. and Bennett, P.G. (2006) 'vCJD and blood transfusion: risk assessment in the United Kingdom', *Transfus. Clin. Biol.*, Vol. 13, No. 5, pp.307–311.

Farrugia, A. (2008) 'Globalisation and blood safety', *Blood Rev.*, Vol. 23, No. 3, pp.123–128.

Garske, T. and Ghani, A.C. (2010) 'Uncertainty in the tail of the variant Creutzfeldt-Jakob disease epidemic in the UK', *PLoS One*, Vol. 5, No. 12, p.e15626.

Ghani, A.C., Donnelly, C.A., Ferguson, N.M. and Anderson, R.M. (2000) 'Assessment of the prevalence of vCJD through testing tonsils and appendices for abnormal prion protein', *Proc. Biol. Sci.*, Vol. 267, No. 1438, pp.23–29.

Gibbs, C.J. Jr. and Gajdusek, D.C. (1973) 'Experimental subacute spongiform virus encephalopathies in primates and other laboratory animals', *Science*, Vol. 182, No. 107, pp.67–68.

Goldfarb, L.G., Petersen, R.B., Tabaton, M., Brown, P., LeBlanc, A.C., Montagna, P., Cortelli, P., Julien, J., Vital, C., Pendelbury, W.M., Haltia, M., Wills, P.R., Hauw, J.J., McKeever, P.E., Monari, L., Schrank, B., Swergold, G.D., Autilio-Gambetti, L., Gajdusek, D.C., Lugaresi, E. and Gambetti, P. (1992) 'Fatal familial insomnia and familial Creutzfeldt-Jakob disease: disease phenotype determined by a DNA polymorphism', *Science*, Vol. 258, No. 5083, pp.806–808.

Herzog, C., Rivière, J., Lescoutra-Etchegaray, N., Charbonnier, A., Leblanc, V., Salès, N., Deslys, J.P. and Lasmézas, C.I. (2005) 'PrPTSE distribution in a primate model of variant, sporadic, and iatrogenic Creutzfeldt-Jakob disease', *J. Virol*., Vol. 79, No. 22, pp.14339–14345.

Hilton, D.A., Ghani, A.C., Conyers, L., Edwards, P., McCardle, L., Ritchie, D., Penney, M., Hegazy, D. and Ironside, J.W. (2004) 'Prevalence of lymphoreticular prion protein accumulation in UK tissue samples', *J. Pathol*., Vol. 203, No. 3, pp.733–739.

Hope, J. (1999) 'Spongiform encephalopathies: breech-birth prions', *Nature*, Vol. 402, No. 6763, pp.737–739.

Jackson, G.S., Beck, J.A., Navarrete, C., Brown, J., Sutton, P.M., Contreras, M. and Collinge, J. (2001) 'HLA-DQ7 antigen and resistance to variant CJD', *Nature*, Vol. 414, No. 6861, pp.269–270.

Jeffrey, M. and Wells, G.A. (1988) 'Spongiform encephalopathy in a nyala (*Tragelaphus angasi*)', *Vet. Pathol*., Vol. 25, No. 5, pp.398–399.

Kirkwood, J.K., Wells, G.A., Wilesmith, J.W., Cunningham, A.A. and Jackson, S.I. (1990) 'Spongiform encephalopathy in an Arabian oryx (*Oryx leucoryx*) and a greater kudu (*Tragelaphus strepsiceros*)', *Vet. Rec.*, Vol. 127, No. 17, pp.418–420.

Kong, Q., Huang, S., Zou, W., Vanegas, D., Wang, M., Wu, D., Yuan, J., Zheng, M., Bai, H., Deng, H., Chen, K., Jenny, A.L., O'Rourke, K., Belay, E.D., Schonberger, L.B., Petersen, R.B., Sy, M.S., Chen, S.G. and Gambetti, P. (2005) 'Chronic wasting disease of elk: transmissibility to humans examined by transgenic mouse models', *J. Neurosci*., Vol. 25, No. 35, pp.7944–7949.

Kong, Q., Zheng, M., Casalone, C., Qing, L., Huang, S., Chakraborty, B., Wang, P., Chen, F., Cali, I., Corona, C., Martucci, F., Iulini, B., Acutis, P., Wang, L., Liang, J., Wang, M., Li, X., Monaco, S., Zanusso, G., Zou, W.Q., Caramelli, M. and Gambetti, P. (2008) 'Evaluation of the human transmission risk of an atypical bovine spongiform encephalopathy prion strain', *J. Virol*., Vol. 82, No. 7, pp.3697–3701.

Krever, H. (1997) *Final Report: Commission of Inquiry on the Blood System in Canada*, p.1138, The Commission, Ottawa.

Legname, G., Nguyen, H.O., Baskakov, I.V., Cohen, F.E., Dearmond, S.J. and Prusiner, S.B. (2005) 'Strain-specified characteristics of mouse synthetic prions', *Proc. Natl. Acad. Sci.*, Vol. 102, No. 6, pp.2168–2173, USA.

Ligios, C., Sigurdson, C.J., Santucciu, C., Carcassola, G., Manco, G., Basagni, M., Maestrale, C., Cancedda, M.G., Madau, L. and Aguzzi, A. (2005) 'PrPSc in mammary glands of sheep affected by scrapie and mastitis', *Nat. Med.*, Vol. 11, No. 11, pp.1137–1138.

Llewelyn, C.A., Hewitt, P.E., Knight, R.S., Amar, K., Cousens, S., Mackenzie, J. and Will, R.G. (2004) 'Possible transmission of variant Creutzfeldt-Jakob disease by blood transfusion', *Lancet*, Vol. 363, No. 9407, pp.417–421.

Manuelidis, L. (2007) 'A 25 nm virion is the likely cause of transmissible spongiform encephalopathies', *J. Cell. Biochem.*, Vol. 100, No. 4, pp.897–915.

Marsh, R.F., Bessen, R.A., Lehmann, S. and Hartsough, G.R. (1991) 'Epidemiological and experimental studies on a new incident of transmissible mink encephalopathy', *J. Gen. Virol.*, Vol. 72, No. 3, pp.589–594.

Marsh, R.F., Kincaid, A.E., Bessen, R.A. and Bartz, J.C. (2005) 'Interspecies transmission of chronic wasting disease prions to squirrel monkeys (*Saimiri sciureus*)', *J. Virol*., Vol. 79, No. 21, pp.13794–13796.

McGowan, J.P. (1922) 'Scrapie in sheep', *Scott. J. Agric.*, Vol. 5, pp.365–375.

Mead, S., Poulter, M., Uphill, J., Beck, J., Whitfield, J., Webb, T.E., Campbell, T., Adamson, G., Deriziotis, P., Tabrizi, S.J., Hummerich, H., Verzilli, C., Alpers, M.P., Whittaker, J.C. and Collinge, J. (2009) 'Genetic risk factors for variant Creutzfeldt-Jakob disease: a genome-wide association study', *Lancet Neurol.*, Vol. 8, No. 1, pp.57–66.

National Creutzfeldt-Jakob Disease Surveillance Unit (2010) *Variant Creutzfeldt-Jakob Disease, Current Data*, October, available at http://www.cjd.ed.ac.uk/vcjdworld.htm (accessed on 23 January 2012).

Peden, A., McCardle, L., Head, M.W., Love, S., Ward, H.J., Cousens, S.N., Keeling, D.M., Millar, C.M., Hill, F.G. and Ironside, J.W. (2010) 'Variant CJD infection in the spleen of a neurologically asymptomatic UK adult patient with haemophilia', *Haemophilia*, Vol. 16, No. 2, pp.296–304.

Porta, M. and Morabia, A. (2004) 'Why aren't we more ahead? The risk of variant Creutzfeldt-Jakob disease from eating bovine spongiform encephalopathy-infected foods: still undetermined', *Eur. J. Epidemiol.*, Vol. 19, No. 4, pp.287–289.

Prusiner, S.B. (1982) 'Novel proteinaceous infectious particles cause scrapie', *Science*, Vol. 216, No. 4542, pp.136–144.

Saá, P., Castilla, J. and Soto, C. (2006) 'Presymptomatic detection of prions in blood', *Science*, Vol. 313, No. 5783, pp.92–94.

Scientific Steering Committee (2000) *Preliminary Opinion, Oral Exposure of Humans to the BSE Agent: Infective Dose and Species Barrier*, p.53, http://www.ec.europa.eu/food/fs/sc/ssc/out71_en.pdf.

Sneath, P.H. (2004) 'Estimation of the size of the vCJD epidemic', *Antonie Van Leeuwenhoek*, Vol. 86, No. 2, pp.93–103.

Supattapone, S. (2004) 'Prion protein conversion *in vitro*', *J. Mol. Med.*, Vol. 82, No. 6, pp.348–356.

Thomzig, A., Schulz-Schaeffer, W., Wrede, A., Wemheuer, W., Brenig, B., Kratzel, C., Lemmer, K. and Beekes, M. (2007) 'Accumulation of pathological prion protein PrPSc in the skin of animals with experimental and natural scrapie', *PLoS Pathog*., Vol. 3, No. 5, p.e66.

Turner, M.L. and Ludlam, C.A. (2009) 'An update on the assessment and management of the risk of transmission of variant Creutzfeldt-Jakob disease by blood and plasma products', *Br. J. Haematol.*, Vol. 144, No. 1, pp.14–23.

Tyshenko, M.G., ElSaadany, S., Oraby, T., Darshan, S., Aspinall, W., Cooke, R., Catford, A. and Krewski, D. (2011) 'Expert elicitation for the judgment of prion disease risk uncertainties', *JTEH Part A*, Vol. 74, Nos. 2/4, pp.261–285.

Wells, G.A., Konold, T., Arnold, M.E., Austin, A.R., Hawkins, S.A.C., Stack, M., Simmons, M.M., Lee, Y.H., Gavier-Widén, D., Dawson, M. and Wilesmith, J.W. (2007) 'Bovine spongiform encephalopathy: the effect of oral exposure dose on attack rate and incubation period in cattle', *J. Gene. Viro.*, Vol. 88, No. 4, pp.1363–1373.

Wells, G.A., Scott, A.C., Johnson, C.T., Gunning, R.F., Hancock, R.D., Jeffrey, M., Dawson, M. and Bradley, R. (1987) 'A novel progressive spongiform encephalopathy in cattle', *Vet. Rec.*, Vol. 121, No. 18, pp.419–420.

Will, R.G., Ironside, J.W., Zeidler, M., Cousens, S.N., Estibeiro, K., Alperovitch, A., Poser, S., Pocchiari, M., Hofman, A. and Smith, P.G. (1996) 'A new variant of Creutzfeldt-Jakob disease in the UK', *Lancet*, Vol. 347, No. 9006, pp.921–925.

Williams, E.S. and Young, S. (1980) 'Chronic wasting disease of captive mule deer: a spongiform encephalopathy', *J. Wildl. Dis.*, Vol. 16, No. 1, pp.89–98.

Wilson, K. (2007) 'The Krever commission – 10 years later', *CMAJ*, Vol. 177, No. 11, pp.1387–1389.

World Health Organization (2006) *WHO Guidelines on Tissue Infectivity Distribution in Transmissible Spongiform Encephalopathies*, p.53, WHO Press, Geneva, Switzerland, available at http://www.who.int/bloodproducts/TSEREPORT-LoRes.pdf (accessed on 23 January 2012).

Wyatt, J.M., Pearson, G.R., Smerdon, T.N., Gruffydd-Jones, T.J., Wells, G.A.H. and Wilesmith, J.W. (1991) 'Naturally occurring scrapie-like spongiform encephalopathy in five domestic cats', *Vet. Rec.*, Vol. 129, No. 11, pp.233–236.

Yamakawa, Y., Hagiwara, K., Nohtomi, K., Nakamura, Y., Nishijima, M., Higuchi, Y., Sato, Y. and Sata, T. (2003) 'Expert committee for BSE diagnosis, and ministry of health, labour and welfare of Japan, atypical proteinase K-resistant prion protein (PrPres) observed in an apparently healthy 23-month-old Holstein steer', *Jpn. J. Infect. Dis*., Vol. 56, Nos. 5/6, pp.221–222.

Yuan, J., Xiao, X., McGeehan, J., Dong, Z., Cali, I., Fujioka, H., Kong, Q., Kneale, G., Gambetti, P. and Zou, W.Q. (2006) 'Insoluble aggregates and protease-resistant conformers of prion protein in uninfected human brains', *J. Biol. Chem.*, Vol. 281, No. 46, pp.34848–34858.