# Challenges of Quantitative Risk Assessment for Rare and Emerging Diseases: The Canadian Experience with vCJD

Susie ElSaadany
*Statistics and Risk Assessment Unit*
*Blood Borne Pathogens Division, Health Canada*
*A.L. 0601E2, LCDC Building, Tunney's Pasture*
*Ottawa, Ontario, Canada, K1A 0L2*
*susie_elsaadany@hc-sc.gc.ca*
Antonio Giulivi
*Blood Borne Pathogens Division, Health Canada*
*A.L. 0601E2, LDCDC Building, Tunney's Pasture*
*Ottawa, Ontario, Canada, K1A 0L2*
*antonio_giulivi@hc-sc.gc.ca*

A four step process for risk assessment is fundamental in addressing rare and emerging diseases, involving: 1) hazard identification, 2) dose-response assessment, 3) exposure assessment, and 4) risk characterization. To aid in the laying of this foundation, we consider risk assessment methodologies specific to a quantitative point of view, including Bayesian Analysis (Brand, 1995), back calculation, Monte Carlo Simulation (Thomson, 1999), and the epidemiological approach of person-time measure. Problem formulation is undertaken by risk assessors and managers, who acquire data as needed and iterate relevant methods to be applied for the characterization of exposure, exposure effects, and risk. Risk assessors then communicate the results of the analysis to risk mangers who, in turn, communicate the issues to interested parties, implement risk management options, and monitor the results.

In considering the best approach for assessing the risk of new variant Creutzfeldt-Jakob Disease (vCJD), the Blood Borne Pathogens Division(BBPD) of Health Canada starts with the worldwide prevalence of vCJD and takes into account many factors over time, including the probability of acquiring, developing, and dying from the disease (ElSaadany et al, 2000). It has been theorized that the consumption of the agent that causes bovine spongiform encephalopathy (BSE) in cattle is responsible for causing vCJD in humans (Will, 1999) (Scott et al, 1999). The only internal risk to Canada would arise from any native cases of BSE. The only such case arose in a cow imported from the United Kingdom (UK) which was destroyed, along with its entire herd. The first step, therefore, is to determine the sources of risk to Canada from Canadian travellers visiting countries reporting cases of vCJD - namely the UK and France - who may have become infected with vCJD by eating specified risk material (SRM) containing the BSE agent. Following this, an analysis was undertaken of the risk posed to Canada from any bovine material imported from countries reporting cases of BSE.

It is important to note that enormous uncertainty surrounds the statistical modelling for vCJD as the number of reported cases are few, there is no information regarding the minimal infected dose, the effect of repeated low doses, and the incubation period, and that theoretical assumptions helped form the bases of the calculations. It must be noted that the BBPD analysis incorporated as much information as was available up until June 26, 2000, and supported the modelling with the following assumptions:

- Among those infected, the infective agent is assumed to infect all ages and both genders alike.
- Any amount of contaminated beef product may be sufficient to infect a human by mouth.
- Differences in dietary patterns between the UK and France are unknown.
- Among those infected, susceptibility to the BSE agent is similar in the UK and France
- The duration of stay in the UK and France was assumed to be constant for different selected time periods (up to 1 month, up to 6 months, up to 1 year, up to 2 years).
- Travelling patterns and dietary characteristics remain constant over time.
- All travellers would consume at least one daily meal contaminated with SRM, which may or may not result in infection.
- The exposure rate is expressed as a relative comparison (ratio) based on the total number of affected cattle in both countries, with the British exposure to SRM being 10 times higher than the French exposure to SRM (Agut et al, 2000).

The estimated total number of infected persons was derived from the estimated number of slaughtered animals with BSE, 1980-1995 and the mean quantity of humans infected by 1 maximally infected bovine (Donnelly, et al). The above described figure was used to estimate the disease rate among possibly infected persons, assuming it exhibits binomial distribution and is much smaller than the estimated mean quantity of infected bovine to which the population may have been exposed (per daily meat meal), and taking into account the total number of cases of vCJD reported in the UK at that time. The estimated probability of acquiring the disease from each meal was calculated, taking into account the estimated mean quantity of infected bovine to which the population may have been exposed per daily meat meal, from 1980-1995. A similar calculation was performed for France.

***Table 1. Probability of acquiring vCJD for Canadian visitors to UK and France***

| Length of stay | Number of (bovine) meat meals consumed | Probability of acquiring the disease for UK travellers | Estimated number of resulting vCJD cases for UK travellers | Probability of acquiring the disease for travellers to France | Estimated number of resulting vCJD cases for travellers to France |
|---|---|---|---|---|---|
| 1 month | 30 meals | 5 in 10 million | 0.27 | 3 in 100 million | 0.007 |

| | | | | | |
|---|---|---|---|---|---|
| 6 months | 180 meals | 3 in 1 million | 0.37 | 2 in 10 million | 0.012 |
| 1 year | 365 meals | 6 in 1 million | 0.4 | 3 in 10 million | 0.002 |
| 2 years | 730 meals | 1 in 100,000 | 0.09 | 6 in 10 million | 0.002 |

To assess the risk of vCJD infection to the Canadian population from bovine material imported from BSE reporting countries, the Canadian risk was estimated by the total Canadian imports of beef from the UK and France, from 1988-2000, in proportion to the total Canadian consumption of beef for this period of time.

***Table 2. Total Canadian Imports of Beef (kg) from Various Countries (1988-2000)***

| **Countries** | **Total Imports** | **Percentage of Total Canadian Imports** | **Percentage of Total Canadian Beef Consumption** |
|---|---|---|---|
| United Kingdom | 226992 | 0.02% | 0.002% |
| France | 85158 | 0.01% | 0.00076% |
| Switzerland | 142 | 0.000001% | 0.0000013% |
| Portugal | - | - | - |
| Belgium | 28 | 0.0000003% | 0.00000025% |
| United States of America | 914993333 | 99.55% | 8.19% |
| Netherlands | 186447 | 0.02% | 0.0017% |
| Total Imports Canadian Beef Imports (kg) from Various Countries, 1988-2000: | 915492100 | | |

Assuming that the UK exposure was 100%, and that Canadian exposure is 0.002%, the Canadian exposure will be 1/50,000 of the UK exposure, from 1988-2000. A similar calculation was performed for France. These calculations led to the conclusion that there was an extremely low risk to Canadians of contracting vCJD from UK and French beef imports.

Following this assessment, it was necessary to consider the possibility of risk to the Canadian blood supply from those who may have contracted vCJD and who then decided to donate blood. Canadian Blood Services and Héma-Québec conducted a survey of their blood donors to determine donor travel trends by length of stay. A decision was needed regarding whether a deferral policy should be implemented for donors spending a significant amount of time travelling to the UK or France. It was also necessary to predict the amount of stress such a deferral policy would impose on the Canadian Blood System and the potential benefit to be gained from the preventive measure.

***Table 3. Travel History: Cumulative Percentage with Risk Reduction, of Surveyed Canadian Blood Donors Who Travel to the United Kingdom***

| **Length of Stay** | **Percentage of Donors** | **Cumulative Percentage of Donors** | **Cumulative Risk Reduction** |
|---|---|---|---|
| 1 month | 14.33 | 21.18 | 100 |
| > 1 - 6 months | 4.34 | 6.85 | 82.93 |
| > 6 - 12 months | 0.98 | 2.52 | 62.24 |
| > 1 - 2 years | 0.67 | 1.54 | 51.77 |
| > 2 years | 0.87 | 0.87 | 37.45 |

Source: (Canadian Blood Services, 1999.)

In terms of the preventative measure of donor deferral, it was estimated that a deferral of donors spending more than 6 months in the UK (2.52% of all donors) would result in a reduction of risk of more than 62%, which would be a tolerable level of stress for the blood system to endure. This reduction in donors would, however, necessitate the recruitment of new donors, which would also create a residual risk. An attempt was made to calculate this residual risk (ElSaadany et al, 2000).

Finally, the most recent issue arising in the vCJD debate is that of assessing the potential risk of vCJD infection from bovine-derived vaccines that may harbour the BSE agent. There are two potential sources of risk from bovine derived vaccines. The first involves the risk from bacterial vaccines derived from a broth that was sourced in Europe - a BSE reporting nation. The main component of fermentation is broth that may or may not contain BSE contaminated bovine brain material. The second involves the risk from the master seeds of viral vaccines whose main growth component is fetal calf serum. Since the early 1990s, however, the FDA has recommended that fetal calf serum be sourced from nations that have not reported a case of BSE (FDA, 2000).

Risk parameters for bacterial and viral vaccines include the risk of infected cows/calves being present in each pool, the number of infectious units per gram of material or ml of serum, the amount of infectious material or serum used per batch, the number of vaccine doses per batch, and the reduction in infectivity related to the route of administration. Both bacterial and viral vaccines have been recommended for Canadian infants and children, and administered to the Canadian population from 1975 -2000. Based on Health Canada's Canadian Child Population and Immunization Guidelines (Division of Immunization, 1998), it was assumed that approximately 500,000 children are immunized per year, that approximately 9 doses of viral vaccine are administered per child, and that approximately 10 doses of bacterial vaccine are administered per child. Work on this risk assessment is ongoing, and considers issues such as other transmissible spongiform encephalopathies (TSEs) and blood safety.

**REFERENCES**


Agut, H, Alperovitch F., Barin F, Courouce A.M., Danic, B., Dormont D., Eloit, M., Follea, G., Hannoun, C, Horaud, F., Leclerc, J, and Sicard, D. Agence Française de Securité Sanitaire des Produits de Santé. Report: "Revision of measures to minimizing the risk of TSE transmission via blood products." February 2000.

Brand, K.P., and Small, M.J. (1995). Updating uncertainty in an integrated risk assessment: conceptual framewirk and methods. Risk Analysis, vol. 15, no. 6, 719-731.

Canadian Blood Services. Survey of Blood Donors to Assess Travel to Countries Endemic for Bovine Spongiform Encephalopathy. 1999.

Division of Immunization, Health Canada. Canadian Immunization Guide, 5th Edition, 1998. Available as a PDF file: http://www.hc-sc.gc.ca/hpb/lcdc/publicat/immguide/index.html

Donnelly, C.A, and Ferguson, N.M. Statistical Aspects of BSE and vCJD - Models for Epidemics. Washington; Chapman & Hall/CRC, 2000.

ElSaadany, Susie, and Giulivi, Antonio. Comprehensive Risk Assessment for vCJD in France and other countries for Canadians and the Canadian Blood Supply. Blood Borne Pathogens Division, Health Canada, 2000.

Food and Drug Administration, USA. CBER and FDA Guidance on Sourcing of Bovine Derived Raw Materials, 2000. Letter to: Manufacturers of FDA-Regulated Products. Available as a PDF file. http://www.fda.gov/cber/bse/bse.htm#bsegde

Scott, M.R, Will, r., Ironside, J., Nguyen, H.O., Tremblay, P., DeArmond, S.J., Pruisiner, S.B. Compelling transgenic evidence for transmission of bovine spongiform encephalopathy prions to humans. Proc Natl Acad Sci - USA. 1999 Dec 21; 96(26): 15137-42.

Thomson, James R. Simulation, a modeler's approach. New York: John Wiley & Sons Inc, 1999.

Will, R.G. The transmission of prions to humans. Acta Paediatr 1999; Suppl 433: 28-32. Stockholm.