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EXPERT ELICITATION ON THE UNCERTAINTIES ASSOCIATED WITH CHRONIC WASTING DISEASE

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ABSTRACT

A high degree of uncertainty exists for chronic wasting disease (CWD) transmission factors in farmed and wild cervids. Evaluating the factors is important as it helps to inform future risk management strategies. Expert opinion is often used to assist decision-making in a number of health, science and technology domains where data may be sparse or missing. Using the "Classical Model" of elicitation a group of experts was asked to estimate the most likely values for several risk factors affecting CWD transmission. The formalized expert elicitation helped structure the issues and hence provide a rational basis for estimating some transmission risk factors for which evidence is lacking. Considered judgements about environmental transmission, latency of CWD transmission, management and the species barrier were provided by the experts. Uncertainties for many items were determined to be large highlighting areas requiring more research. The elicited values can be used as surrogate values until research evidence becomes available.

INTRODUCTION

Asking for expert advice on complex scientific issues that have high uncertainty occurs routinely for decision-making as a way to allocate resources and implement appropriate management responses. Usually, the solicitation of expert opinion is conducted in an informal way with experts meeting to hear and discuss evidence, and then attempt to articulate some form of consensus opinion. However, such an unstructured process may be influenced by experts who are more persuasive, forceful or who appear more certain in their answers (Langfeldt, 2006; Tversky and Kahneman, 1974). The approach can give rise to the loss of other opinions that may have equally valid value for a fully complete decision. To improve the consensus process and minimize bias in expert group decision-making a structured expert judgement elicitation method can be used. In this approach expert judgements are treated as scientific data using a formal process with transparent methodological rules which then can be statistically quantified. The structured expert elicitation method due to Cooke (1991) has been used previously in many studies spanning different scientific disciplines. It produces good, feasible outcomes for problems where expert opinion is the most comprehensive and sometimes only source of available information to quantify levels of uncertainty (Cooke and Goossens, 2008).

Chronic wasting disease (CWD) is a progressive, fatal, neurodegenerative disease affecting elk, mule deer and white-tailed deer. The disease belongs to a larger group of related diseases called transmissible spongiform encephalopathies (TSEs) and includes: bovine spongiform encephalopathy (BSE) in cattle; scrapie in sheep and goats; exotic ungulate encephalopathy (EUE) in Nyala and greater kudu; transmissible mink encephalopathy (TME) in mink; feline spongiform encephalopathy (FSE) in cats; and Creutzfeldt-Jakob Disease (CJD), fatal familial insomnia (FFI), kuru, and Gerstmann-Sträussler-Scheinker syndrome (GSS) in humans (Imran and Mahmood, 2011). The agent responsible for the occurrence of TSEs is widely believed to be a misfolded form of the prion protein (Prusiner, 1998).

Properly folded prions expressed in the brain and other tissues can be induced to misfold so that the tertiary structure is altered. The newly, misfolded prions are also capable of interacting with normal prion proteins *in vivo*, perpetuating additional conversions to the misfolded form (Cashman and Caughey, 2004).

Several risk factors and areas of uncertainty exist for CWD that require expert evaluation. Questions regarding environmental transmission, latency of transmission, disease management and the species barrier may be informed by expert opinion. The areas chosen possess high degrees of uncertainty due to a dearth of available peer review literature.

METHODS

Expert advice is often used to inform science-based decision-making. Using a structured method to elicit a variety of opinions from experts is helpful to explore the issues and generate effective options. In this context, seeking a "rational consensus" refers to a group decision-making process in which a formalized approach is followed, based on performance-based scoring rule optimization. The Cooke method of weighting expert opinion is the only one currently available that has the attribute of genuine empirical control on the resulting individual scores (Cooke, 1991).

The CWD expert elicitation workshop used the Cooke Classical Model and the EXCALIBUR software package (© TU Delft, Delft, the Netherlands; available freely from http://risk2.ewi.tudelft.nl/oursoftware/6-excalibur). The workshop was held on May 16 2011 in Montreal, Quebec, Canada. More than 20 people attended the elicitation workshop, and 14 participated actively in the elicitation exercise (one expert participated in the workshop by teleconference and submitted their elicitation judgements via e-mail). For reporting the findings of the elicitation exercise, experts' answers were anonymized with each expert being identified by a number

only and not by name. The experts invited to participate in this exercise were chosen for their knowledge of CWD and prion diseases based on their contributions to the peer reviewed scientific literature. Experts were also identified through a snow-ball recruitment process by through referral by other experts consulted during the selection process. Identified experts were then assessed based on peer review scientific literature publications and involvement on CWD expert panels."

The EXCALIBUR procedure merges experts' subjective probabilities based on mathematical and statistical theory, and is therefore more rigorous than other, less formalized, approaches. The aim is to combine several distributions, given by different experts, into a single distribution that is representative of the entire spectrum of their opinions. Aggregating the answers can use either simple equal weights (Equal weights solution) which is an arithmetic combination of the distributions provided by the experts or it can use a performance-based weighting scheme based on expert calibration (labelled as 'Pooled' in the accompanying figures). The aim of the latter is to create a basis for achieving rational consensus. Since each individual has their own subjective probability, it is necessary to find a way of achieving this convergence.

The expert elicitation procedure asks the individuals in the expert group (where E is the number of experts) to assess a set of n variables $\{X_1, ..., X_n\}$ within their field of knowledge. The first questions are 'seed items' that are taken from the peer review literature and the true values are known. Each expert expresses his or her views as uncertainty distributions with quantitative support across selected inter-quantile ranges. The true values or the realizations are denoted as $\{x_1, ..., x_n\}$ of the variables $\{X_1, ..., X_n\}$. The experts' responses to these seed items are treated as statistical hypotheses and are scored with regard to the statistical likelihood that their distributions over the set of questions are consistent with the observed or measured results based on a chi-squared test. From this each

expert is given a calibration score, and they are also scored by a measure of informativeness compared to a given background distribution, usually a uniform or log-uniform distribution, (information score).

for instance, expert e was asked to give their best estimate or guess (the median $x_{50,i,e}$) and the 5% and 95% confidence bounds $x_{5,i,e}$ and $x_{95,i,e}$, respectively, for each of the i variables $(i = 1, 2, ..., n)$. These percentiles split up the variable's range into 4 intervals $I_{1,i,e} \equiv [m_i, x_{5,i,e}]$, $I_{2,i,e} \equiv (x_{5,i,e}, x_{50,i,e}]$, $I_{3,i,e} \equiv (x_{50,i,e}, x_{95,i,e}]$, and $I_{4,i,e} \equiv (x_{95,i,e}, M_i]$ with 5%, 45%, 45%, and 5% confidence level in each interval, respectively, where the intrinsic range $[m_i, M_i]$ of variable i is the smallest interval such that $m_i < x_i < M_i$ and $m_i < x_{q,i,e} < M_i$ for all $q = 5, 50, 95$ and $e = 1, 2, ..., E$. The intrinsic range is also calculated based on the physical properties of the variable, *e.g.,* $[m_i, M_i] \equiv [0, 1]$ if the variable is a probability.

Expert e is considered to be well-calibrated if, and only if, the intervals $I_{j_1,1,e}, ..., I_{j_n,n,e}$ happen to contain the realizations $x_1, ..., x_n$ that are drawn independently according to the probability distribution $p = (p_1, p_2, p_3, p_4) = (.05, .45, .45, .05)$ with $\Pr(\text{drawing } I_{j,i,e}) = p_j$. The hypothesis that expert e is well-calibrated is given by H_e. In order to determine the calibration score for expert e, the proportion of times the variables' values $\{x_1, ..., x_n\}$ lie in one of the 4 intervals $I_{j,i,e}$ by

$$s_j(e) := \frac{1}{n} \sum_{i=1}^{n} \chi_{I_{j,i,e}}(x_i) \quad ; j = 1, 2, 3, 4 \text{ and } e = 1, 2, ..., E \tag{1}$$

where $\chi_I(x) = 1$ if $x \in I$ and zero otherwise. Let $s(e) = (s_1(e), s_2(e), s_3(e), s_4(e))$ be the probability distribution for expert e $(e = 1, 2, ..., E)$ is calculated.

The relative information of S with respect to the background distribution P is defined by:

$$\mathrm{I}(S \mid P) = \sum_{i=1}^{4} S_i \ \ln(\frac{S_i}{P_i}) . \qquad (2)$$

The amount $\chi_3^2 = 2n \ \mathrm{I}(S \mid P)$ is chi-squared distributed with 3 degrees of freedom (Cooke, 1991). The calibration score $\Theta(e)$ of expert e is the *p-value* of the statistical test of hypothesis that the expert is well-calibrated, that is

$$\Theta(e) = \Pr(\chi_3^2 > \chi^2(e) \mid H_e) \qquad (3)$$

where $\chi^2(e) = 2n \sum_{i=1}^{4} s_i(e) \ \ln(\frac{s_i(e)}{p_i})$.

On the other hand, the information score evaluates the extent of concentration of the elicited distribution with respect to some background distribution. For each variable i, we use the uniform distribution g_i on $[L_i, U_i]$ as the background distribution where L_i and U_i are found via the k % overshoot rule (Cooke, 1991)

$$L_i = m_i - \frac{k}{100} \ (M_i - m_i)$$

and

$$U_i = M_i + \frac{k}{100} \ (M_i - m_i)$$

where k is chosen by the analyst. The continuous version of the relative information defined in equation (2) is given by

$$\mathrm{I}(f \mid g) = \int_L^U f(x) \ln\left(\frac{f(x)}{g(x)}\right) dx. \tag{4}$$

for any two probability density functions f and g. We characterize the information score $\Lambda(e)$ for expert e by the average relative information for all of the variables

$$\Lambda(e) = \frac{1}{n}\sum_{i=1}^{n} \mathrm{I}(f_{i,e} \mid g_i) \tag{5}$$

where $f_{i,e}$ is the minimal informative density function with respect to the prior g_i such that $F_{i,e}(x_{q,i,e}) = q/100$ and where $F_{i,e}$ is the cumulative distribution function of $f_{i,e}$. In the case of a uniform prior g_i on $[L_i, U_i]$, the density function $f_{i,e}$ is a step function given by

$$f_{i,e}(x) = \frac{.05}{x_{5,i,e} - L_i}\chi_{I_{1,i,e}}(x) + \frac{.45}{x_{50,i,e} - x_{5,i,e}}\chi_{I_{2,i,e}}(x) + \frac{.45}{x_{95,i,e} - x_{50,i,e}}\chi_{I_{3,i,e}}(x) + \frac{.05}{U_i - x_{95,i,e}}\chi_{I_{4,i,e}}(x) \tag{6}$$

for $-\infty < x < \infty$ where here $I_{1,i,e} \equiv [L_i, x_{5,i,e}]$, $I_{2,i,e} \equiv (x_{5,i,e}, x_{50,i,e}]$, $I_{3,i,e} \equiv (x_{50,i,e}, x_{95,i,e}]$, and $I_{4,i,e} \equiv (x_{95,i,e}, U_i]$.

Therefore,

$$\mathrm{I}(f_{i,e} \mid g_i) = \ln(U_i - L_i) + .05\ln\left(\frac{.05}{x_{5,i,e} - L_i}\right) + .45\ln\left(\frac{.45}{x_{50,i,e} - x_{5,i,e}}\right) + .45\ln\left(\frac{.45}{x_{95,i,e} - x_{50,i,e}}\right) + .05\ln\left(\frac{.05}{U_i - x_{95,i,e}}\right) \tag{7}$$

for all i from which the information score $\Lambda(e)$ follows.

After these two performance measures are calculated they are pooled to form a weight for each expert termed the expert's 'calibration score'. These weights are constructed to strictly proper scoring rules in that the experts receive their maximal expected weight by, and only by, stating their true degrees of belief over all the items. The weights are defined by:

$$w_\alpha(e) := \chi_{(\alpha,\infty)}(\Theta(e)) \times \Theta(e) \times \Lambda(e) \qquad (8)$$

Where the characteristic function $\chi_{(\alpha,\infty)}(\Theta(e))$ gives zero weights to the opinions of those who have a *p-value* less than α. This α is not the classical significance level and is to be determined in maximizing the combined score in the following step. In this scoring scheme, statistical accuracy (calibration) strongly dominates informativeness and an expert cannot compensate for poor statistical performance.

When the calibration score is determined the experts are then elicited individually regarding their uncertainty judgments in relation to questions of interest (Target Items) for which values are sparse or missing due to lack of published peer review research. Target Items are within their domain of CWD expertise. The previously determined performance-based calibration scores are applied to the individual responses to these target questions to obtain weighted poolings of the group of experts' uncertainty distributions $h_{i,e}$ giving what Cooke and Goossens (2008) call the 'decision maker' (DM). The DM can be expressed in several forms; the following example of the weighted average is representative of the DM used during the EXCALIBUR analysis:

$$DM_\alpha(i) = \frac{\sum_{e=1}^{E} w_\alpha(e)\ h_{i,e}}{\sum_{e=1}^{E} w_\alpha(e)}.$$

The parameter α is found such that the weight $w_\alpha(DM_\alpha) = \Lambda(DM_\alpha) \times \Theta(DM_\alpha)$ is a maximum.

Analyses using EXCALIABUR were performed on both expert elicitation groups' answers. Result outputs from EXCALIBUR were plotted graphically to display individual best answers with low and high uncertainty ranges.

In brief, the EXCALIBUR, expert weighting for the performance weights solution is determined from the participating experts' responses to a set of 'calibration' or seed questions. These calibration questions and answers are drawn from existing peer reviewed scientific literature. While the realization values are known to the facilitator *a priori*, the experts are not expected to know these values but are expected to be able to judge suitable credible intervals that contain them. All 14 experts provided responses to the small number of seed items used for calibration and performance weighting (data not shown).

For the target questions where values and/or uncertainties are not yet established from data or research all 14 experts provided responses to the 13 questions. No re-calculations of the optimal weighted solutions in EXCALIBUR were needed for the elicitation group as the top weighted experts completed all of the target questions. The expert judgements for each target item provide five data points (the minimum, 5th percentile, median, 95th percentile, and maximum estimate). When pooled jointly, the empirical distribution across experts is used to represent the uncertainty distribution as a nonparametric smoothed cumulative distribution that can be used in a probabilistic risk assessment. The 90% uncertainty interval, spanning the 5th to 95th percentiles, is referred to as the 'credible range'. A detailed description of the mathematical weighting scheme is provided in Cooke (1991). The expert elicitation method has been used previously for bovine spongiform encephalopathy uncertainties with good results (Tyshenko et al., 2011; Tyshenko et al., 2012). For further details about the method and equations describing the expert weighting we refer readers to Cooke (1991), Appendix 1 in Tyshenko et al. (2011), and the summary in Tyshenko et al. (2012).

RESULTS

Expert responses to the 13 target items are shown in Figures 1 – 13 (and also summarized in Table 1). For each question the 14 individual expert responses (Exp. 1-14) are shown with the central value representing the median of the uncertainty distribution for that expert and the upper and lower limits of the ranges shown corresponding 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 ('Pooled') and the equal weights ('Equal') solutions. 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 shown in Figures 1-13 and summarized in Table 1.

[Insert Table 1 here]

Analysis of Target Questions Regarding Environmental Transmission

Target Question 1 (assume a 10 year time frame): What is the likelihood that CWD can transmit from infected cervids (deer, elk, or moose) to caribou through environmental routes of exposure in the wild to CWD (0-100%)?

The Pooled solution credible interval is significantly narrower than the Equal weights solution for this question, implying the experts with higher performance-based calibration scores had greater certainty in their response. The Pooled solution suggests about a 1-in-50 chance of caribou being infected from other cervids in 10 years, with an upper bound of about 1-in-4 (Figure 1).

[Insert Figure 1 here]

Target Question 2 (assume a 50 year time frame): What is the likelihood that CWD can transmit from infected cervids (deer, elk, or moose) to caribou through environmental routes of exposure in the wild to CWD (0-100%)?

Question 2 is identical to the first question but extends the time frame to consider the next 50 years. The Pooled solution credible interval is narrower than the Equal Weights (Equal) solution, again implying greater certainty in responses from experts with higher performance-based calibration scores. The solution indicates about a 1-in-14 chance of caribou being infected from other cervids within 50 years, with an upper bound probability of 60% suggesting that transmission to caribou in the wild, if it occurs, would not be an unanticipated event (Figure 2).

[Insert Figure 2 here]

Considering Questions 1 and 2 the experts believe that CWD will continue to spread over time to a wider geographical area and eventually move into the caribou host range with a chance of CWD transmission to this species. United States Geological Survey (USGS) surveillance data from the late 1960s to present shows a slow but continuous spread of CWD geographically, as reflected by ongoing cervid surveillance program testing results (USGS, 2013). The migratory and herd ranges of caribou overlap with mule deer, white-tailed deer, elk and moose ranges in both provinces in Canada where CWD is established (Alberta and Saskatchewan) (Happ et al., 2007; Li et al., 2007). Analysis of the caribou genotype has revealed that the caribou prion alleles are nearly identical to wapiti, moose, mule deer and white-tailed deer (Happ et al., 2007; Li et al., 2007). It is established that white-tailed deer, mule deer and elk can acquire CWD in the wild (Miller and Williams, 2004; Williams and Miller 2002). Reindeer are a close relative of the caribou and oral inoculation of CWD prions in reindeer resulted in CWD transmission (Mitchell et al., 2012). However, one allele, the S138N single nucleotide polymorphism (SNP) has been linked with disease resistance in fallow deer (Hamir et al., 2008a; Rhyan

et al., 2011); this S138N allele was found in 50% of the caribou from three sampled herds when analysed by Happ et al., (2007) and it may have the potential to confer some protection against CWD infection.

Target Question 3: How long do you think CWD prions can persist in clay-enriched soil and be infectious for other animals (years)?

The Pooled and Equal Weights solution credible intervals are very similar and extend from less than 1 year to more than 250 years indicating considerable uncertainty in estimating prion survival in clay-enriched soils. The majority of the experts (78.5%) indicated that their best estimate was that prions may persist in clay-enriched soil for lengthy time periods (between 10 and 100 years) (Figure 3).

[Insert Figure 3 here]

Different types of soil can act as environmental reservoirs for infective prions which could contribute to the horizontal transmission of CWD (Saunders et al., 2012a). Clay-enriched soil content increases the odds of CWD infection (Johnson et al., 2007; Walter et al., 2011). Prions bound to inorganic micro-particles found in soils remain bio-available if ingested and retain infectivity for long periods of time (Johnson et al., 2006; Johnson et al., 2007; Saunders et al., 2011b; Seidel et al., 2007). Cervid behaviours tend to support potential exposure for disease transmission by soil since it is estimated that deliberate and incidental soil consumption contributes to at least two percent of a deer's diet by mass (Schramm et al., 2006). In addition, prions are resistant to rumen digestion and remain infective (Saunders et al., 2012b). Walter et al. (2011) insist that soil clay content and related environmental properties deserve greater attention when assessing the risk of prion disease outbreaks and management, both on farms and in the wild.

Target Question 4: How long can CWD prions persist in soil enriched with manganese oxides (years)?

Soil has been suggested as a reservoir of and vector for prion infectivity (Schramm et al., 2006). The influence of soils on prion fate in the environment is thought to be complex and abiotic soil components may affect the stability of prions if present. Some common minerals, serine proteases (found in lichens), ultra-violet light with ozone and certain soil conditions can act to degrade prion proteins and reduce infectivity in soils (Ding et al., 2013; Johnson et al., 2009; Johnson et al., 2011; Russo et al., 2009; Saunders et al., 2011a, 2011b). Manganese oxides (MnO_2) are known to be among the strongest natural oxidants in soils that can degrade organic molecules. Russo et al. (2009) showed that manganese oxides can act to fully degrade prions and other proteins in soil.

The Pooled results for Target Question 4 are similar to those obtained for Question 3, except that two experts' distributions now encompass very short survival times as well as extending out to about 100 years. Comparing questions 3 and 4, the Pooled expert opinion found the persistence time of prions in soil to be similar, either clay-enriched (7.21 years, range 0.51 to 287.5 years) or manganese-enriched (7.16 years, range 0.01 to 202.2 years). The answers show large uncertainty ranges of 200 to nearly 300 years, which suggests the experts collectively are very uncertain about what the true value may turn out to be (Figure 4).

[Insert Figure 4 here]

The comparable answers derived for Target Questions 3 and 4 may appear to be incongruous but available research known to the experts provides a reasonable explanation. Russo et al. (2009) investigated manganese oxide degradation of prions and found that under experimental conditions δ-MnO_2-mediated prion degradation occurred over relatively short time periods (several hours to a few

days) and reduced prion-converting activity by at least a factor of 10,000 fold. Degradation appeared to be influenced greatly by pH and substantial PrP^{TSE} remained following reactions at pH values ≥ 6. Moreover, decreased reactivity toward organic molecules over the course of MnO_2 reactions was noted. The similarity in times given by the experts whether soil was either clay-enriched or manganese oxide-enriched signifies that experts likely considered additional factors when answering Target Question 4, including: continual prion loading in "hotspot" areas over longer time periods (decades) compared to the more rapid exhaustion of manganese oxide reactions in soil (within hours to days); variable geographic manganese oxide concentrations; low manganese oxide concentration in some soil types and pH effects.

Target Question 5: What is the likelihood that CWD can be transmitted through a still water source (0 - 100%)?

The lack of evidence to support CWD transmission in the environment through standing water (on farms or in the wild) appears to have split the expert group into three schools of thought: six of the experts opted for relatively high probabilities that standing water can act as a vector while five other experts believed the probability of transmission was much lower. The remaining three experts choose a 50-50 probability with wide uncertainties. The Pooled and Equal Weights solutions produce very different medians, but both distributions span virtually the whole range of possible values. The Pooled expert value (14.52%) suggests the experts believe there is a chance that standing water can act as a vector (Figure 5).

[Insert Figure 5 here]

Results by Nichols et al. (2009) would have been known to the experts who determined that the large uncertainty surrounding water as a prion vector was due to the sensitivity limitations of conventional assays that do not detect environmental prion loads in soil and water. Nicols et al. (2009) used the serial protein misfolding cyclic amplification (sPMCA) assay to amplify a 1.3×10^{-7} fold dilution of CWD-infected brain homogenate 'spiked' in water samples. Using this validated assay for water samples, CWD agent was detected in one environmental water sample from a CWD enzootic area collected at a time of increased water run-off from melting winter snow. Bioassays indicated that the PrP^{CWD} detected in the collected water samples was below infectious levels. The experts' Pooled answer with wide credible range intervals shows a high degree of uncertainty whether standing water can act as a disease transmission vector. It is possible that the current finding stems from the knowledge gap surrounding environmental transmission through standing water (as opposed to snow melt run off). Further work would be needed to better inform judgements for this question.

Analysis of Target Questions Regarding the Latency Period in CWD Transmission (Q.6 to Q.8)

Target Question 6: For what proportion of the incubation period are cervids shedding prion infectivity in saliva (0-100%)?

[Insert Figure 6 here]

Target Question 7: For what proportion of the incubation period are cervids shedding prion infectivity in feces (0 - 100%)?

[Insert Figure 7 here]

Target Question 8: For what proportion of the incubation period are cervids shedding prion infectivity in urine (0 - 100%)?

[Insert Figure 8 here]

Questions 6-8 asked the experts to judge the proportion of the incubation period likely to shed prions in saliva, urine or feces. The expert judgements appear to fit well with what is known about prion disease etiology. The incubation period before clinical symptoms has been estimated for various cervid species and the susceptibility of elk, white-tailed deer and mule deer to CWD is closely associated with their PRNP genotype. Mule deer have incubation times of 14 to 18 months, post-infection, depending on the S225F codon genotype (Fox et al., 2006). White-tailed deer exhibit post-infection incubation periods ranging from 16 to 23 months depending on the G96S genotype, this polymorphism is reported to be over-represented in CWD-infected deer (Hamir et al., 2008b; Johnson et al., 2003). Finally, elk display incubation times ranging from 23 to 61 months post-infection with homozygous M132 appearing more susceptible to CWD (Hamir et al., 2006; O'Rourke et al., 2007).

Considering the amount of time that prions are secreted in saliva, Target Question 6 results show the Pooled and Equal Weights solutions have very wide uncertainties associated with them. The median value of 73% suggests that the experts estimated that prion shedding in cervid saliva may take place for a significant portion of the incubation period, but this inference is not held with conviction by any one expert (Figure 6). Previous work by Mathiason et al. (2006) may have informed the experts' judgement as saliva from CWD positive deer transmitted prion disease to other deer within 12 months following oral challenge.

Considering the amount of time that prions are excreted in feces, results for Target Question 7 show both the Pooled and Equal Weights solutions possess very wide uncertainties associated with them. The median value of 63% suggests that the experts estimated that prion shedding in feces occurs for the majority of the incubation period (Figure 7). Experimental oral infection of deer showed that prion accumulation progresses rapidly with widespread involvement of lymphatic tissues within 90 days post-infection (prion deposits are detectable in Peyer's patches, ileocecal lymph nodes, retropharyngeal lymph node and tonsils) (Sigurdson et al., 1999). Later tissue involvement includes the central and peripheral nervous system, the endocrine system, and eventually cardiac tissues at terminal stages (Jewell et al., 2006; Spraker et al., 2002). In one study, mule deer incubating CWD after oral challenge did not show prion infectivity in feces within the first 3–4 months post inoculation but prion infectivity was detected after 9 months through to clinical disease at 16 to 20 months (Tamgüney et al., 2009).

Considering the amount of time that prions are shed in urine, Target Question 8 results show the median value given by the expert Pooled solution is shorter than either saliva or feces at 38% or just over one third of the incubation time (Figure 8). There is evidence that comorbid, moderate nephritis can result in urine with prion agent detectable by sPMCA assay and transmission of CWD-infectivity by mouse bioassay (Haley et al., 2009). The reduced amount of prion infectivity detectable in urine (Gonzalez-Romero et al., 2008) and the expert judgement of a shorter time frame for prion excretion in urine suggests other excreta (saliva and feces) may be more significant for transmission and environmental contamination.

CWD prions have been detected in saliva, urine and feces of asymptomatic deer (Haley et al., 2009; Mathiason et al., 2006; Tamgüney et al., 2009). Experts appear to believe that excreta can contain biologically relevant amounts of prion infectivity that could support the horizontal spread of CWD through direct animal contact or environmental contamination. The estimates of the length of time that

prions are shed via these three routes appear to have been very difficult to assess by the experts as evidenced by the wide range estimates. The uncertainty reflected by the range estimates is not surprising since the duration of both asymptomatic and clinical disease phases of CWD can be highly variable.

Analysis of Target Questions Regarding CWD Control and Management (Q.9 to Q.11)

Target Question 9: What is the likelihood that an effective treatment against CWD will be available for captive cervids in the next 10 years (0 - 100%)?

During the elicitation exercise an "effective treatment" was deemed to be a vaccine that could be administered to captive cervids. The Pooled solution credible interval is narrower than the Equal Weights distribution, with a lower median and less skew to greater probability. One expert (Exp. 12) is more hopeful than the rest of the group that a vaccine will be available within the next decade. The Pooled result estimates there is about a 1-in-25 chance that an effective CWD vaccine will become available within the next 10 years. Rather than the scientific challenge, this pessimism may be due to the reality of vaccine development which is a lengthy, complex process often lasting more than a decade involving prolonged phases of animal testing and regulatory approval (Figure 9).

[Insert Figure 9 here]

Target Question 10: What is the likelihood that CWD infection is transmitted from wild to farmed cervids (0-100%)?

This question was answered with a very clear response by the expert group. The experts believe that it is almost certain that CWD infection is transmitted from wild to farmed cervids (98%). Only one expert (Exp. 12) appears less confident with a 60% central value that transmission between wild and

farmed cervids can occur. The Pooled solution credible interval is narrower than the Equal Weights solution, reinforcing the strength of opinion for a high probability that this transmission route is viable. Two-way transmission of CWD between wild and free-ranging farmed cervids is believed to occur due to animal contact along fence lines (Williams et al., 2002; Williams and Miller, 2003). Using track plots and motion-activated video it has been determined that interactions through game farm fences between captive and wild cervids (mule deer, white-tailed deer, and Rocky Mountain elk) do occur. Factors affecting the number of interactions at fence boundaries included stocking rates (animal density), the proximity of males to females, feeding procedures, human activity along fence perimeters and types of fencing (VerCauteren et al., 2002) (Figure 10).

[Insert Figure 10 here]

Target Question 11: What is the relative importance of social/behavioural (direct contact) vs. environmental transmission in the spread of CWD in wild cervids (where X=1 means equally important, X<1 means environmental more important, X>1 means environmental less important]?

This question is formulated in terms of a ratio, and the experts' responses are plotted on a log scale. The Equal Weights solution has a very wide credible interval due, in large part, to two experts (Exp. 8 and 9) who indicate that social/behavioural factors are far stronger than environmental factors in the spread of wild cervid CWD, with weaker support from experts 4 and 6. Expert 1, 3, and 14 indicated views for the opposite tendency, while the remainder are balanced about unity. The Pooled distribution is skewed towards environmental factors being more important, but has a median value close to unity with a wide credible interval, reflecting major and varying uncertainty on this topic within the expert group (Figure 11).

[Insert Figure 11 here]

The mechanisms of CWD transmission are thought to occur horizontally by direct contact and indirectly from environmental sources; although the exact mechanisms for environmental transmission are not well understood. Existing evidence shows support for both direct contact and environmental transmission. On the one hand, deer behaviours such as licking, nose to nose contact, shared water sources and communal food sources may allow for prion transmission through direct contact with body fluids (saliva, feces and urine). Cohabitation of naive and infected deer resulted in transmission of CWD (Miller et al., 2004). On the other hand, environmental contamination as a factor for transmission is supported by several examples. An infected deer carcass left in a pasture for two years was a source of CWD to infect other deer (Miller et al. 2004). Similarly, continual exposure of confined, uninfected deer to pasture previously inhabited by infected deer also resulted in CWD transmission (Miller et al., 2004). Environmental transmission in naïve captive deer occurred when exposed to water, feed buckets, and bedding used previously by CWD-infected deer (Mathiason et al., 2009). The multiple routes of transmission for both social and environmental transmission that needed to be considered by the experts when answering this question may account for the resulting median value.

Analysis of Target Questions Regarding the CWD Species Barrier (Q.12 and Q.13)

Target Question 12: What is the likelihood that CWD can transmit from cervids to humans through oral consumption of meat (containing peripheral nerves) contaminated with CWD prions (0 - 100%)?

The Pooled solution credible interval is substantially narrower than that given by Equal Weights solution and the median value probability is much smaller, representing a chance of about 1-in-1,000. Experts who indicated a significant probability that CWD transmission to humans could occur under the stipulated conditions generally expressed their judgements with very wide uncertainty bounds (Figure

12). The finding of just a 0.09% likelihood of transmission from meat comes as no surprise as there have been no reports of CWD-like disease among individuals who have consumed venison from CWD enzootic areas (Belay et al., 2004). It is known that CWD prions are found in skeletal muscle (Angers et al., 2006) and many tissues of an infected animal including the central nervous system, cardiac muscle, fat, several endocrine glands, several organs, and peripheral nervous tissues (Sigurdson 2008). Transgenic mice expressing human PrP inoculated with elk CWD brain inocula failed to develop disease (Kong et al., 2005). Tamgüney et al. (2006) also reported that transgenic mice over-expressing human PrP did not develop prion disease after inoculation with CWD prions from elk or deer brain inocula.

[Insert Figure 12 here]

Target Question 13: If CWD is transmissible to humans, what is the likelihood that the syndrome will resemble that of a known clinico-pathological phenotype of human prion disease (0 - 100%)?

A previous study investigating a causal link between CWD of deer and elk with Creutzfeldt-Jakob disease cases in humans postulated that transmission of CWD to humans might clinically manifest symptoms very similar to CJD. The investigators reviewed "unusual" cases of CJD that occurred among persons with an increased risk from exposure to potentially infected CWD deer or elk meat. No causal linkage was established suggesting the risk of transmission to humans is quite low (Belay et al., 2004). Several transgenic mice studies expressing human and cervid prion protein show that a significant species barrier exists between cervids and humans (Belay et al., 2004; Kong et al., 2005; Sandberg et al., 2010; Tamgüney et al., 2006; and Wilson et al., 2012).

The experts answered Target Question 13 with wide uncertainty regarding the likelihood that a human form of CWD would resemble a known phenotype of human prion disease. While the Pooled median value suggests the experts acknowledge CWD in humans, if it occurred, would display prion-like pathology, the wide credible interval range shows they are very uncertain that it would resemble an

existing phenotype. During discussion the experts found the current question difficult to answer as it was assumed, from the previous question, that human infection by CWD agent was not a likely possibility. Due to the uncertainty of the expert group there is little information to be extracted from the responses (Figure 13). Further elicitation and discussion would be needed to clarify this answer.

[Insert Figure 13 here]

CONCLUSION

In the present exercise, nearly all of the Target Question solutions have large credible range intervals associated with them, indicating extensive uncertainty among the 14 experts in relation to the questions posed. Notably, the Equal Weights solution spreads for several questions tended to be almost identical to those for the Pooled solutions; this is interpreted not as a failure of the elicitation but more a demonstration of the extent of scientific uncertainty that exists related to many of the issues surrounding CWD infection processes, transmission and risk factors.

Knowledge gaps appear to exist in relation to several of the questions posed to the experts. For example, the likelihood that, if CWD is transmissible to humans, the ensuing set of symptoms will resemble that of a known clinico-pathological phenotype of human prion disease (Target Question 13) provided little consensus and the experts appeared to have difficulty judging this question.

Target Question 5 (What is the likelihood that CWD can be transmitted through a standing water source?) appeared to split the expert group into three schools of thought on the issue. The Pooled and Equal Weights solutions produced quite different median values, while the distributions spanned wide, and over-lapping, ranges of possible values. Target Question 11 yielded a similar result with the expert group split into three subgroups showing that the relative importance of social versus environmental

transmission risk was difficult to assess given the lack of available research evidence available on the topic. This may be a case where re-visiting the question with more discussion and a re-elicitation of views might have reduced the divergence. However, it is also possible that the current knowledge gap on this topic (and others like it) is substantial, and further research would be needed to better inform judgements.

While, the elicitation produced apparent null outcomes on some questions, in the context of assessing our present knowledge base such findings are themselves informative since the questions would not have been posed to the expert group for consideration had the relevant issues been clear-cut. At the very least the questions highlight areas needing further research.

The group's responses to certain questions (Target Questions 6-8) can provide some guidance for determining the amounts and timing of prion shedding which is important for designing appropriate decontamination and management strategies for cervid farms. Expert judgement for the persistence of prions in soil and the transmission through water with modulating effects of clay and minerals (Target Question 3, 4 and 5) are similarly important for managing identified CWD enzootic hotspots. The experts' judgements can help provide proxy variables for those attempting to model environmental loading and disease transmission.

In contrast, Target Question 10 displayed a notable agreement among the experts. From the experts' responses it seems almost certain that CWD infection is believed to be transmitted from wild to farmed cervids or *vice versa*. The judgement on this issue is supported by research into horizontal transmission between cervids. Such information can be helpful in revisiting fence-line management on cervid farms.

The present structured expert elicitation for CWD uncertainties should be regarded as an initial attempt to identify where significant knowledge gaps exist, to quantify related uncertainties, and to

identify issues and factors that might be amenable to targeted research or further work. It is hoped that the findings on CWD will provoke new lines of thinking for management and prompt new ideas about research topics that could be pursued to remediate the knowledge gaps identified by this elicitation exercise.

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Figures

FIGURE 1. Performance weights solution (Pooled) and equal weights solution (Equal) are indicated above the 14 individual, anonymized expert responses (Exp. 1 -14) for Target Question 1 that asked: What is the likelihood that CWD can transmit from infected cervids (deer, elk, or moose) to caribou through environmental routes of exposure in the wild to CWD (0-100%), assuming a 10 year time frame? The individual expert responses and pooled results are shown with the central value representing the median of the uncertainty distribution for that expert and the upper and lower limits of the ranges shown corresponding to the 5th and 95th percentiles of the uncertainty distribution for that expert (Exp. 1-14, triangles; Equal result, stars; Pooled result, circles).

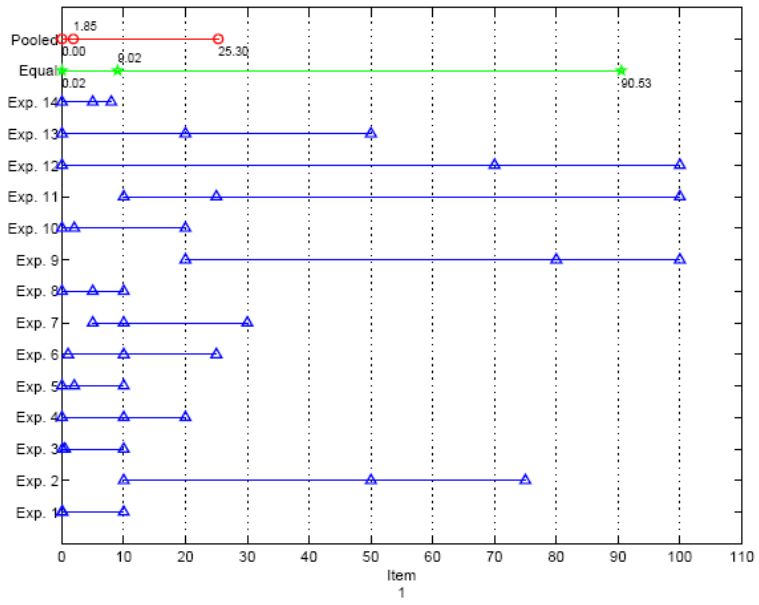


FIGURE 2. Performance weights solution (Pooled) and equal weights solution (Equal) are indicated above the individual, anonymized 14 expert responses (Exp. 1 -14). To Target Question 2 that asked: What is the likelihood that CWD can transmit from infected cervids (deer, elk, or moose) to caribou through environmental routes of exposure in the wild to CWD (0-100%), assuming a 50 year time frame? The individual expert responses and pooled results are shown with the central value representing the median of the uncertainty distribution for that expert and the upper and lower limits of the ranges shown corresponding to the 5th and 95th percentiles of the uncertainty distribution for that expert (Exp. 1-14, triangles; Equal result, stars; Pooled result, circles).

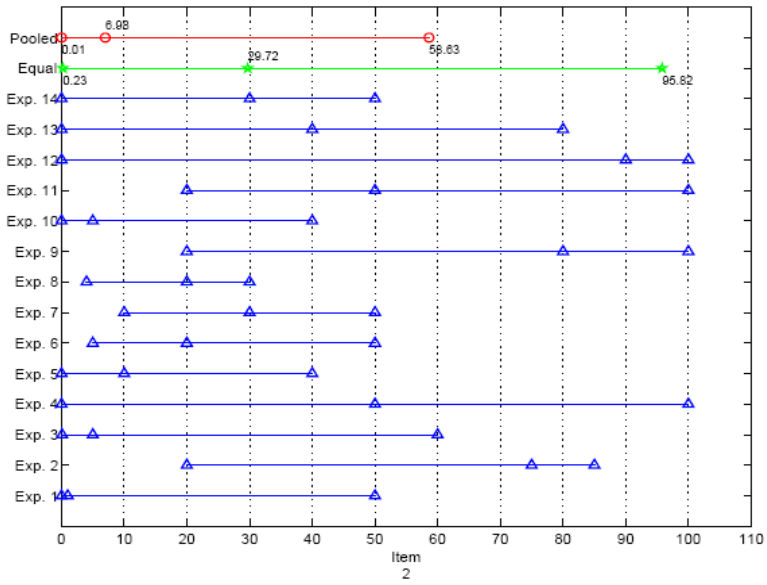


FIGURE 3. Performance weights solution (Pooled) and equal weights solution (Equal) are indicated above the individual, anonymized 14 expert responses (Exp. 1 -14) for Target Question 3 that asked: How long do you think CWD prions can persist in clay-enriched soil and be infectious for other animals (years)? A Log scale was used for time estimates. The individual expert responses and pooled results are shown with the central value representing the median of the uncertainty distribution for that expert and the upper and lower limits of the ranges shown corresponding to the 5th and 95th percentiles of the uncertainty distribution for that expert (Exp. 1-14, triangles; Equal result, stars; Pooled result, circles).

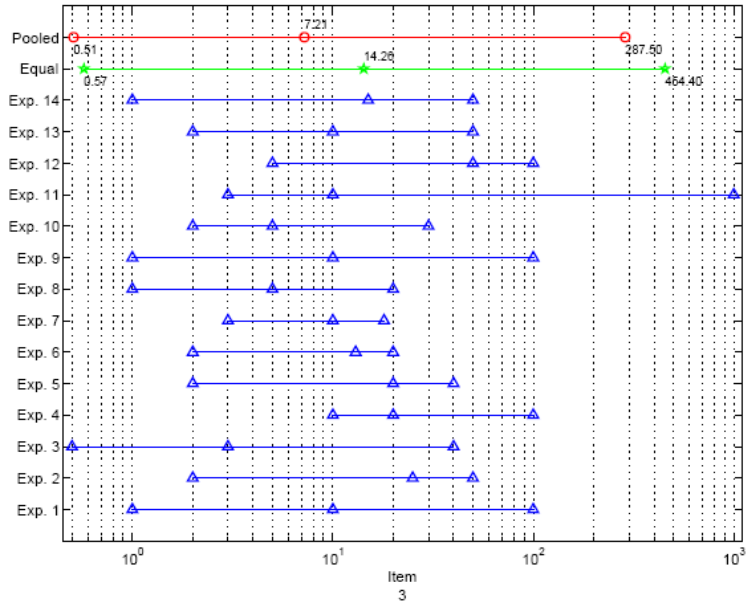


FIGURE 4. Performance weights solution (Pooled) and equal weights solution (Equal) are indicated above the individual, anonymized 14 expert responses (Exp. 1 -14) to Target Question 4 that asked: How long can CWD prions persist in soil enriched with manganese oxides (years)? Note a Log scale was used for time estimates. The individual expert responses and pooled results are shown with the central value representing the median of the uncertainty distribution for that expert and the upper and lower limits of the ranges shown corresponding to the 5th and 95th percentiles of the uncertainty distribution for that expert (Exp. 1-14, triangles; Equal result, stars; Pooled result, circles).

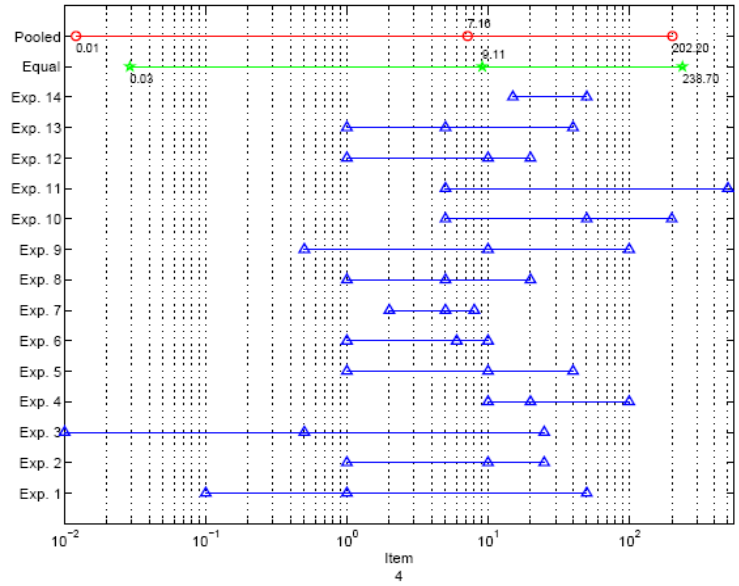


FIGURE 5. Performance weights solution (Pooled) and equal weights solution (Equal) are indicated above the individual, anonymized 14 expert responses (Exp. 1 -14) for Target Question 5 that asked: What is the likelihood that CWD can be transmitted through a still water source (0 - 100%)? The individual expert responses and pooled results are shown with the central value representing the median of the uncertainty distribution for that expert and the upper and lower limits of the ranges shown corresponding to the 5th and 95th percentiles of the uncertainty distribution for that expert (Exp. 1-14, triangles; Equal result, stars; Pooled result, circles).

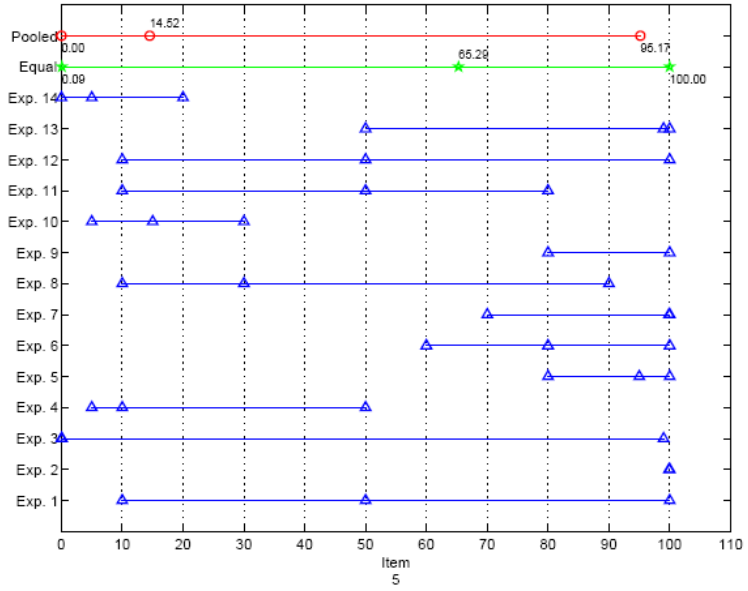


FIGURE 6. Performance weights solution (Pooled) and equal weights solution (Equal) are indicated above the individual, anonymized 14 expert responses (Exp. 1 -14) for Target Question 6 that asked: For what proportion of the incubation period are cervids shedding prion infectivity in saliva (0-100%)? The individual expert responses and pooled results are shown with the central value representing the median of the uncertainty distribution for that expert and the upper and lower limits of the ranges shown corresponding to the 5th and 95th percentiles of the uncertainty distribution for that expert (Exp. 1-14, triangles; Equal result, stars; Pooled result, circles).

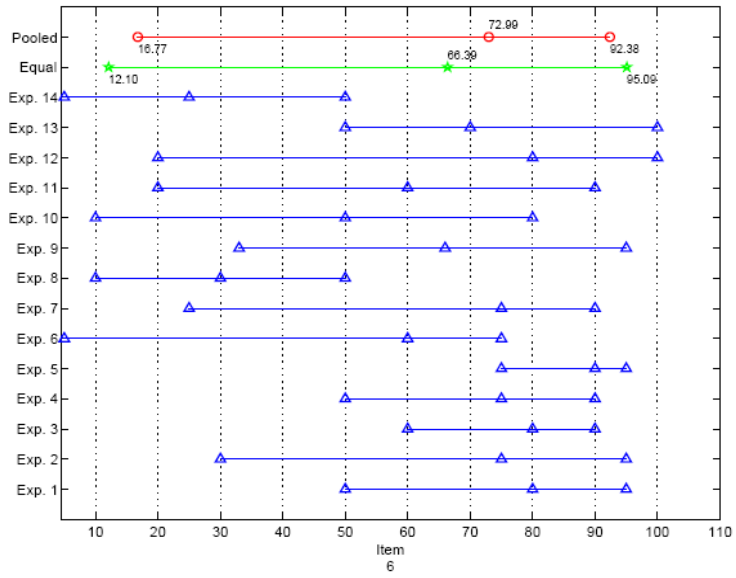


FIGURE 7. Performance weights solution (Pooled) and equal weights solution (Equal) are indicated above the individual, anonymized 14 expert responses (Exp. 1 -14) for Target Question 7 that asked: For what proportion of the incubation period are cervids shedding prion infectivity in feces (0 - 100%)? The individual expert responses and pooled results are shown with the central value representing the median of the uncertainty distribution for that expert and the upper and lower limits of the ranges shown corresponding to the 5th and 95th percentiles of the uncertainty distribution for that expert (Exp. 1-14, triangles; Equal result, stars; Pooled result, circles).

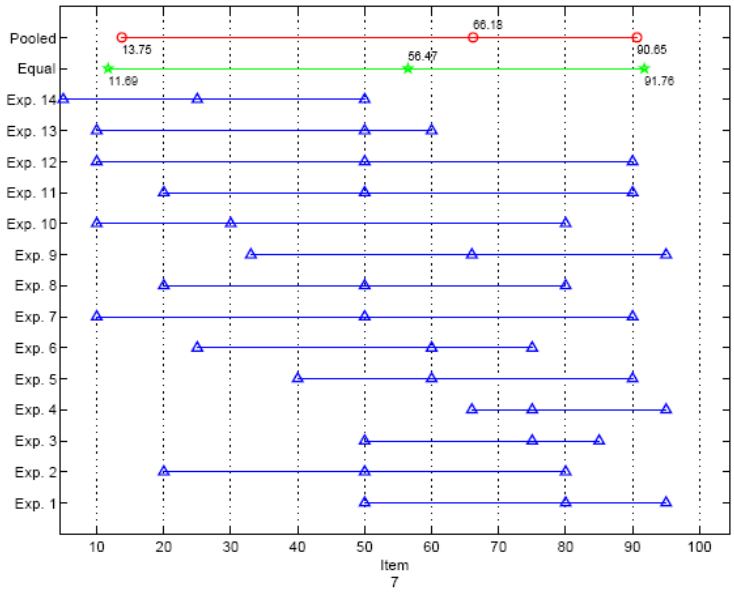


FIGURE 8. Performance weights solution (Pooled) and equal weights solution (Equal) are indicated above the individual, anonymized 14 expert responses (Exp. 1 -14) for Target Question 8 that asked: For what proportion of the incubation period are cervids shedding prion infectivity in urine (0 - 100%)? The individual expert responses and pooled results are shown with the central value representing the median of the uncertainty distribution for that expert and the upper and lower limits of the ranges shown corresponding to the 5th and 95th percentiles of the uncertainty distribution for that expert (Exp. 1-14, triangles; Equal result, stars; Pooled result, circles).

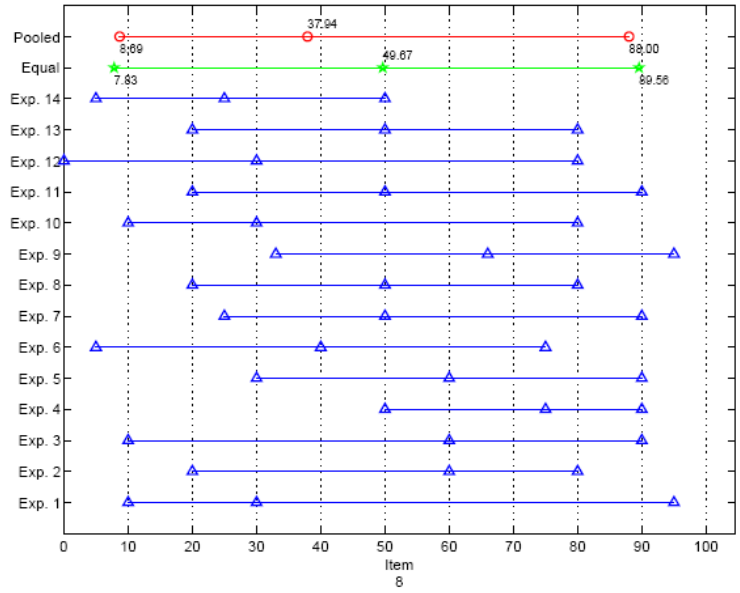


FIGURE 9. Performance weights solution (Pooled) and equal weights solution (Equal) are indicated above the individual, anonymized 14 expert responses (Exp. 1 -14) for Target Question 9 that asked: What is the likelihood that an effective treatment against CWD will be available for captive cervids in the next 10 years (0 - 100%)? The individual expert responses and pooled results are shown with the central value representing the median of the uncertainty distribution for that expert and the upper and lower limits of the ranges shown corresponding to the 5th and 95th percentiles of the uncertainty distribution for that expert (Exp. 1-14, triangles; Equal result, stars; Pooled result, circles).

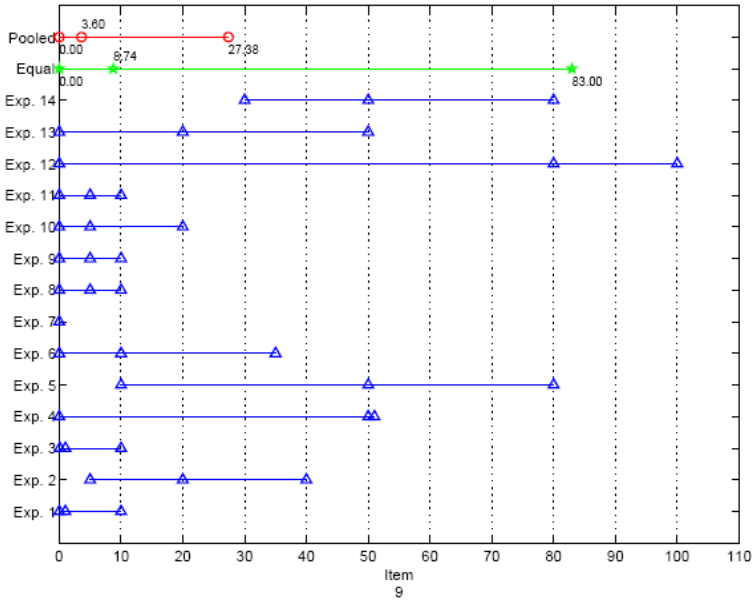


FIGURE 10. Performance weights solution (Pooled) and equal weights solution (Equal) are indicated above the individual, anonymized 14 expert responses (Exp. 1 -14) for Target Question 10 that asked: What is the likelihood that CWD infection is transmitted from wild to farmed cervids (0-100%)? The individual expert responses and pooled results are shown with the central value representing the median of the uncertainty distribution for that expert and the upper and lower limits of the ranges shown corresponding to the 5th and 95th percentiles of the uncertainty distribution for that expert (Exp. 1-14, triangles; Equal result, stars; Pooled result, circles).

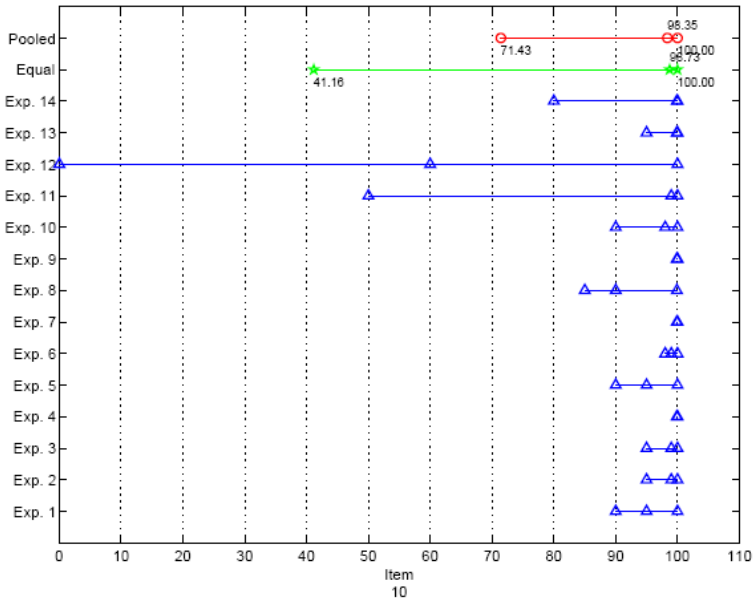


FIGURE 11. Performance weights solution (Pooled) and equal weights solution (Equal) are indicated above the individual, anonymized 14 expert responses (Exp. 1 -14) for Target Question 11 that asked: What is the relative importance of social/behavioural (direct contact) vs. environmental transmission in the spread of CWD in wild cervids given that X=1 means equally important, X<1 means environmental more important, and X>1 means environmental less important? The individual expert responses and pooled results are shown with the central value representing the median of the uncertainty distribution for that expert and the upper and lower limits of the ranges shown corresponding to the 5th and 95th percentiles of the uncertainty distribution for that expert (Exp. 1-14, triangles; Equal result, stars; Pooled result, circles).

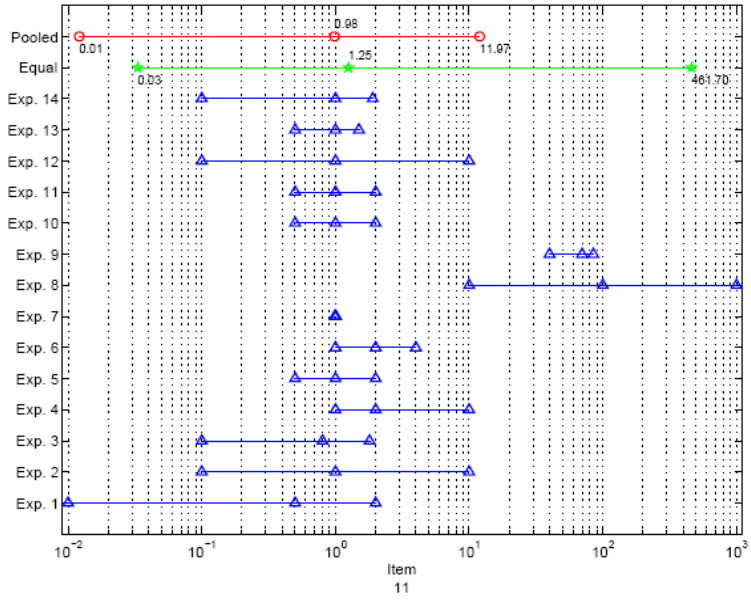


FIGURE 12. Performance weights solution (Pooled) and equal weights solution (Equal) are indicated above the individual, anonymized 14 expert responses (Exp. 1 -14) for Target Question 12 that asked: What is the likelihood that CWD can transmit from cervids to humans through oral consumption of meat (containing peripheral nerves) contaminated with CWD prions (0 - 100%)? The individual expert responses and pooled results are shown with the central value representing the median of the uncertainty distribution for that expert and the upper and lower limits of the ranges shown corresponding to the 5th and 95th percentiles of the uncertainty distribution for that expert (Exp. 1-14, triangles; Equal result, stars; Pooled result, circles).

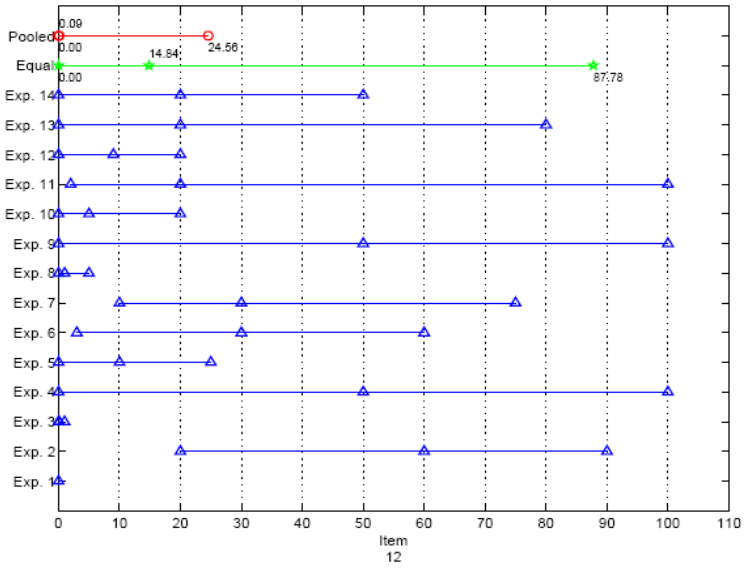
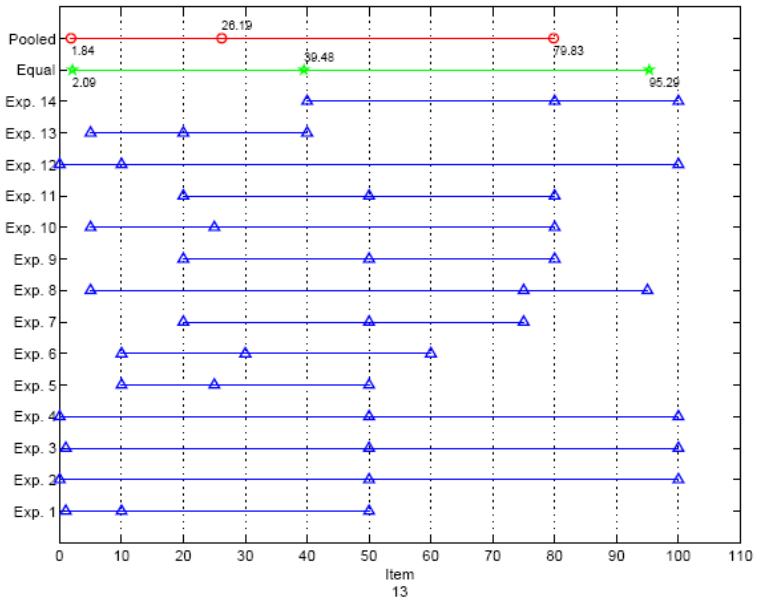


FIGURE 13. Performance weights solution (Pooled) and equal weights solution (Equal) are indicated above the individual, anonymized 14 expert responses (Exp. 1 -14) for Target Question 13 that asked: If CWD is transmissible to humans, what is the likelihood that the syndrome will resemble that of a known clinico-pathological phenotype of human prion disease (0 - 100%)? The individual expert responses and pooled results are shown with the central value representing the median of the uncertainty distribution for that expert and the upper and lower limits of the ranges shown corresponding to the 5th and 95th percentiles of the uncertainty distribution for that expert (Exp. 1-14, triangles; Equal result, stars; Pooled result, circles).



Table

TABLE 1. Median of responses provided by the experts to Target Questions Q1–Q13, for Equal Weights (Equal) and Performance-Based Weights (Pooled) judgements, with the 90% credible intervals shown in parentheses.

		Median (90% Credible Interval)	
Target Question (Units)		**Equal Weights (Equal)**	**Performance Weights (Pooled)**
Q1	What is the likelihood that CWD can transmit from infected cervids (deer, elk, or moose) to caribou through environmental routes of exposure in the wild to CWD, assuming a 10 year time frame? (0-100%)	9% (0.02 to 90.5%)	1.8% (0.0 to 25.3%)
Q2	What is the likelihood that CWD can transmit from infected cervids (deer, elk, or moose) to caribou through environmental routes of exposure in the wild to CWD, assuming a 50 year time frame? (0-100%)	29.7% (0.01 to 95.8%)	6.9% (0.01 to 58.6%)
Q3	How long do you think CWD prions can persist in clay-enriched soil and be infectious for other animals? (years)	14.25 (0.57 to 464.40)	7.21 (0.51 to 287.50)
Q4	How long can CWD prions persist in soil enriched with manganese oxides? (years)	9.1 (0.03 to 238.70)	7.16 (0.01 to 202.20)
Q5	What is the likelihood that CWD can be transmitted through a still water source? (0 - 100%)	65.29% (0.09 to 100%)	14.52% (0.0 to 95.17%)
Q6	For what proportion of the incubation period are cervids shedding prion infectivity in saliva? (0-100%)	66.39% (12.10 to 95.09%)	72.99% (16.77 to 92.38%)
Q7	For what proportion of the incubation period are cervids shedding prion	56.47% (11.59 to	66.18% (13.75 to 90.65%)

	infectivity in feces? (0 - 100%)	91.76%)	
Q8	For what proportion of the incubation period are cervids shedding prion infectivity in urine? (0 - 100%)	49.67% (7.83 to 89.56%)	37.94% (8.69 to 88.0%)
Q9	What is the likelihood that an effective treatment against CWD will be available for captive cervids in the next 10 years? (0 - 100%)	8.74% (0.0 to 83.0%)	3.6% (0.0 to 27.38%)
Q10	What is the likelihood that CWD infection is transmitted from wild to farmed cervids? (0-100%)	96.73% (41.16 to 100.0%)	98.35% (71.43 to 100.0%)
Q11	What is the relative importance of social/behavioural (direct contact) vs. environmental transmission in the spread of CWD in wild cervids given that X=1 means equally important, X<1 means environmental more important, and X>1 means environmental less important?	1.25 (0.03 to 461.70)	0.96 (0.01 to 11.97)
Q12	What is the likelihood that CWD can transmit from cervids to humans through oral consumption of meat (containing peripheral nerves) contaminated with CWD prions? (0 - 100%)	14.84% (0.0 to 87.785)	0.09% (0.0 to 24.56%)
Q13	If CWD is transmissible to humans, what is the likelihood that the syndrome will resemble that of a known clinico-pathological phenotype of human prion disease? (0 - 100%)	39.48% (2.09 to 95.29%)	26.19% (1.84 to 79.83%)