Decision-Making Under Conditions of Uncertainty Regarding Rare and Emerging Diseases, with Special Focus on the Human Impact of Transmissible Spongiform Encephalopathy

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Opening Remarks

Diane Gorman
Assistant Deputy Minister
Health Products and Food Branch, Health Canada

Diane Gorman welcomed participants to this important meeting on decision-making under conditions of uncertainty regarding rare and emerging diseases, with special focus on the human impact of transmissible spongiform encephalopathies (TSEs). Today, Canada is considered free of bovine spongiform encephalopathies (BSEs), and the most effective strategy for health protection is to prevent the emergence of these diseases in Canada. Scrapie and chronic wasting disease (CWD) have been found only in certain species and have no proven link to human disease. Nonetheless, although the risk is theoretical, the government has taken a pro-active stance to reduce it. In the fall of 2001, discussions began at the Deputy Minister and Assistant Deputy Minister level to identify gaps and priorities across departments. Included were Health Canada, the Canadian Food Inspection Agency (CFIA), Agriculture and Agri-Food Canada, the Department of Foreign Affairs and International Trade, the Privy Council Office and Environment Canada. As a result, Deputy and Assistant Deputy Ministers’ Interagency TSE advisory committees have been established and Health Canada is the Chair for both committees. The role of the committees is to identify knowledge and resource gaps and prioritise requirements across Health Canada and other Government Agencies. To manage, support and encourage a horizontal approach to TSEs, the TSE Secretariat was created. The TSE Secretariat’s role is to support the DM and ADM Inter-Agency TSE Committees, the TSE Science and Policy teams and to be the lead and focal point for TSEs in the Department.

Canada has taken some important steps. First, all live ruminants and ruminant products and by-products have been prohibited from countries not recognized by Canada as being free of BSE. The CFIA enforces Health Canada policies regarding the safety of our food supply. The CFIA also develops policy and enforces regulations on animal health, including animal feeds. Second, Canadian blood operators are operating under tightened measures to reduce the theoretical risk of transmission of variant Creutzfeldt-Jakob disease (vCJD) through the blood supply. Third, Health Canada is co-ordinating meetings such as this one to share information and expertise in assessing the risk under conditions of uncertainty and their impact on human health.

Scott Broughton
Assistant Deputy Minister
Population and Public Health Branch, Health Canada

Scott Broughton welcomed the participants of this important collaborative meeting, which brings together a number of experts to look at the challenges presented by vCJD. To date, the cumulative totals of definite or probable cases of vCJD in the world are 116 in the United Kingdom, 5 in France, 2 in Italy, 1 in Ireland and 1 in Hong Kong. The number is small, but because the outcome is always fatal, action is necessary.

Because evidence suggests that vCJD is the result of the consumption of beef infected with the BSE agent and because of the theoretical risk of transmission through blood transfusions and vaccines, Health Canada and its provincial and territorial (P/T) counterparts collaborate with a variety of agencies to protect the health of the public against this emerging threat. The federal TSE secretariat, established to facilitate and co-ordinate expertise in TSEs, is assisted by the work of the
Health Canada Statisticians Working Group and today’s hosts, the Statistics and Risk Assessment Section.

Health Canada adopts a prudent approach to risk, recognizing that the absence of full scientific certainty should not be used as a reason to postpone decisions when faced with the threat of serious or irreversible harm. Statisticians, epidemiologists and others have a vital role in guiding decision-making, despite the uncertainties involved. Thus, one of the objectives of this meeting is to gather national and international experts to discuss the challenges in modelling rare and emerging diseases. It will explore the state of current knowledge, the analytical tools needed to advance the science, the structures and capabilities of various methods of analysing and modelling uncertainty and the assumptions used in TSE modelling. It will consider the development of methodology responding to urgent issues and producing timely results, communicated in a meaningful fashion. Finally, it is hoped that this meeting might be a first step toward an international conference and workshop.

Ms. Susie ElSaadany, Chief
Statistics and Risk Assessment Section, Health Care Acquired Infections Division
Centre for Infectious Disease Prevention and Control, Population and Public Health Branch
Health Canada

The Statistics and Risk Assessment Section was created to provide rapid response to questions of risk assessment involving rare and emerging diseases. Some of the section’s most significant work has involved the estimation of the theoretical risk of vCJD to the Canadian public from food, drugs and vaccines, as well as to estimate the impact of preventive measures. The effects of policies to manage risks, such as the blood donor deferral directive, have been re-evaluated as part of Health Canada’s dynamic risk assessment structure. The assessments have involved collaborations with many in-house groups as well as offering the opportunity for collaboration with modellers worldwide. At this meeting, experts from the United States, Canada, Austria and Switzerland will share information about TSEs, vCJD, risk perception, challenges in modelling and more.
European Perspective on TSE Safety of Blood

Dr. Herbert Budka, Director
Institute of Neurology, University of Vienna

Concerns about blood safety and TSE agents or prions exist because the nature of the agent is still unknown, despite a number of theories. Prions resist conventional sterilizing methods. A protective species barrier is absent between humans. Human-to-human transmission has been documented (iatrogenic CJD). Validated screening tests that would allow for the identification of preclinically infected and diseased individuals are lacking. For vCJD, the risk appears to differ from that with classical CJD, which is sporadic and therefore of low risk. Even rare cases of transmission may be unacceptable.

Literature review

Important scientific data on prions and blood safety include experimental infectivity bioassays (with both human and animal blood), studies on TSE pathogenesis, epidemiological studies, tests for the disease-associate prion protein, factors in the processing of blood and donor factors.

Experimental infectivity assays have focused on the critical factors of the lack of species barrier (thus, there may be an under-estimation of infectivity) and the route of inoculation (intracerebral vs. intravenous). For example, P. Brown and colleagues have estimated that 5 to 10 times more infectivity is needed to transmit disease by the intravenous than by the intracerebral route. M. Bruce and colleagues reported in Lancet last year that two mice inoculated intracerebrally have not transmitted disease. J. Collinge is doing extensive inoculation into mice, but thus far, CJD and vCJD blood fractions have not led to successful transmission.

There are two reports of the successful experimental transmission of BSE-infected blood. In Lancet in 2000, Houston and colleagues reported the development of a TSE in a sheep transfused with whole blood taken from another sheep during the symptom-free phase of an experimental TSE infection. However, there are a number of limitations in that study, including the poor quality of Western blot documentation, the lack of confirmation of the BSE strain and the indefinite confirmation of transmission. More important is the 2001 report by C. Lasmézas and others (Proc Natl Acad Sci USA) that BSE can be transmitted from one primate to another intravenously in just 25 months.

What is needed is a diagnostic test for blood and biologic fluids. The most widely used marker cannot be infectivity, because infectivity bioassays are laborious. They need many animals and are time-intensive because of the length of incubation. The pathological isoform PrP^{Sc} is therefore used as a surrogate marker of infectivity; unfortunately, the relationship between PrP^{Sc} and infectivity is not fully understood. PrP^{Sc} may be detected by Western blot, but it is difficult to establish a Western blot sensitive enough for the very low concentrations that might be expected in blood. Recently, Wadsworth and colleagues (Lancet 2001) reported using a Western blot with high sensitivity-enhanced chemiluminescence and finding that the buffy coat from vCJD patients was negative for PrP^{Sc}.

Given the huge worldwide market for a test that could detect PrP^{Sc} in blood, many companies are eager to develop one, and a number of such tests are being evaluated. One test,
which detects very tiny aggregates of PrPSc in biological fluids, has been tested on cerebrospinal fluid (CSF). The sensitivity is about the same as has been shown previously with infectivity bioassays in CSF. Another test using capillary electrophoresis has shown some promising results with Scrapie and CWD, but there are rumours of problems with human blood. The confirmation-dependent immunoassay developed in San Francisco is an interesting approach being evaluated with five other tests in a field trial. Whether it will work on human blood is still unknown. Perhaps the most exciting test under development is the protein misfolding cyclic amplification technique, which allows rapid conversion of large excess PrPSc into a PrPSc-like form in the presence of minute quantities of PrPSc. The formed aggregates are disrupted by sonication to generate multiple smaller units. After cyclic amplification, more than 97% of the protease-resistant PrP present in the sample corresponds to newly converted protein. The PrPSc can be readily detected with methods of lower sensitivity. Thus far, the technique has worked well in hamsters and poorly in mice.

Epidemiological studies always have limitations. Patient numbers are small, there is a limited time of follow-up and there is a lack of knowledge about when, if ever, blood infectivity is present in preclinical individuals; therefore, caution is needed in the interpretation of such studies. A case-control study using hospital controls did not identify any connection between blood transfusions and CJD infection. In a study using community controls, there appeared to be some connection with surgical procedures, but not blood transfusions. Case reports indicate that there may be some relationship with blood donation, but the relationship is not confirmed. Cohort studies (haemophiliacs) have not shown any relationship between transfusion and CJD.

Studies on TSE pathogenesis usually use Scrapie. Every single individual TSE in a given host may behave differently from any other, so caution must be exercised in extrapolating results. However, it could be expected that any TSE in sheep would be similar to Scrapie and vCJD in pathogenesis. The most important message from these studies is that in contrast to all other human TSEs, vCJD is characterized by prominent deposition of the disease-associated isoform PrPSc and infectivity in lymphoid tissues even before the appearance of symptoms. Therefore, the pathogenesis may be different. It is thus possible that blood and blood products from a person harbouring vCJD infectivity could be contaminated, as could surgical instruments used on that person.

The disease manifests finally in the brain, but food-associated prions are taken up from the gastrointestinal tract. They must bypass the epithelial barrier and then reach the Peyer’s patches. They infect the follicular dendritic cells there and then the lymphoid organs. Lymphotxin-beta, which is produced by beta cells, induces maturation of the follicular dendritic cells and is essential for the spread of prions. In the late stages of disease, infectious prions are detectable in the peripheral and central nervous system, were they aggregate and cause neural damage and cell death.

BSE-exposure risk

Europe has begun surveillance for vCJD. One prerequisite of adequate surveillance is to evaluate human BSE-exposure risk, both locally and for travellers.

BSE is a severe disease in cattle that can be easily recognized by laypeople once the disease has developed. There must have been BSE in Europe during the second half of the 1990s, but many countries did not report it. In the United Kingdom, the first cases were described in 1986. After studies clearly indicated that meat and bone meal (MBM) was the medium for infectivity, a ban on materials going into ruminant feed was introduced in 1988. The ban was largely effective, because after about five years (the mean incubation time for BSE in the field), the epidemiological
curve began to drop. However, the drop was not as rapid as might have been expected, and more and more cases in animals “born after the ban” (BABs) began to be identified. It was recognized that the original ban only to cattle was not efficient. It became apparent that if the same feed was used for pigs, poultry and fish and if the same production facilities, trading areas and farms were used, contamination must be widespread. In November 1989, specified risk materials (SRMs) were banned from the human food chain. In 1996, when the public and media outcry was at its height, the United Kingdom introduced a complete ban for all mammals for MBM. In 1996 they announced complete feed assurance. Today, BSE cases “born after the real ban” (BARBs) are being seen (14 cases to date). All cases are investigated in detail. Initially, it was thought that these might be cases of vertical transmission, but there are no data supporting such transmission. The most likely explanation is that there is still a small pool of contaminated feed being used. It is an important lesson for all controlling authorities if you want to eliminate BSE, the controls cannot be stringent enough.

In 1989, BSE appeared to be limited to the British Isles. By 1995 it had been documented in France, Switzerland and Portugal. Today, it is in almost all countries in the European Union. There appears to be an area in Central-Eastern Europe with no cases, but it is likely that those countries just do not have the means for proper surveillance. There is a growing need to help these countries. It must also be remembered that TSEs are not just a health issue, but also an economic and a cultural issue.

The European Commission has categorized all countries according to their geographical BSE risk. Category 1 includes countries where risk is very unlikely (e.g., Australia, Norway). Category 2 is for countries where BSE is unlikely but not excluded (e.g., Canada, United States). Category 3 includes countries where there is a great risk that BSE exists, even if not yet reported (e.g., most European countries). Category 4 is for countries at great risk (e.g., Great Britain, Portugal).

According to the Office international des Epizooties (OIE), the total number of confirmed BSE cases in the European Union is 183,000. Only 2,500 of those are outside the United Kingdom. The absolute numbers are less interesting than their development over time. For example, France and Ireland appear to be in the upsurging part of an epidemic, whereas Portugal and Switzerland appear to be on the downward side. Between 1999 and 2000 there was a big increase in France, but more than half of the increase was contributed by the newly established active surveillance program. Nonetheless, between 2000 and 2001 there was another big upsurge, so there is cause for concern. Ireland had about twice as many cases in 2001 as in 2000.

Across the European continent in 2001, almost 800,000 risk animals were tested and a huge number of healthy animals were slaughtered, but fewer than 1,000 cases of BSE were detected overall. Thus, although the problem is significant, the devastating epidemic experienced by the United Kingdom does not appear likely.

**CJD surveillance**

The second prerequisite for adequate vCJD surveillance is adequate all-form CJD surveillance, including adequate referrals of young patients. A multi-national European CJD surveillance group has developed sets of diagnostic features for defining all types of CJD.

European surveillance plus the systems in Canada and Australia have clearly shown that CJD has a normal annual incidence of about one case per million. Although the mean age for sporadic CJD is 64, genotyping indicates a link between the PRNP codon 129 and age. In young
people, almost half of the cases have an odd valine-valine (VV) genotype and an odd clinical expression (compared to older patients). Genotyping is essential to determining the form of CJD. Variant CJD occurs predominantly but not exclusively in younger (<50 years) people. Some countries have well-developed referrals of these younger people (e.g., Italy, with 183 referrals and 0 confirmed cases of vCJD), but others (e.g., Canada, 9 referrals and 0 cases) have few referrals. From 1996 through mid-2000, France referred 317 people under the age of 50 for CJD testing but only 2 cases have been detected, whereas the United Kingdom has identified 70 vCJD cases out of only 198 referrals.

**Diagnostic criteria**

The third prerequisite for adequate vCJD surveillance is defined diagnostic criteria. With the experience of dozens of cases, the United Kingdom was able to develop a detailed list of diagnostic symptoms, including specific features in the magnetic resonance image (MRI) of the brain such as the so-called pulvinar sign. Overall, these signs and symptoms are 77% sensitive and 100% specific. They include (1a) progressive neuropsychiatric disorder, (1b) duration greater than 6 months, (1c) the exclusion of alternative diagnoses, (1d) the lack of potential iatrogenic exposure, (2) early psychiatric symptoms including persistent painful sensory symptoms, ataxis, chorea or dystonia or myoclonus and dementia, (3a) no periodic EEG, (3b) pulvinar sign on MRI and (4) positive tonsil biopsy.

**Data**

The mean age of death of the vCJD cases in the United Kingdom is 29 (range = 14-74). The mean age at onset is 28 (range = 12-74). The peak range is age 20-29. Mean duration is 30 months, which is much longer than sporadic CJD (4 months). All cases tested thus far are methionine-methionine (MM) at codon 129 of the PrP gene. To the beginning of March 2002, there have been 125 cases of vCJD worldwide (116 in the United Kingdom).

It is difficult to predict how the disease will go forward. Some experts are predicting that the disease is burning out; others say that it will expand logarithmically. In truth, the future is unpredictable. What is important for Europe is to make all efforts to block possible pathways not only between animals but also between animals and humans and between humans and humans. BSE originated from contaminated feed. Since the start of 2002, there has been a total feed ban on animal-derived parts throughout the European Union. The offspring of BSE-infected cows are culled. Potentially infected material (such as specified risk material, or SRM) has been banned. The challenge today is to make all efforts to prevent secondary transmission through hospital procedures or blood donations.

Unfortunately, prions are so stable that they can survive some methods of decontamination that had been thought effective. Only four methods have been proven somewhat effective: high-concentration sodium hypo chlorite (16,500 ppm available chlorine), autoclaving at 121°C after sodium hypo chlorite treatment, autoclaving at 121°C in sodium hydroxide or boiling in sodium hydroxide.

**Conclusions**

There is still substantial ignorance about the pathogenetic involvement of the blood in human TSEs. Experimental bioassays have not convincingly demonstrated TSE infectivity in vCJD.
The few reports claiming infectivity contain severe inconsistencies. Negative results on vCJD are preliminary. Successful transmission of experimental BSE occurred within primates and possibly within sheep. Data from both experimentally induced and natural TSEs in animals suggest that blood has the potential to transmit disease, with low infectivity in blood measurable in the late stages of the incubation period and during clinical illness.

Epidemiological studies have not convincingly linked CJD with blood and blood products. Reasons for the discrepancy between some positive experimental laboratory evidence and the equally important negative epidemiological evidence are probably multiple. These include the absence of significant blood infectivity until the onset of symptomatic disease, comparatively low levels of infectivity during the symptomatic stage of disease, the need for 5 to 10 times more infectious agent to transmit by the intravenous than the intracerebral route and, for plasma products, the further reductions of infectivity during the course of plasma processing.

In conclusion, transmission of CJD by blood and blood products either does not occur or does not contribute to the CJD epidemiology. Although a hazard cannot be excluded, a real risk is not recognizable. However, the same statement cannot be made for vCJD, because experience is limited.

Questions and comments

1. What happened to bovine offal not used in human food when the ban was initiated in the United Kingdom?

Truckloads of thousands of tons of this meat still exist and are rotting. Much has been stored in old airplane hangars (often rendered, which leads to a reduction of infectivity of about 3 logs). Rodents are consuming it. It is possible that part of the rodent population could adapt to BSE. It is also a problem in continental Europe. There are rumours from both the United Kingdom and the other European Union countries of illegal exports C a criminal act which must be prosecuted as much as possible. Attempts have been made to burn the offal, but in the United Kingdom the capacity is low and it could take years. Attempts in Austria have led to sludging in the burning furnaces. In general, the public health issue has been primarily resolved, but the result is a huge environmental problem.
Prions as Adventitious Agents

Dr. Neil Cashman
Centre for Research in Neurodegenerative Diseases, University of Toronto

The first human TSE seen (1957) was kuru in Papua New Guinea. It was contracted through mourning rites by the consumption of prion-infected tissue. In the early part of the last century, CJD (1920) and Gerstmann-Sträussler-Scheinker syndrome (1928) were identified. Novel genetic variants of CJD, including fatal familial insomnia (1986) and vCJD (1996) are now being recognized. Animal TSEs are well known and include Scrapie (since about 1750) in sheep and goats, BSE in cattle, CWD in deer and elk, transmissible mink encephalopathy (TME) (1947) and feline spongiform encephalopathy (FSE).

The clinical features of CJD include rapid progression, with death usually in 6 to 9 months (90% mortality within a year); dementia; personality changes; difficulty in mental activity; loss of coordination; myoclonus; pyramidal, extrapyramidal, visual and lower motor neuron involvement; cortical blindness; Parkinson-like symptoms; and involvement of motor nerve cells of the spinal cord, mimicking Lou Gehrig’s disease. The incidence of disease is low (1/million/year), and it occurs most frequently in persons over 60. Until the mid-1990s there were three recognized forms: sporadic (85%), familial (15%) and iatrogenic (1%).

Variant CJD is a distinct syndrome from classic CJD both clinically and pathologically. The mean age of onset is 29, and many adolescents are affected. Progression is slower (9 to 35 months). The pathology is distinctive, with a daisy plaque in the cerebral tissue and a high burden of PrPSc.

Iatrogenic transmission through medical treatment or vaccines is uncommon but not unknown. The first incidence of iatrogenic transmission was the passage of sheep Scrapie through vaccine (affected about 1,000 sheep). Human-to-human iatrogenic transmission of prion disease has been documented in corneal transplantation (3 cases), instrumentation of the brain (6 cases), cadaver-pituitary-derived hormones (about 100 cases) and dura mater (about 120 around the world).

A number of the distinctive properties of vCJD and BSE pose particular concerns related to iatrogenic transmission. They are resistant to inactivation and denaturation of infectivity. Conventional prions seem to be hampered by the species barrier, but BSE is a type of prion infectivity that does not respect species barriers. There have been a number of secondary epidemics, not only in humans but also in house cats and zoo primates, animals that are usually protected through a profound prion species barrier. When prions are transmitted across species lines, they are often associated with detection of infectivity in the blood. With vCJD, infectivity accumulates to high levels not only in the brain, but also in lymphatic tissues, tissues that are bathed in blood daily. The root of infectivity to the brain in vCJD is through the gut and lymphoid tissue. The young age of onset of vCJD gives more time for transmission between humans. People over age 65 are less likely to be donating blood than are people in their teens and 20s; thus, if a younger person is incubating the disorder, there is an increased likelihood of transmission through blood donation, plasma fractionation, etc. The greatest risk factor is the lack of scientific knowledge about vCJD. Classic CJD has been studied for almost 100 years, there has not been enough time to accumulate sufficient epidemiological and scientific knowledge to make intelligent policy decisions.
Vaccines

The possibility of vaccine transmission of vCJD poses a much greater threat than transmission through blood donation, given that a relatively small number of people receive blood products, but all children receive a series of vaccines to prevent the communicable diseases of childhood. The young age of inoculation means that an infectious agent has decades to develop to cause disease in a person’s 40s to 60s.

There are three areas where prion infectivity could emerge in vaccines: cell substrates, media supplements and excipients.

In cell substrates, infectivity could emerge spontaneously. In the most common theory of prion infectivity, there is a normal cellular protein (PrP<sup>c</sup>) rich in alpha-helical content and highly soluble. For unknown reasons, that protein can refold into an abnormal isoform that has the same sequence of amino acids, but folded differently. It then acquires some physical-chemical properties: loss of solubility, tendency to aggregate, resistance to proteases and, most importantly, the ability to provide a template for refolding of the normal cellular protein. Thus, the refolded protein (PrP<sup>sc</sup>) is catalytic, leading to an exponential accumulation of abnormal isoforms.

If a cell that expresses a large amount of prion protein undergoes a misfolding favouring mutation, then it is possible that the disease could start in this one cell. Once this event occurs, whether through a misfolding itself or a somatic mutation that favours it, there is exponential recruitment on a post- translational level. Sporadic CJD is rare. People have about 100 billion neurons, so a productive de novo infection occurs in 10<sup>-17</sup> per neuron per year. Considering the number of substrate cells used for vaccine, there would have to be 100,000 batches of vaccine to see the event once.

There is a familial variant of CJD as well as familial variants of other prion diseases (e.g., fatal familial insomnia), which are passed on in autosomal dominant fashion. Half the members of each generation therefore develop disease. If all of a person’s neurons share one copy of the mutant cell, the chance of developing disease is 100%. It is important to apply that knowledge to what might be happening with vaccine substrate cells in vitro. It is thought that the mutation rate for dividing cells is about 10<sup>-10</sup> per base pair per cell division. If prion infectivity is less than 1000 base pairs, then it is possible that 10<sup>-7</sup> could acquire a mutant prion cell. If cells undergo about 100 divisions in a year, then 10<sup>5</sup> cells per year will acquire a mutant prion protein. All this is theoretical, as there are no data on mutation rates. Nonetheless, it is important to try to begin to make these measurements.

The infectibility of substrate cells is an issue for which there is no science. Some cells can be infected in vitro. Deterrents to substrate cell infection are the species barrier, the low abundance of surface PrP<sup>c</sup> and rapid cell growth (as cells divide, they compartmentalize prion infectivity). There are also barriers relating to cell biology, unquantifiable at present.

The other potential sources of prion infectivity in vaccines are media supplements and excipients. Cells might be infected in vitro from media supplements such as bovine serum and human serum albumin. Vaccines are stabilized with protein (excipients) prior to their use in inoculation of people, and pigskin gelatin is used in many vaccines. Although there have been no spontaneous cases of a TSE in a pig, pigs do seem to be susceptible to BSE when it is injected.
directly into the brain. Human serum albumin is also used as an excipient in MeaslesBMumpsBRubella (MMR) vaccine and rabies vaccine.

There are a number of measures that could minimize the risk of transmission through vaccines. The most obvious is restrictive sourcing, which is being done. There could be biological manipulation of substrate cells (e.g., include prophylactic agent). Prion prophylaxis and neutralization could be done. There is a validation step in vaccine production for every infectious agent except prions; this must change. Tests for PrP\(^{Sc}\), which is a good surrogate marker of prion infection, have been described in the literature and could be used for bioassays of vaccines. Information must be shared among companies, despite proprietary concerns, to identify potential problems in the vaccine pathway. Finally, more research is essential; only a more complete understanding of vCJD and BSE will lead to assured solutions.
Challenges in Modelling Rare Diseases and Emerging Events, with Special Focus on TSE, BSE and vCJD

Dr. Robert G. Rohwer, Director
Molecular Neurovirology Laboratory, Maryland

A comparison of the BSE epidemic curve in the United Kingdom with the graph of vCJD cases raises the question of how the two relate temporally. If the curve of human deaths relates to the confirmed BSE cases, then it is likely that there is a relatively short incubation period in humans, and the deaths may be reaching a maximum now. However, if the cases were acquired when the BSE epidemic was just beginning, there could be many more human deaths to come.

Modelling

Modelling is an important tool for focusing attention on the key parameters likely to drive an epidemic. Unfortunately, with TSEs, much of the parameter data is not of high quality. In addition, models themselves deserve at least as much scepticism as the data from which they are derived, and all too often that critical consideration of modelling is not done. For example, could the models being used to predict the course of BSE today predict the historical course of Scrapie in Europe, Iceland and North America?

Where are we now?

The immediate problem has been identified, and surveillance has picked it up in Europe. Risk assessments have been and are being done in numerous countries. First-line defences (feed ban, SRM bans, deferral policies for blood and tissue donation, import controls) are in place. However, there are still many gaps.

Preclinical diagnostics are needed to identify which animals and people are infected. More knowledge about how transmissions occur is essential to prevent transmission. More knowledge about the pathogenesis is needed to identify the vulnerable stages of disease at which to direct therapeutics and treatments and thus arrest the progression of preclinical disease. Similarly, therapeutic targets need to be identified to enable the treatment of incubating and clinical cases. Finally, more must be known about BSE and vCJD to forestall surprises from yet-undiscovered TSEs (it must be anticipated that other TSEs exist in other wild animals).

What does science know about whether the defences are working? Empirically, the feed ban in the United Kingdom has worked, turning back the BSE epidemic in cattle. But the same degree of feed ban has not been implemented in North America. Is the North American feed ban good enough? The details could be addressed experimentally but have not been. Similarly, more faith is placed in the SRM bans than is merited by the data. There is no good explanation for why young people were infected C perhaps it was through childhood vaccine, instead. There is no way to know that it has been implemented well enough, and no way to know if it would work even if it was well implemented. Deferrals for blood donation are directed toward those risk factors that science has identified, which is only 20% of exposure cases. Similarly, geographically based deferrals lead to about an 80% reduction in exposure. In terms of import controls, the Animal and Plant Health Inspection Service in the United States admits that it samples imports randomly C the volume is too great. The United States has an open border with Mexico for cattle imports. The
legacy of trans-shipped U.K. MBM materials must still be considered to be with us. Finally, the possibility of bioterrorism using BSE must be considered a risk.

Science-based policy-making and regulation

If science does not have the answers needed to inform decision-making, then policymakers must assume the worst case. The fallout is huge social, economic and quality-of-life impacts that might be unnecessary if there was better information. Science-based policy is essential. TSE research is more costly than some other diseases, but almost all the outstanding questions about TSEs C questions that policy-makers and regulators must have answered C are subject to experimental investigation.

There are at least eight outstanding questions:

1. What is the tissue distribution of TSE infectivity? Does infectivity exist in milk and semen?
2. What are the prevalence rates for Scrapie, BSE, CWD and vCJD in North America?
3. Are TSEs transmissible in blood and blood products?
4. What are the natural routes of transmission?
5. What is the parameter space for effective TSE inactivation?
6. What are the parameters for effective TSE removal?
7. What level of decontamination is needed for surgical instruments?
8. What is the molecular pathogenesis of TSEs?

A lack of science does not justify disruptive policies that provide no real benefit. Four specific examples of areas where policies have been made in the absence of science are the withdrawal of plasma products, the destruction of surgical instruments, geographical deferrals and leukoreduction.

Withdrawal of plasma products: It is estimated that there are 10,800 classic CJD carriers in North America C people in whom the disease is not detectable. Given the blood donor rate and blood pool sizes, withdrawals cannot be rationalized on the basis of clinically identifiable cases. Potential exposure from an undiagnosed carrier exists, but virtually all pools would have to be exposed to the undiagnosed case. U.S. epidemiologists show no evidence of CJD related to transfusion; European surveillance concurs. Withdrawals are not effective and could lead to shortages. For all these reasons, the U.S. Public Health Service rescinded the withdrawal policy. A risk is acknowledged by the Surgeon General, but in the meantime, cloned substitutes were to be encouraged by removing financial impediments to their use.

Surgical instruments: All surgical instruments are presumed to be contaminated after use and are harshly sterilized. Clinical cases of CJD in hospital are rare, but when they do occur and can be identified, the instruments used on them are often destroyed. What must be remembered is that there are cases that are not identified, and instruments used with these people are processed normally. If one of these cases should later become clinical, it makes no sense to then destroy any
instruments used in the past, as has been done. Rather than having a policy of destroying instruments used with identifiable CJD cases, policies should be in place for the effective sterilization of all instruments. Thus, more research on effective instrument sterilization methods is critically needed.

**Geographic deferrals:** Geographic deferrals of blood products lead to an 80% reduction in exposure, but that does not equal an 80% reduction in risk. Also, if the reasons for implementing geographic deferrals prove eventually to have been well founded, 80% reduction will not be enough.

**Leukoreduction:** One presumption of CJD infectivity is that it is associated with white blood cells. Thus, if the white cells are removed by leukoreduction, the risk of infectivity should also be removed. Experiments, however, have shown that by high-speed centrifugation, about 10% of infectivity is not removed. Also, plasma-associated infectivity is not removed. The association between infectivity and cell stability has not been tested; disruption of cells may liberate infectivity and increase virulence. Infectivity might be retained by adsorption.

Some leukofiltration experiments have found no reduction in infectivity. The process is very precise, however, and repeated experimentation is needed. Scaled-down experiments might be possible, but require further validation.
In 1998, the United States Department of Agriculture (USDA) asked the Harvard Center for Risk Analysis and the Centre for Computational Epidemiology, College of Veterinary Medicine, Tuskegee University to identify and characterize possible sources and pathways of BSE infectivity in U.S. cattle, cattle feed and the human food supply and to evaluate the implications over time of the possible introduction of BSE into the U.S. agricultural system.

After study of the available science and a thorough review of how cattle and feed move in the country, a quantitative model was built. Simulation was used because of the lack of historical data and because it would enable accounting for time (e.g., incubation period of BSE). In addition, simulation would allow quantitative comparison of the importance of different pathways of spread and different risk management actions. Also, it would help identify information needs to best direct research dollars. Challenges in modeling included the lack of knowledge about TSE science (pathogenesis, transmission, etc.), understanding the U.S. agricultural system, making the model flexible and extensible and identifying the key quantities to track and report.

Underlying the model is the key assumption that the prevailing hypothesis of how BSE spread in the United Kingdom is correct. There is a population of animals, which are used in a variety of ways for human consumption, offering the opportunity for exposure to infectious or contaminated material. Parts are also used in ways that could go back to cattle. The model tries to describe all the different points at which infectivity can come into the system. Animal age, type and gender are all factors in the spread of BSE. The infection rate has a number of important factors, including feeding practices, susceptibility, maternal transmission and spontaneous disease. Incubating animals could be incubating for 4 to 5 years. They could be taken for slaughter or die in that time, or they could live to the end of the incubation period and develop clinical signs.

Numerous assumptions had to be made. For example, susceptibility is assumed to be high in young cattle but drops off rapidly with age. Assumptions also had to be made about the development of infectivity: Levels of infectivity are not constant throughout the development of disease and are not the same in different tissues; the model has to account for increasing levels of infectivity and a variable incubation period. The time course shows that infectivity is relatively low until the animal develops clinical disease. (Infectivity was expressed in terms of cattle oral ID$_{90}$ [infectious dose], i.e., the amount of infective material that would, on average, cause 50% of exposed cattle to develop BSE.)

Because the USDA was interested in human exposure to BSE infectivity, the slaughter process was modeled to look for points of potential human infectivity. The researchers went to slaughtering plants to review the whole process (from animal inspection through stunning, exsanguination, disposition of brain, splitting of spinal cord, inspection and disposition of spinal cord to meat processing). The model is as realistic as possible. For example, although ruminant materials from rendering are prohibited in animal feed, the model considers the possibilities of contamination in the process or non-compliance with the rules.

The resulting model can track incremental, stock and cumulative quantities over a simulation.
period (e.g., 20 years). Incremental tracking shows year to year information, stock tracking shows results for any given time, and cumulative tracking shows the results after the full time course (e.g., how many animals became clinically ill after 20 years). All the answers play a role in decision-making. Most importantly, however, the model allows evaluation of the relative contributions of different pathways to increase BSE spread in animals and potential human exposure.

A variety of analyses were done using the model. In the “base case” scenario, it was assumed that BSE is not present in the United States. Ten infected animals were introduced into the system and followed for 20 years. Various risk management options were analyzed, such as a ban on rendering cattle that die on the farm or the effect of a U.K.-style SRM ban. The options were tested with the introduction of 10 infected animals, followed for 20 years. Another scenario looked at the potential of pre-1989 imports from England to introduce BSE to the United States. Because the model cannot be validated (there is no “control” country), data from a small, well-described outbreak in Switzerland were used to check how close the model’s predictions might be to empirical observations.

Base case scenario

Ten sick animals were introduced into the U.S. system and the model was run 1,000 times. Few new cases of BSE occurred (mean = 29, 95th percentile = 11 new cases). Almost the only way that animals were infected was through leaks in the feed ban. Forty per cent of animals predicted to die on farm introduced 96% of the infectivity to the system. In all 1,000 runs, BSE was gone within 20 years of introduction; some new infectivity occurred, but the disease could not propagate itself. The number of animals reaching clinical status was very low, which in some ways is good but does mean that surveillance is likely to be ineffective.

Only a small amount of potentially infective tissue would reach the human food supply (mean = 35 cattle oral $ID_{50}$s, 95th percentile = 170) over 20 years (e.g., T-bone steak having a bit of spinal cord on it). Infective tissue included brain (26%), beef on bone (11%), advanced meat recovery (AMR) meat (56%) and spinal cord (5%). AMR accounted for half of the $ID_{50}$s potentially available for human consumption.

When the model was run with the scenario of one infected animal imported, there was on average less than one new BSE case in 20 years. When 500 sick animals were introduced, an average of 200 cases resulted and the disease lasted longer than 20 years, but it still disappeared.

Some uncertainty analysis was done. For a number of uncertain variables, high and low potential values (best case and worst case) were input and the model was run 1,000 times. One of the big uncertainties is the rate of misfeeding on the farm C i.e., on farms that have cattle as well as either pigs or chickens, do farmers give pig or chicken feed to cattle if they run out of cattle feed? There are no good data on this possibility. In the United Kingdom, inspectors went farm to farm, but in the United States there is much greater uncertainty because the system includes both prohibited and unprohibited feed. Another possible reason for misfeeding is mislabeling.

Two key management points were identified through modeling. First, BSE spread in a cattle herd is mostly due to leaks in the feed ban as well as some maternal transmission. Animals that die on the farm represent the greatest amount of infectivity being introduced to the animal feed system. Second, potential human exposure is most affected by the handling of the brain and spinal cord in processing. For example, the Food and Drug Administration processing facilities are using AMR to remove the spinal cord first, but it must be assumed that the removal does not work perfectly. Some of the primary routes of exposure for humans C cattle brain, spinal cord, beef on bone and AMR
meat C may be recognized as potentially infectious; others may not.

Risk management options

The base case scenarios modeled what would happen if the United States continued with the risk management measures that are currently in place. The model was also run to evaluate two potential new risk management options, again using the importation of 10 BSE infected cows to challenge the system.

The first of these options was a U.K.-style ban on SRM in human and animal food. On average, the SRM ban would reduce BSE cases by 80% and reduce potential human exposure by 95%. The second option was a ban on rendering cattle that die on the farm. On average, this option would reduce BSE cases by 77% and reduce potential human exposure by 20%. In sum, managing risk earlier in the process makes feed ban compliance (which was an uncertainty) less important.

Imports from England before 1989

The model was used to evaluated the potential for U.K. cattle imported into the United States before 1989 to have introduced BSE and the implications of that potential. Various groups have identified 334 animals brought into the United States between 1980 and 1989. The USDA has traced these animals and has determined that 161 were disposed of in a manner that poses no risk to humans or other animals. For the remaining 173, the modelers used information on birth year, export year, animal type, sex, last sighting and more to estimate the likelihood and potential magnitude of introductions of BSE infectivity to US cattle feed.

The analysis indicated that there is more than an 80% chance that the import of these animals resulted in no exposure of U.S. cattle to BSE infectivity. Even if U.S. cattle were exposed, there is a significant chance that the exposure resulted in no new cases. The results were further challenged in the model with the introduction of greater amounts of infectivity into the feed supply in 1980 to determine what level of infectivity could have existed and not been noticed through surveillance. Even in those cases of higher infectivity, the number of infected animals declined as the effect of feed ban kicked in; the same gradual elimination of the disease is shown (in this scenario, peaking at year 2000 and then declining).

Other results

To test the plausibility of the model, the small Swiss BSE outbreak was modeled, working with experts in Switzerland to identify appropriate values. The model under predicted the total number of infected animals, but reasonably reproduced the time course and size of the outbreak.

The model was also run under the hypothesis of spontaneous occurrence of BSE. The results indicated a mean of 2 cases per year and fewer than 100 cattle oral ID50s to humans over 20 years.

The model also looked at the hypothesis that Scrapie could be transmitted to cattle (no American Scrapie is known to infect cattle). If transmission were possible, it would cause a mean of 2 BSE cases per year and fewer than 100 cattle oral ID50s to humans over 20 years.
Conclusions

This analytic approach has a number of strengths. It identifies key assumptions and data, although it would be useful to get some of the assumptions underpinned by further data. It helps in understanding the relative importance of different pathways of infection. It can compare the relative effectiveness of different risk management measures. It allows a “value of information” approach to the next steps: where to focus data collection or scientific research to reduce uncertainty and give the most confidence in decisions.

Weaknesses include the potential for overconfidence in the results; it must be remembered that the model is just a tool. It is dependent on the underlying structure and assumptions. The real world had to be simplified to enable the model, and the assumptions about the disease learned from the U.K. experience are significant. It is difficult to calibrate and validate the model; the Swiss-outbreak scenario offers some confidence, but is imperfect as a validation tool.

Nonetheless, there are few alternatives to this type of modeling in this type of case. Best estimates and hypotheses based on the best science available are all that exist to aid decision-making. Quantitative analysis can be very helpful in decision-making under conditions of uncertainty.

For further details, please see the full on-line report of the risk assessment at www.fsis.usda.gov/oa/topics/BSE.htm.

Questions and comments

1. The model is interesting, and seems to justify the control measures taken by the Europeans. However, if the model has been used to state that the United States is free of BSE, that statement must be considered questionable, especially if it is indicated that BSE would be cleared from the system despite infective cattle imports before 1989 and even if no feed ban had been in place. The argument that it would have been detected by surveillance is weak, especially given the European experience and the correspondingly greater magnitude of the U.S. cattle population.

This report has not been used to say that the United States is disease free; rather, the USDA is stating that BSE could exist in the country and be undetected, but that the risk management measures in place have made the system robust against the spread of BSE infectivity. Extrapolations from European experience are difficult, in that some European countries continued to import U.K. cattle after the United States had stopped such imports, and in that the surveillance systems differ. It would be useful to have more experts argue through the calculations used in the model to identify potential weak points and improve the model.

2. How many chance variables are there within your model, and are all the assumptions spelled out in detail on the USDA web site?

As the model is running, dozens of random events can occur (e.g., an infected cow may give birth to a calf during the period of incubation). There are also parameters that define distributions. Overall, there are probably several dozen variables. All the assumptions and their rationale are detailed in the report on the USDA web site.
3. How much seeding would be required for BSE infectivity not to die out in 20 years?

With 10 infected animals and 1,000 runs of the model, BSE infectivity always died out; however, with 10,000 runs, it probably would not always die out. When more infected animals were introduced at the beginning of the simulation, there was a 90% chance that after 20 years infectivity would die out. If the number of new infections that can start from one infected animal is less than one, then infectivity will always die out. It is recognized that there is uncertainty in the understanding of infectious units. ID$_{50}$s were used as the infectious units; extending that up or down was reviewed, but did not change the performance of the system much. Nonetheless, that would be a good exercise.

4. Could the model be used to identify why the BARBs are occurring in the United Kingdom? If they are not due to breakdown in the feed ban, could they be due to Scrapie? It would be interesting to see the model used for Scrapie, which has a low incidence rate but maintains itself over decades. Could the model account for the fact that Scrapie does not self-extinguish?

Scrapie is very different from BSE, but it could be looked at in a similar way. The model could be adapted to that disease. Also, the full report does discuss concerns about the BARBs in the United Kingdom.

5. The most to be learned may be by calibrating this model over the U.K. experience, where a corner has been turned, but odd events are still occurring. For international value, it would be worth taking the richest experiences and calibrating the model over it. Collaboration is needed in agreeing on the underlying structures and then fitting the model to different national experiences.

Agreed. The model and the analyses are currently undergoing peer review. It is expected that some modifications will be done. Then, experts from various countries will be coming in to review the model. The coding can be made available.

6. It appears that the feed ban is the single most important measure in the United States to keep BSE from spreading. How inefficient can the feed ban be and still stop the spread?

In the simulations, a number of parameters relating to the feed ban were repeatedly varied, and in no case did BSE keep spreading. However, it would be of interest to keep exploring those parameters to determine at what point infectivity continued. This could be of great global value.

7. What advice should be given to a country that identifies one case? The report seems to indicate that a first step would be banning rendering of animals on farms, the second would be an SRM ban and the third a feed ban; however, if the World Health Organization were to recommend those measures now, they would not be adopted.

Not all of those measures necessarily must be taken. It may not be feasible to ban the rendering of animals on farms. It would be of great interest to help the WHO find cost-effective ways to determine best measures.
8. Does the modeling provide any insight on why only one animal per herd was infected in the United Kingdom?
   No. There may be a number of factors, including dose-response relationship, how infectivity spreads, age-dependent susceptibility, etc.

9. In response to the BARBs in the United Kingdom, the regulators keep shortening the age at which an animal is killed for beef consumption. In the United States, do they kill animals before a certain age? Did the model look at that issue?
   The model assumptions were based on slaughter statistics, for which there is good data. The United States has a younger herd than the United Kingdom did a few years ago.

10. Given the number of variables in the model and the degree of uncertainty that exists in them, how is the number of iterations determined in order to have as much confidence as possible in the results.
   In this case, the modelers just looked at how much the results varied. They were comfortable that with 1,000 runs (each having its own random events) they could distinguish reliably between important and unimportant results. Overall, about 30,000 runs were done with different sets of assumptions. Univariate testing of the assumptions was done (i.e., change one assumption at a time to see how it affects results). However, in the sensitivity analyses, only a handful of parameters (e.g., number of infected cattle) appeared to be really important. There did not appear to be correlations among the other variables that would be significant in changing the outcomes.

11. BSE is usually transmitted very early in an animal’s lifespan, which could mean either increased susceptibility or another mode of infection. There have been suggestions that milk replacers play a major role in transmission. Can the model test this suggestion?
   It could be looked at. This model is based on U.S. practices; it could be adapted for U.K. practices.

12. Could the model be used for CWD?
   Changing the model for CWD would require more than tweaking, as it would be going from domestic animals to wild animals, but it could be done. There would be significant data gaps.

13. In vCJD modeling, a slight change in the magnitude of the susceptibility distribution or infectivity distribution will significantly change the outcome of the model.
   Those were not tested in this model, so it is not known to what extent they would influence outcomes.

14. How is this model being applied? Can it be used by other countries?
   The more people who use this model and adapt it for their circumstances, the better it will
be and the greater the confidence in the results. The U.S. government has started doing some training so they know how to use it, and the USDA is working with North American partners. It is hoped that many organizations and countries will make use of this model.
Rare Events, Uncertainty and Blood Safety: Communicating with Policy-Makers

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The Royal Commission on the Safety of the Blood Supply (Krever Commission) examined many aspects of blood operators and blood regulators in terms of blood safety, with special focus on emerging threats such as HIV. Key lessons for the government were that government cannot delay action waiting for scientific certainty, government cannot ignore even possible harm and the precautionary principle should be a guiding concept for regulators.

The precautionary principle has many interpretations. International environmental law says that “in the face of uncertain risk and inadequate data, the regulator should exercise restraint.” In the health field, the precautionary principle indicates that the exercise of restraint, even in the face of uncertain risk, may not be the best option. The course of the disease may be known and the outcome predictable, and restraint could lead to no therapy. Restraint could introduce secondary problems, as in the blood system. Thus, in health, the precautionary principle must recognize that balanced risk reduction may be the most “precautionary” measure.

Balanced risk reduction is a strategy to minimize more than one interrelated health concern. For example, in the blood system, the deferral of possibly infected donors must be balanced against the loss of blood donors sufficient to result in a blood supply shortfall. Care is needed not to compromise either risk reduction effort. A stepwise reduction may be the best way to achieve the balance (e.g., staged donor deferral as new donors are identified and recruited).

Donor deferral is perhaps the most cost-effective of all safety strategies. Much effort goes into identifying high-risk donors (epidemiologically). If high-risk donors are not eliminated, then at some point other technologies will fail.

vCJD and blood

Variant CJD is a significant new threat to the blood supply. There are no technologies yet to mitigate that threat. A new disease that is 100% fatal, vCJD is showing a steep epidemic curve (first case identified in 1995; more than 110 cases by the end of 2001) and thus offers substantial risk.

To date, no cases have been identified as being the result of blood transfusion in humans. Nonetheless, animal studies support the potential for transmission by blood. Leukoreduction may reduce prion load, but data are inconclusive. Strategies to reduce potential spread by donor deferral could threaten the adequacy of the blood supply. Canada’s multicultural population includes a significant proportion of people who have traveled to the United Kingdom and other areas where BSE exists. For blood regulators such as the Therapeutic Products Directorate (TPD), balanced risk reduction is the challenge.

The TPD turns to colleagues such as the Statistic and Risk Assessment Section of the Population and Public Health Branch to do risk modeling. Many assumptions must be taken in the process of that modeling, such as the frequency of prion transmission in diet, genetic predisposition in the population, the presence of prions in peripheral blood, the frequency of transmission in blood...
transfusion and the consumption of high-risk materials. Some assumptions have had the opportunity for refinement as science grows. For example, the duration of exposure increases risk, but how much? Does one need to be exposed repeatedly? Should individuals be deferred based on spending 10 years in a certain area of the world? 5 years? 5 months? 5 weeks? In addition, the magnitude of domestic risk of vCJD irrespective of transfusion must be considered. Because it is considered that the risk of acquiring vCJD in Canada through other means is close to zero, risk reduction efforts for the blood supply focus on travel.

The precautionary principle applied to vCJD-related donor deferral tries to balance risk with the domestic demand for blood supply. In 1999, after the first modeling exercise, the TPD concluded that deferring donors who had spent 6 months aggregate time in the United Kingdom from 1980 to 1999 would provide a 78% reduction in theoretical risk, and the consequences of applying that deferral would be a 3.5% reduction in the donor population in Canada. Thus, a substantial risk reduction could be achieved with minimal negative effect. The TPD then consulted extensively with blood operators and public groups dependent on blood transfusion to determine whether such a reduction was acceptable. That percentage was accepted, but the TPD determined that it would not go beyond that in a single year (e.g., deferring anyone who had spent 4 months aggregate time in the United Kingdom would have reduced the donor population by 6.5%).

In 2000, TPD extended the deferral policy to include 6 months aggregate time in France. The theoretical risk differed, but TPD was trying to establish measures that would easily screen the donor population without imposing a substantial interpretation on Canadian blood operators. The extra measure was taken only after extensive discussion with patient advocacy groups. The addition of this measure introduced some problems because U.S. rules differed (they did not include the France-related policy) and Canada imports a substantial amount of blood product from the United States. A number of exemptions had to be made.

In 2001, Canada started a new deferral policy for those spending 3 months in the United Kingdom or France, or 5 years in Europe (theoretical risk reduction 91%, lost another 3% of donors). In the United States, a 2001 draft proposal was for deferral after 3 months aggregate in the United Kingdom, or 5 years in Europe (including France). In France, a domestic deferral is clearly not feasible; their deferral is based on time in the United Kingdom.

Conclusions

Although modeling is helpful in the risk considerations involved in this type of challenge, modeling of the risks associated with the disease process by itself will not give enough answers. The risks associated with different policies must also be considered. Thus, the precautionary principle has some substantial limitations in health. Balanced risk reduction is a better direction to take, based on known risks vs. theoretical risks. In addition, a stepwise approach to risk reduction allows the overall target risk reduction to be achieved over time without presenting significant hardships to the other side of the scale. Nonetheless, assumptions and subsequent deferral strategies must be continuously reviewed and revised as the science continues to grow.

Questions and comments

1. There has been talk about extending the age range of donors. Is that a possibility for the TPD?

There may be substantial advantages to the blood supply by extending age ranges; however, the TPD considers that issue to be separate from vCJD issues.
2. Is recruiting more donors a possibility? What lessons were learned from the impact of September 11 on blood donations?

First, the TPD recognizes that recruitment offers both the potential for increasing the donor pool and the secondary potential for introducing risks. A dramatic increase in the donor pool could also dramatically increase risks more than blood operators could handle. Recruitment does and must continue, but other measures must also be considered. For example, the TPD has looked at increasing the number of visits per year that a donor can make. It has also looked at data from Héma-Québec and the Canadian Blood Services that indicate that the introduction of new donors will not substantially increase risk. What new risk is introduced can be mitigated through such measures as the quarantining of blood from new donors for a set period of time. There are extensive testing requirements for new blood.

September 11 demonstrated the great willingness of people to give to others in an emergency. The important issue for blood operators is to ensure that measures are in place to enable it to handle extra blood capacity in the face of a disaster.

3. In terms of using statistical models as a tool, how did the TPD integrate them into the policy decision process?

Originally, TPD hoped that modeling using aggressive statistical methodology would offer complete solutions to the uncertainty of risk and uncertainty of data. Of course, statistical modeling will not solve either of those. It will help understand the impact of potential policy options in terms of percentage reduction in theoretical risk and percentage reduction of the donor pool. In the final analysis, the model is vital in assessing the relative impacts of decisions being made in the absence of other clear indicators, but models will not make the decisions.

4. Has TPD balanced the risk from blood donation against, for example, iatrogenic risk? Is donor deferral (which considers primary spread) a more important precaution than taking precautions in the medical setting (secondary spread)?

The model suggested that there could be a case or incubating case of vCJD in Canada at this time. It is assumed that the case will be related to travel. Certainly, just as that person offers a risk to the blood supply, he or she would also offer a risk in terms of contamination of surgical instruments. The two risks have not been compared by TPD, but the questions are certainly valid. In a Canadian context, the value might be lower than in the European context. It would be of great value to see the results of European measures or studies on primary vs. secondary transmission.

5. The percentage reduction in theoretical risk is the basis for the TPD policy decisions. Is TPD looking at actual risk, also?

Risk in Canada remains theoretical. The policy decisions looked both at theoretical risk and at what measures the blood system would tolerate.
Health Canada’s Blood Safety Program: Surveillance Functions

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Two laws important to Health Canada’s role in the safety of the blood supply are the Food and Drug Act and the Department of Health Act. The Food and Drug Act is the backbone of the mandated programs of the regulatory authorities of Health Canada. It focuses on the regulation of manufacturers and post-marketing surveillance. The Department of Health Act gives Health Canada a mandate to protect the people of Canada against risks to health and the spreading of diseases and to investigate and do research on public health issues, including the monitoring of diseases. Health actions are done in collaboration with the provinces and territories because of their responsibilities for health.

In terms of post-marketing surveillance, serious events must be reported by manufacturers to Health Canada. For surveillance of most adverse events of transfusion, there is no specific legislative authority. Nor is there provincial/territorial legislation for mandatory reporting; all reporting is done voluntarily, a collaborative federal/provincial/territorial system that seems to work well. There is buy-in from physicians, hospitals and scientists.

The goal of the blood safety program is to conduct surveillance and targeted research leading to risk assessment of transfusion-related blood-borne pathogens and injuries. Within that goal are two specific objectives: to capture data on adverse events and errors of transfusion, and to support risk management activities by assessing the risk of adverse events and errors due to transfusion of blood or blood products.

Health Canada’s specific surveillance functions are several. It supports a comprehensive surveillance system using post-marketing surveillance. It enhances public health investigation of emerging blood-borne pathogens using laboratory and epidemiological surveillance. It monitors the most vulnerable populations and conducts outbreak investigations for known blood-borne pathogens. It conducts statistical analysis and risk assessment, as well as epidemiological investigations of prion diseases. These functions arise from the recommendations of the Krever Commission and are supported by the provincial/territorial ministries of Health as well as Canadian physicians and surgeons. At the heart of the program is the concept that safety is paramount.

Surveillance functions are supported through new organizational structures at Health Canada and interdepartmental links within the government. They are also linked to provincial institutions and collaborate with blood operators. Surveillance is linked to networks with physicians and hospitals.

Surveillance initiatives

Four surveillance initiatives of the Blood-Borne Pathogens Division relate to transfusion-transmitted injuries, community-acquired blood-borne infections, CJD surveillance and research,
and statistics and risk assessment.

By the end of 2002, it is hoped to have all provinces and territories (currently in four pilot provinces) linking in to a national surveillance and research program for transfusion-transmitted injuries. It will include surveillance of high-risk patients such as bone marrow and stem cell patients, apheresis patients and hemophilia patients.

Community-acquired blood-borne infections include hepatitis, HIV and new pathogens. The provinces and territories conduct passive surveillance for hepatitis; in addition, there is active surveillance at six provincial centres and a Centre of Excellence in Hepatitis. There is a strong HIV network, and surveillance is also conducted for new pathogens.

The CJD surveillance system has been monitoring the occurrence of any new cases and has provided valuable information for risk assessment in Canada. It is supported by the Blood-Borne Pathogens Division, transfusion-transmitted injuries surveillance and the Statistics and Risk Assessment Section and interacts with the National Microbiology Laboratory in Winnipeg.

The Statistics and Risk Assessment Section is supports a wide variety of organizations and initiatives, including the Therapeutic Products Directorate and the surveillance systems and research for the various blood-borne pathogens. Partners include the provinces and territories, universities, hospitals, the Centre for Infectious Disease Prevention and Control and international institutions.

Maintaining Canada’s blood safety is a balance of leadership, safety, supply and demand, with both federal and provincial/territorial responsibilities.
Risk Management, Risk Perception and the Precautionary Principle

Dr. Daniel Krewski, Director
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A few years ago, the University of Ottawa started developing a design for an institute for population health that would look at all determinants of health. It was recognized that population health was a transdisciplinary issue, needing individuals from different disciplines working together to address key issues in new, meaningful ways. The Institute includes all nine faculties at the university and has now set up five research centres, including the McLaughlin Centre for Population Health Risk Assessment. The McLaughlin Centre looks at all the determinants of health, interventions for population health, best clinical practice, health policy and global health.

Risk is characterized using the best science available, and then various options for managing those risks are assessed. For the Committee on Environmental and Population Health, the Centre reviewed over 200 studies in the literature and identified 10 major principles to guide risk management decision-making. Two seemingly opposing principles are the precautionary principle (to take action in the face of uncertainty when there are serious threats to health) and risk-based decision-making (to take risk management actions only in proportion to the demonstrated level of risk). The tension between those two principles provides a balance.

Precautionary principle

The idea behind the precautionary principle is “better safe than sorry.” When uncertain, it is better to take some action that could reduce the possibility of the risk occurring. The active appeal of this principle has prompted its incorporation into a number of environmental statutes around the world. Its application to health issues is less clear, and there has been considerable debate on its definition, scope and implementation. There are 14 different interpretations currently in use. In addition, there are arguments against it, including that it unfairly impedes economic and technological development. In other words, precaution costs money.

Underlying concepts include a presumption in favour of health and safety and an acknowledgement of the limitations of science in defining the magnitude of risks. It recognizes that prevention of harm is preferable to the abatement of harm after it has occurred. It focuses on solutions to problems (i.e., risk aversion) instead of current levels of risk (i.e., risk assessment) and their acceptability (i.e., assimilative capacity). Ultimately, the precaution principle is about preventing harm, not assessing risks.

Historically, the precautionary principle can be traced to European environmental law of about 30 years ago. It was first used internationally in 1987 in the context of marine pollution control. In 1992, the United Nations Conference on the Environment and Development (held in Rio de Janeiro) established the most widely used definition of the precautionary principle. The Rio Declaration states, “Where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation.” Thus, the key conditions for applying the precautionary principle are seriousness of the effects, the lack of scientific certainty (about probability, magnitude and prevalence of harm and about the efficacy of measures to prevent harm), the existence of cost-effectiveness measures to prevent harm and the power to make a decision about preventive
measures. Thus, the Rio Declaration acknowledges the cost-benefit analyses that underlie many risk management decisions.

The application of the precautionary principle may include a combination of the following elements: duty to act, shift in the burden of proof, relaxation of standards of evidence of risk required to invoke precautionary measures, cost-benefit analysis, proportionality (significant risk would allow more resources) and a provisional nature (new science could be expected to generate a clearer picture of how to manage the risk).

Examples

**Climate change:**

Climate change is clearly upon us. The weight of scientific evidence indicates that the average temperature of the planet is increasing slowly, largely from automobile emissions and industrial activity. Actions now might still take decades to achieve meaningful reactions. The cost of actions is enormous, and actions require global co-operation. The concept of adaptation vs. mitigation is key: Will we mitigate the risk or will we accept that the world will be warmer and try to adapt through social and other infrastructures?

For mitigation, possible actions are emission limitation, clean production methods and use of the best available technology. Industry could be required to make environmental impact assessments, take emission inventories, do audits and on-going emissions monitoring and make a full examination of alternatives. The burden of proof shifts to proponents. Procedural requirements would include reporting requirements and the issuance of emissions permits or licenses, which could be allocated to different countries and thus traded for economic benefit. These actions would slow down the potentially harmful effects of climate change and buy time for looking at other options. They would also both allow and require public participation.

**Variant CJD:**

BSE and vCJD are threats to animal and human health, as well as the animal farming industry and the Canadian economy. Scientific uncertainty is present (transmission of TSE between animals, transmission to humans via consumption of beef, transmission between humans via blood), and there is no confirmed case of vCJD in Canada. Therefore, any preventive measures taken here would be precautionary.

Measures taken around the world include bans on the importation of European beef, restriction of imports of beef from any country not designated as BSE-free, bans on feeding rendered protein from ruminant food animals to other ruminants, tight restrictions on animal and animal feed movements in Europe, the quarantine or slaughter of animals for which there is reasonable suspicion of infection and the prohibition of blood donations from people who have spent certain amounts of time in the United Kingdom, Europe or France after 1980. All are precautionary measures.

BSE and vCJD satisfy all the conditions required for the invocation of the precautionary principle: threat of harm, lack of full scientific certainty, existence of preventive measures and ability to make a decision about preventive measures. When applied to vCJD, the precautionary principle is not likely to generate the “typical” opposition seen with measures to mitigate climate change (e.g., arguments that the principle stifles technological or
economic development). The bottom line is that the precautionary principle is a valid, effective and easily operationalized tool in the management of the risks associated with BSE and vCJD in Canada.

Questions and comments

1. One of the elements of the precautionary principle is cost-effectiveness. With vCJD, where is the cost-effectiveness?

   The precautionary principle as defined in the Rio Declaration does not require a full cost-effectiveness analysis. Rather, it implies that the decision-makers need a sense that they are not spending disproportionately. Most applications to vCJD in the literature have not carried out full formal cost-benefit analyses, but they do include some discussion of the magnitude of the cost.

2. If the precautionary principle is applied to vCJD, a harm may be introduced, i.e., a reduction in the supply of blood for transfusion. How does the principle resolve the harm being introduced?

   The precautionary principle is only one of the 10 principles in risk management decision-making. By itself, it looks narrowly, focusing on the potential serious risk it is attempting to avoid. The other 9 principles help to balance that narrow focus.

3. There seem to be two interpretations of the precautionary principle, one being “when in doubt, take action” and the other being “when in doubt, take the best action that you can.” Is there something more to the principle than acting as wisely as possible, and is the decision-maker supposed to spend in proportion to real risk or perceived risk?

   First, “when in doubt, take action” is too simplistic an interpretation. One is always in doubt, but would not always take action, for example, when the risk is trivial. The precautionary principle is based on more than just uncertainty. It is applicable when there is a high degree of uncertainty and when the consequences of inaction are significant, and it is meant to be applied in a cost-effective way. The 10 principles are guides only. In the end, an element of judgment must be used. Second, proportionality with the precautionary principle applies more perceived risk, because the real risk has not been characterized.

3. Does the literature have any examples of legal challenges to risks created by applying the precautionary principle (e.g., creating the real risk of reduced blood supply through a decision to deal with the perceived risk of vCJD)?

   No examples were noted. The legal challenges would more likely arise in terms of economics than in terms of health (i.e., spending large sums to control a risk not yet substantiated).

4. Does public perception come into the precautionary principle?

   Public perception of risk cannot be ignored. However, with both climate change and vCJD, public perception has heightened concern, but has not been the driving factor. For both issues, there is enough scientific evidence to warrant concern.
Uncertainty About the Global Spread of BSE and vCJD

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The European Commission (EC) is conducting geographic-based risk assessments for BSE in countries that request it. The assessments are guided by a document created by the EC's Scientific Steering Committee. The assessment applies the precautionary principle and is used as a tool in making decisions about whether to allow importation of meat and meat products. It considers the risk of BSE existing in the country, entering the country and being recycled in the country. Countries must provide a considerable amount of information on practices related to agriculture, the meat and other industries, importation and exportation.

The EC has categorized all countries according to their geographical BSE risk. Category 1 includes countries where risk is very unlikely (e.g., Australia, New Zealand, Argentina). Category 2 is for countries where BSE is unlikely but not excluded (e.g., Canada, United States). Category 3 includes countries where BSE either is present at low level or where it is highly likely to be present, even if not yet reported (e.g., most European countries). It is useful that Category 3 includes two groups, as many countries have shifted from the “likely” group to the “present at low level” group. Category 4 is for countries where BSE is present at higher rates (e.g., Great Britain, Portugal).

The consideration of risk includes a wide variety of questions, including the following: Was any potentially infected material imported (including potentially contaminated animal feed and live animals and including illegal importation)? How was the imported material used? Specifically, did cattle have access to it? Is there a rendering industry? (If not, then humans or other animals will consume all the risk and there will not be much recycling. If there is an efficient rendering system, then the disease could be recycled, and the possibility of an epidemic exists.)

International trade has contributed to international exposure to the agent, through trade in food, MBM, human and bovine tissue used in biologicals, blood and blood products, and pharmaceuticals. (The last three are considered of unknown risk.) For example, although the feed ban for MBM was introduced quickly in the United Kingdom, MBM was still exported, fully legally, and labeled for use in non-ruminant animals. When the SRM ban for humans was introduced in 1990, what happened to the high-risk tissues? The EC document suggests that these materials were not destroyed, but were put into animal feed. Thus, for a brief period there would have been a spike of infectivity introduced in animal feed. Eventually, the SRM were not allowed in animal feed, but the mechanical methods used to remove the risk materials from an animal (stripping of spinal cord or removal of brain) were ineffective in view of what is now known about the distribution of BSE infectivity in the bovine. Hence, potential infectivity in bovine tissue based animal feeds and human food could have become lower, but it would not have dropped to zero. The sale of MBM was not prohibited until 1996, after the recognition of the first vCJD case in the world.

A comparison of the graphs of the BSE epidemic curves for Europe and the United Kingdom show similarly sharp rises in the number of cases, although they are orders of magnitude different. The effectiveness of the U.K. measures is clearly visible, and a shift of risk occurs between the United Kingdom and Europe. Data supplied by the Office International des Epizooties in 2002 show that in 2001, there were more cases of BSE in continental Europe than in Great Britain. In continental Europe to date, BSE has been reported in Austria, Belgium, the Czech Republic, Denmark, Finland, France, Germany, Greece, Italy, Liechtenstein (in 1998), Luxembourg (in 1997),...
the Netherlands, Poland, Portugal, Slovakia, Slovenia, Spain and Switzerland. Of note, Italy, Spain and Germany did not report their first non-imported cases until 2000 and 2001, respectively, which is when they put active surveillance in place. This experience demonstrates that active surveillance is essential. Internationally, there must be concern about countries that do not use an active surveillance system for BSE.

When considering the public health implications of the first reported cases of BSE in a country, it is important to recognize that the extent of spread of infection could be widespread or limited: it is highly unlikely that there will be only one infected animal by the time the first case is reported, and since the average incubation period of BSE is around five years, infection will almost certainly have been present in the bovine herds for some time before the first case appears.

Attempts to predict the extent of spread of BSE globally by using data on exports from the United Kingdom from 1980 to 1997 have some limitations. Export data may not tally with the import data of other countries because of repackaging and onward sales. Also, illegal or uncontrolled movements were not reported. The data do not show how the imports were used. It is impossible to define how much infectivity was in these exports (nor even if there was substantial bovine tissue), or when the risk of infectivity was high and when low. Regardless, MBM continued to be exported until 1990, particularly into South East Asia, some parts of Northern Africa and parts of continental Europe. Live bovines continued to be imported from 1988 to 1993, both purebred and non-purebred, again, particularly to continental Europe. It is appropriate for these countries to be concerned about their risk and to conduct internal risk assessments in order to undertake risk amelioration activities as quickly as possible.


The WHO, the Food and Agricultural Organization (FAO) of the United Nations and the OIE held a joint consultation in Paris in June of 2001. All agreed that BSE is a global problem, and three specific problem areas were identified. (1) Central and Eastern European countries have a very high risk of BSE. (2) Mediterranean and North African countries are at risk, particularly if small ruminants are a problem. (3) Some countries of South East Asia could be at risk if they have bovine populations, or if pigs and poultry contaminate the environment, or if there is an efficient rendering system.

Europe is taking an intensive look at the problem of BSE in sheep; if BSE is present in sheep, the disease may spread laterally between sheep, as with Scrapie. In that case, feed bans would not be sufficient to prevent transmission in sheep populations. Other ruminants such as water buffalo, cervids and camels may have been given feed containing MBM and may be susceptible to BSE, but they have not been studied. Experiments have shown that BSE can jump the species barrier to fur-bearing mammals (e.g., minks); it is essential that these animals not be recycled to animals used for human food. Because fish are fed MBM, there is ongoing research on their susceptibility to BSE. Other farm animals of concern are pigs and poultry; little is known about residual infectivity in these animals. Similarly, there appears to be a naturally occurring spongiform encephalopathy in some types of ostrich; it does not appear to be transmissible, but data are limited. For horses, no BSE-like disease has yet been identified in horses in the United Kingdom, which is where exposure would have been most likely. Cats are known to be susceptible to BSE. Dogs have presumably been exposed in the United Kingdom, yet no BSEs in dogs have been identified.

Another issue identified is the passage of infectivity. Experiments with mice have shown that
TSE infectivity can pass through the gut into the feces and thus contaminate the environment. The conclusion at the joint consultation was that digestive contents and fecal material from livestock or poultry currently being fed with MBM potentially contaminated with BSE should not be used as a feed ingredient for animal feed. Nonetheless, such environmental contamination may have been going on for years in the United Kingdom and Europe.

**BSE in other countries**

In addition to the geographical risk assessments being done by the EC, the OIE will review voluntary applications to determine if countries are in compliance with the OIE Code on Animal Health to be considered BSE-free. This program has just started and is still voluntary, but because the Code informs the World Trade Organization, it may be a powerful incentive for countries to take action against BSE risks. In addition, risk assessments will be requested of all OIE member countries by the International Committee of the OIE. Some Central European, East European and African countries may not have the financial resources for this assessment; other countries may have to assist. The joint consultation in Paris also recommended that all countries require notification and surveillance systems for TSEs of sheep and goats.

For public health assessments, the WHO makes the following assumptions: BSE and vCJD are caused by same agent. The BSE epidemic in cattle was caused by BSE-contaminated MBM. The principle source of exposure for humans is bovine-based food, particularly specified bovine offal and mechanically removed meat (often in meat preparations). Human-to-human transmission is a possible secondary route. There is, as yet, no test to detect the agent in food or in living asymptomatic animals. Therefore, to control vCJD in humans, the BSE epidemic in animals must also be controlled.

The WHO has established standard surveillance methods for vCJD (in collaboration with the EC) and for BSE (in collaboration with the OIE, FAO and EC). Recently, the WHO revised the case definition for vCJD. The WHO has also done regional training in surveillance in collaboration with the two principle surveillance systems (EuroCJD and NeuroCJD). The EC has funded SEEC-CJD for surveillance in South East Asian countries and China. The WHO has a series of TSE collaborating centres being used by different countries, and is working with partner organizations to push for BSE risk assessments to be done.

In summary, the principle under which the WHO is trying to work is that eradication of BSE must remain the principle public health objective of national and international animal health control authorities.

**Questions and comments**

1. **Are there any data on what human plasma products might have been exported from the United Kingdom during the 1990s?**

   Not available at WHO. I do not know if such data exists.

2. **When the blood agencies and regulators in Canada considered upgrading the geographic deferrals, it was considered that France was a likely place to find most of the food exposure outside the United Kingdom because of the import of U.K. beef products. Based on export data, is Italy also highly exposed?**

   It is likely that Italy had at least a moderate degree of exposure. Available data could be
examined to determine the extent of exposure on a country by country basis.
How to Make Good Risk Management Decisions with Inadequate Data: Applications to Blood Supply Safety

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Even with imperfect information, good decisions can be made with the aid of a good risk analysis, for which a risk model is needed. A risk model relates actions to their probable consequences. All models have inputs (actions) and outputs (outcomes of the actions).

In a deterministic risk model, the inputs are known and the analyst calculates the outputs. In the area of blood safety and BSEs, there is no credible deterministic model. In an inverse model, the outcomes are known and the analyst calculates the possible inputs that might best explain the observed output. Another application of inverse models is to begin with a defined desire (e.g., no more than $x$ cases of $y$ in a year) and to calculate how to achieve that desire. Typically, the combination of inputs that produces an output is not unique; therefore, there is room for an optimization model. An optimization model looks at which of multiple ways of reaching an output is the “best” (e.g., most cost-effective). A probability model is similar to a deterministic model, in that the analyst uses the inputs to calculate the probability of certain outputs. A dynamic model is a further iteration of the probability model over a longer time. All these are well developed types of models. Having a trustworthy model is essential to decision-making, but the question is how and when can we get from the incomplete information available to a trustworthy model? Not surprisingly, there is no one unique model that should be used. In many situations, decision-makers need to work with multiple models.

**Decision analysis framework**

For the individual decision-maker, seven statements capture rational decision-making through risk models:

1. All decisions can be represented by choices among risk profiles (probabilities of consequences), of which there is one per action. Many models for decision-making do not just compare risk profiles. For example, models that look at regret look at what other consequences might have occurred had a different action been taken, and how much regret would be involved with one action or the other. Nonetheless, the orthodox principle of rational decision-making is that of risk profiles.

2. Consequences are represented by numerical values on one or more outcome scales. For example, for blood supply safety, one might look at how often there are supply shortages, how often someone contracts an emerging disease from the blood supply, how often someone contracts hepatitis from the blood supply, etc.

3. The best decision is one that maximizes expected utility. This is the golden rule of rational decision-making. Importantly, however, “utility” must be correctly defined.

4. Utilities reflect subjective preferences for consequences and risk attitudes. Different preferences are captured in different utilities. Because two people with identical biases may still disagree about the best action, this individual decision-making point
may not hold true for public decision-making.

(5) Uncertainties are represented by probabilities, derived from explicitly stated models.

(6) Learning takes place by conditioning on data (via Bayes’ Rule and model-based likelihood functions). People used to worry that posterior beliefs depended on prior beliefs (before looking at data), but now many sophisticated techniques exist that emphasize driving out as much subjectivity as possible from estimations of probabilities.

(7) Models can be represented by influence diagrams, which show what causes what and what influences what. These seven principles are the major components of the individual decision analysis framework, which is used for good risk management decisions in the face of uncertainties.

There are three simple justifications for using this decision-analysis framework. The most compelling is that all people should prefer a higher probability of gaining a preferred outcome. In other words, when considering an option that does not have to be taken, one can walk away, with the probability of gaining zero toward the preferred outcome, or one can take the option, with the probability of more than zero toward gaining the preferred outcome. This justification means that the precautionary principle is either meaningless or redundant. A second justification is that the decision analysis framework gives a well-defined value of information for multi-stage and sequential decision-making. The third justification is that this framework offers a universal recipe for prescribing what to do. That recipe is to identify the risk management options, identify relevant consequences, create causal modes and quantify risk profiles, clarify values trade-offs (assign utilities to outcomes), optimize the decision, implement the decision, monitor results, refine the model and repeat.

Missing from the decision analysis framework are consideration of where the models come from (outside decision analysis per se), why others should believe them, how to involve multiple stakeholders and how to communicate the rationale, obtain the needed inputs and gain legitimacy for decision-making.

Applying the decision analysis framework to blood safety

The first ingredient in the decision analysis recipe is to identify risk management options. Often, this step requires a lot of expertise. One option is optimal screening and surveying of donors. Another is optimal deferral of donors. A third is optimal sampling, testing and inspection of blood supply as test kits are introduced. A fourth but probably impractical option might be to involve recipients in risk management decisions; for example, a recipient is offered the choice of a blood product that is available now, but is risky or a product that will be assured safe, but will not be available for months.

Second, the analyst identifies the relevant consequences of the different options. In the rest of this example, the option referred to will be that of donor deferral strategies. Key consequences (both positive and negative) are impacts to the frequencies of blood supply shortages (i.e., blood availability), donations from first-time donors (i.e., blood safety), donations from people infected with HIV, HBV and HCV, and donations from potential carriers of vCJD. There may be other impacts as well, such as costs. Ideally, the analyst should consider the value trade-offs involved in these different attributes relative to one another.

Third, the analyst creates a quantitative causal model. A causal models may be as simple as
a table of the actions and the responses, based on all the variables. The probability of each response is based on the probability of each input. Causal models take a tremendous amount of work; looking at the data, consulting the experts, using defined estimates and assumptions, etc. In this case, the decision is the details of the deferral policy based on expected utility. It must include an estimate of the size of the epidemic in Canada and the effects of the deferral policy on that (excluded vCJD cases) as well as on other factors (blood supply, first-time donations, HIV, etc.). Change the deferral policy, and look at the results again.

One thing to understand and either accept or challenge is that once a consequence model and value model have been developed (and validated if possible), optimizing a deferral policy is not hard. This is exciting news. The toughest part lies not in picking the right policy, but in coming up with value rates and good estimates of the consequences of decisions. In addition, multiple plausible models can be included. One of the big realizations in recent years is that it is okay to acknowledge that no one model is right. One can and should use a variety of models and average them out (Bayesian model-averaging). One of the hardest things in decision-making is the value trade-offs, and only partly because of scientific uncertainties. Nonetheless, the decision analysis framework for risk management decisions can help to structure and solve the decision problem. It can also help to explain, communicate and justify risk management decisions and deferral policies. If the basic breakdown is difference in values or beliefs, that will become clear. If the basic conflict is risk attitude, that too can be clarified.

Conclusions

In conclusion, decision analysis methodology can help make and define “good” decisions even when consequences are very uncertain. Decision analysis requires a credible model to relate alternative decisions to their probable consequences. For vCJD, such models can be built using existing components and data (for epidemic size, travel rates, effectiveness of deferral, competing risks, etc.). The decision framework outlined here provides a useful starting point to structure and solve the risk management problem, but effective multi-stakeholder participation, communication and buy-in require a well-designed decision process.

Questions and comments

1. Health Canada used a variety of methods and data to assess the risk of vCJD for food, blood and vaccine. Unfortunately, the uncertainties are wide in scope, yet policy-makers need to be able to communicate the rationale for their decisions. How does one make, defend and communicate a decision based on such a wide uncertainty range?

When people differ in their value rates, utility can be very different. What decision analysts do is to assign a risk certainty equivalent to each possible outcome to assist in calculations. The certainty equivalent depends on the risk profile (consequences and probabilities) and the risk attitude. That risk certainty can be plotted against the value judgments for a more or less robust rationale for the decision ultimately made. Nonetheless, there must still be a value judgment to consider. There is no way to dodge making that difficult judgment or the subsequent decision based on it. Values clarification (step four in the decision analysis “recipe”) is essential and depends on the decision-maker, not the analyst.
Uncertain Times, Appropriate Actions: Bayer’s Experience with CJD in Canada

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There is a large international industry producing therapeutic products derived from human plasma. These products are widely used in critical care and in chronic treatment (e.g., genetic or acquired deficiencies). Immunoglobulin products are used in a great number of indications (probably about 100 in Canada) for passive immunization or immune modulation (1.5 million grams used in Canada per year). Pathogen safety is a primary concern for all, but it must be remembered that patients have diverse views about what is good for them.

Some, but not all, plasma products can be replaced by recombinant products. Almost all recombinant products are made in mammalian cell lines and almost all of these are exposed to human or animal plasma proteins in the fermentation or purification processes. Most recombinant proteins and most vaccines include human albumin in the formulation. Recombinant proteins are therefore similar to plasma-derived proteins in formal risk assessments.

Pathogen safety is a vital issue to industry and to patients. Following the infection with HIV of haemophiliacs in the 1980s, the Krever Commission examined the blood products industry exhaustively. Most problems were in coagulation products; other plasma-derived proteins generally did not transmit pathogens because the manufacturing process was protective to some degree. Currently, these products are extremely safe because of the overlapping safety layers in the industry. Unfortunately, public perception has not yet caught up. Industry has initiated viral safety measures at the levels of donor screening, donor testing, inventory management, NAT (nucleic acid testing), plasma pooling, viral removal/inactivation and patients. By the time a product gets to the patient, the safety level for viruses is very high.

The plasma industry and patients have suffered because of CJD-related product withdrawals. The first CJD-related withdrawal was in the United States for several lots of Bayer’s Prolastin in 1994; it was a company-initiated withdrawal. There was no replacement product for patients, because Bayer was the only manufacturer. Canada’s first withdrawal (albumin and IVIG) was triggered by a Red Cross donor in 1995. Over 2 days, Bayer stocks went from plentiful to zero. There was nothing to replace that product, either. Initially, the regulatory agencies had no policies for dealing with CJD and plasma-derived products, but most countries quickly developed such policies and withdrawals followed in most countries. These policies evolved as scientists gathered data. The inevitable consequence of CJD-related withdrawals was a series of product shortages for a variety of plasma-derived products in the late 1990s. Many products were lost to patients who needed them.

A risk dilemma is the result. The transmission of CJD by blood products is a theoretical risk, never demonstrated. Conversely, the product withdrawals create real and serious risks for the patients who depend on these therapies. Gathering data to permit appropriate decisions is the only way out of this dilemma.
Bayer safety goals

Several years ago, Bayer looked at CJD and developed related goals: (1) Reduce the pathogen load in manufacturing pools through appropriate testing procedures. (2) Meet appropriate guidelines and standards for virus reduction (regulatory/industry/Bayer). (3) Introduce a global reduction factor based on mechanistically independent reduction steps (centrifugation, filtration, etc.).

The initial Bayer risk assessment in 1995/96 determined that no one could routinely measure CJD infectivity in plasma donations; therefore, it was impossible to rely on donor screening measures. Manufacturers could not inactivate CJD infectivity without destroying their protein products, nor was there any evidence that manufacturers could clear CJD infectivity with their established processes. In addition, significant changes in manufacturing biological products would require new clinical trials to re-establish the safety and efficacy of the products.

Research planning took a pragmatic approach. Because of the time involved in infectivity experiments (one year for standard mouse model) and the significant expense that would have been involved in running multiple such experiments, it was decided to focus on manufacturing. It was decided to put the emphasis on developing a rapid method for screening scaled-down manufacturing steps.

A strong internal research team was established. They refined the Western blot test to the point where it could measure small amounts of PrPres. Selected manufacturing steps were scaled down and proven to duplicate the large-scale step. Western Blot experiments were conducted in replicates. The team relied heavily on external advisors, collaborators and contract research organizations. In addition, the team worked with regulatory agencies around the world to learn as much about the problem as possible. In addition, research information was shared with others to enable rapid progress.

Initially, the researchers were able to test prion clearance for one step at a time. However, because fractionation is linked, tests began to look at the steps linked in series. This provided another check on the process, because whether assayed together or separately, the same results should occur. Eventually, the research team was able to accomplish that with up to three sequential steps (more than three results in too low a titer), giving confidence that infectivity could be cleared.

After six years of international research and development, the manufacturing processes show significant and reproducible clearance. The clearance of infectivity (as shown by bioassay) always parallels the clearance of PrPres. Clearance studies have been repeated with spikes from many sources, both animal and human. Most testing has been published or is in press, and the technology has been licensed out for free use by competitors.

The future

Tests using vCJD material to spike the manufacturing steps are under way. Bayer is collaborating with Health Canada and others to conduct these experiments as quickly as possible. All of the research has been done with brain homogenates. The next step will be to evaluate the infectivity that actually appears in blood and plasma. Internal and external projects to study the molecular nature of the infectivity in plasma are being considered. The level of research effort has not diminished.
Science is necessary, but is it sufficient? Patients in the real world depend on plasma products for their lives. Industry must deal with their concerns, which are not concerns of science. In 1997, bioethics were formally incorporated into Bayer’s decision-making processes through the Bayer Advisory Council on Bioethics. The Council published its first report on CJD in October 1998. Although controversial, this report stimulated useful discussion in Canada and elsewhere. The Council followed it a year later with a report on plasma product supply and demand.

The Council’s report was one voice of many recommending new blood donor exclusion criteria to lessen the risk of vCJD. Although controversial, donor exclusion criteria appear to have been a manageable burden to the blood system around the world and represent an important balance of risk.

*Science, bioethics and policy in a crisis: the Utah donor*

In December 1999, Bayer learned that a regular plasma donor from Utah had developed CJD at a young age. Plasma from this donor had been used in a lot of human albumin used in fermentation for recombinant FVIII (Kogenate). Health Canada put a brief hold on Kogenate until experts could confirm the diagnosis as classical CJD, and then removed the hold. These were the most appropriate actions imaginable, but the Canadian haemophilia community reacted strongly.

In most holds of blood products, manufacturers can put a hold on their own facilities immediately and can reach hospitals promptly; a product is easily held for a few days. Kogenate is self-administered. Bayer had to call every individual to tell them not to use the product and why. It was devastating to the community. It caused a crisis in confidence that took many months to diminish, and many effects remain today. Many people have a high level of distrust of companies, of government agencies and even of the blood system operators. People trust other people more than they trust institutions. It takes a long time to regain trust.

Interestingly, the Utah donor caused a major crisis of confidence in Canada, but only in Canada. The donor was discussed widely in the United States but was not a major concern among American patient groups.

The haemophilia population remains the group that generally argues on the side of absolute pathogen safety in plasma products. Other chronic patient groups, such as those with immune deficiencies or other genetic deficiencies, often focus on product supply as their dominant safety issue. Manufacturers, the medical community and regulators have to balance these needs, treat people respectfully and give people the information they need to go on with their lives.

Lessons for industry are several. Manufacturers must always strive to have the best scientific basis for decisions and fund internal pathogen safety programs without interruption. They must speak to all patient groups about pathogen safety on a regular basis C not just when a crisis occurs B to ensure that clients understand the on-going risk assessments and research efforts. Manufacturers must work collaboratively not only with regulators and academic scientists, but also competitors to identify and fill in gaps in knowledge and policy as quickly as possible. Industry must not compete on safety.

*Questions and comments*

1. Both Aventis and Bayer have fine pathogen groups. What will happen if the companies merge?
Bayer and Aventis have signed a non-binding letter of intent to discuss a joint venture. No details are out as yet.

2. *What about other precautions in manufacturing, such as decreasing pool size?*

Typically, 5,000 to 10,000 liters of plasma are pooled, which means it could be plasma from 10,000 human individuals. Some products are present in low amounts in plasma; therefore, the manufacturer can take intermediate material and combine plasma further. Because of the risk of wider spread of a pathogen with greater pool size, industry and regulators agreed years ago that no product would have more than 60,000 donors. There is probably a lower limit as well for reasons of economy and biological safety.

3. *As a risk management step, do plasma product manufacturers restrict their suppliers to certain geographic areas?*

Manufacturers occasionally buy and sell intermediates. Bayer purchases intermediates only from manufacturers who are qualified by our internal quality regulations, and only in North America. The former is part of the licensing provisions of the regulatory agency.

4. *What about vaccine safety?*

Albumin is a common constituent in vaccine. When Bayer was assessing CJD clearance for its products, it came up with a figure of least 10 logs of clearance C a small level of infectivity would be cleared many times over. However, that will differ for other manufacturers’ albumin. A common understanding is needed of manufacturing processes is needed.
Response to the Theoretical Risk of Transmission of vCJD by Blood Transfusion: A Global Standpoint

Dr. Luc Noel, Co-ordinator

Blood Transfusion Safety, World Health Organization Secretariat

The theoretical risk of vCJD transmission by blood transfusion was identified by the United Kingdom and other countries sharing a number of characteristics: public concern about transfusion-transmitted infections, effective prevention of established transfusion risks, objectives of maximal rather than optimal transfusion safety, nationally co-ordinated transfusion services, detection measures for BSE and vCJD and resources to implement precautionary policies. For several reasons, the risk is global. Blood donors who traveled may have been infected through the food chain in countries with BSE. In most countries, indigenous risk must be considered possible because of the potential for imported infected bovine material in human foodstuffs or because of imported or indigenous cattle fed infected MBM. Secondary transmission through transfusion could present broad dissemination of vCJD, and there could be human adaptation. Both would present a major obstacle to the global eradication of vCJD.

Decisions about responses must balance the theoretical risks of transfusion against the risks presented by the safety measures. In addition, the balance must be economically, scientifically and publicly acceptable.

Globally, there are 75 million blood donations per year. About 60% of those donations are used in developed countries, which collectively have only about 20% of the world’s population. Developing countries severely lack access to blood transfusion therapies. The picture is even bleaker when the source of donations is examined. The safest donations are from voluntary, non-remunerated donors. Almost all the donations in developed countries are from such sources. In developing countries, well over half of donations are from family members or paid donors. The poorest countries rely almost solely on family replacement donations. Moreover, data in the WHO global database on blood safety indicate that 23% of countries do not test all blood donations for syphilis, 13% for HIV, 48% for HCV-antibody and 19% for HBs-Ag. Overall, the developed countries test 100% of the blood supply for the main transfusion-transmitted agents; in the developing countries, 43% of the blood is untested for those agents. In sum, 80% of the world has access to only 20% of the safe blood supply.

Variant CJD and the global blood supply

The WHO has been asked to advise on the global blood supply safety in relation to vCJD. There has been consensus (see the Weekly Epidemiological Record of 24 November 2000 and 14 December 2001 at the WHO web site: www.who.int) that the theoretical risk of vCJD transmission should not lead to depriving patients of vital transfusion therapy. It should not increase the established risk by recruiting new donors from populations previously considered unsafe. It should not divert resources from established risk prevention or other health care needs of the country.

Those agreements led to six practical recommendations for optimal safety and the best use of resources. (1) Countries should strengthen the appropriate use of blood with consideration to known, unknown and theoretical risks. (2) Prevention of known risk is the priority. (3) Donor deferral
is an option as long as it is not detrimental to the management of known risks. It requires appropriate counseling to alleviate donor anxiety. (4) Pre-stored leukodepletion may not be cost-effective in light of the health care needs of the country. (5) Evaluation must occur at the country level (resources and capacity for evaluation are issues). (6) Regular reviews of policy should be undertaken in consideration of growing knowledge and changing circumstances.

The ability to react at a national level is an indicator of the quality of transfusion services. It is also part of the gap between developed and developing countries. A nationally co-ordinated transfusion service enables the capacity to recognize, prioritize, plan, implement and evaluate blood safety measures. It comes from government commitment and sustained support, efficient oversight by national health authorities and international exchanges. Global collaboration is essential for blood safety.

Given the need for the ability to react at a national level, how many countries can? The WHO database indicates that 35% of countries have a specific co-ordinating organization, a blood policy and national regulation. Twenty-one per cent of countries have a national executive body, advisory groups and a medical director or manager for blood transfusion services. Thirty-four per cent have some type of quality system, but only 23% have a trained quality manager or officer. Forty-six per cent of countries have a specific budget for blood transfusion services, but 60% of countries do not have costing procedures.

The WHO strategy for blood safety starts by stating that nothing significant can be done if there is not a nationally co-ordinated blood transfusion service. Government commitment and support are essential to blood safety. Voluntary, non-remunerated blood donors from low-risk groups of the populations are critical. All donated blood must be screened for the relevant agents. There must be a reduction in unnecessary transfusions. A quality management system must be in place.

If science should demonstrate that vCJD can be transmitted by blood transfusion, it could dramatically weight the scale of risks (risk from transfusion vs. risks introduced by safety measures) toward the side of transfusion. If that occurs, then more radical measures could be used to ensure the safety of the blood supply. Unfortunately, that would further widen the gap between the developing and developed countries.

Summary

BSE/vCJD is a product of the developed world. Secondary human-to-human transmission through health products of human origin is a potential global issue. Precautionary measures are a luxury for most countries faced with basic access and safety issues. As a result, there is a widening gap in transfusion safety between developed and developing countries. There is a need for better identification of national responsibility and the national ability to make and enforce decisions. There is also a need for global harmonization through communication and international assistance.

Questions and comments

1. *Might it be appropriate to defer people who have received a blood transfusion in the past? It is probably not a huge group, so there would not be a huge impact on supply.*

   Some countries have implemented such a measure, but not without difficulties, particularly in explaining the reasons. Who is considered a past recipient: those who have received
labile blood components? fractionated products? Even if recipients of labile components are deferred, it can have a significant impact on supply, as past recipients are often the best advocates of donation. People who owe their life to transfusion often want to give back. In addition, people may not know if they have been transfused while anaesthetized. The issue must be pondered country by country.

2. **Blood testing is enormously expensive, but developed countries do it to maintain a high degree of blood safety. How realistic is global collaboration with most developing countries that do not have testing procedures?**

   The important thing to cultivate and nurture is communication. Blood safety issues should be highly visible as well known by the public as other health care issues. If properly informed, people at all levels can make the right decisions. Most issues are linked to improved communications.

3. **Is there a plasma fractionation industry in the developing world?**

   Yes, especially in transitional countries. All regions of the world have a fractionation industry.
Modeling and Projection in the CIDPC: Roles and Context

Dr. Ping Yan, Chief
Division of Modeling and Projection, Centre for Infectious Disease Prevention and Control
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Currently, the Division of Modeling and Projection is staffed by statisticians, with master degrees or doctorates in statistics or biostatistics. In the future, the Division’s scope will be broader than statistics and biostatistics. For example, it will include biomathematics, operations research and computer simulation. Modeling and projection is a broader concept still, incorporating statistical, mathematical, epidemiological, economic and demographic models. The image of the statistician as a passive observer obsessed with ideal analyses must be replaced by that of an active, goal-oriented doer and leader.

How do modeling and projection apply to infectious disease prevention and control? First, prevention and control is about the spread of disease and, if possible, its elimination. Information is used to develop strategies, defined by policies and programs. Second, to control the size and consequences of disease, information is used to make assessments that lead to policies and programs. To achieve either of these, surveillance is essential. That means collecting, synthesizing and disseminating information, which is a function of modeling and projection. Similarly, turning knowledge into policies and programs is also a function of modeling and projection. These concepts lead to the three primary roles for modeling and projection in the context of the Centre for Infectious Disease Prevention and Control: (1) Modeling and projection provide public health information for policy and planning by synthesizing multiple sources of data and information, by analyzing that information and by translating information collected through surveillance, special investigations and epidemiological research into public health options. (2) Modeling and projection provide guidance for data collection and surveillance. (3) Modeling and projection provide services to the Centre such as assisting epidemiology analysis and research in different areas and statistical consultation.

A famous statistician once said, All models are wrong, but some are useful. Models are useful for what they are intended for. The chosen models and the data collected must be relevant to the intended objectives. Sensibly used, models are tools for understanding the epidemiological process. They can create conceptual clarity by finding links between observed and unobserved quantities. They suggest what kinds of data need to be sought. Therefore, the person using the model must first establish directions and objectives to ensure that the collected data are appropriate and to ensure that the policy and program objectives can be met.

Turning knowledge into policies and programs

In the context of preventing, controlling and, if possible, eliminating disease, the policymaker must first consider the disease category. There are many ways to classify infectious diseases: by route (direct transmission vs. vector transmission), by extensiveness (household or small community vs. widespread), by natural history, genetics or immunology (no silent carriers vs. silent carriers, which leads to concerns about vertical transmission through the blood supply), by prevalence (rare vs. common), by newness (emerging vs. endemic) and by preventability (vaccine preventable vs. no vaccine yet). (Do TSEs or vCJD fall into any of these categories?) Once the category is established, prevention or elimination strategies, model design, data collection and operations research must be tailored accordingly. Information needed to come up with a set of options includes transmission routes, determinants toward transmission, possible prevention
strategies and the effectiveness and adverse consequences of those strategies.

In the context of controlling the size of disease, the policy-maker must consider the initial size (the expected size at Day 0, defined as when the first case is identified by a public health worker), as well as the final size (if possible, based on the best available eradication strategy, what is the expected cumulative number at the time of extinction). Information needs include access to treatment and care, health promotion efforts and economic impact, all of which depend on the determinants toward transmission and the prevention strategies. In the context of controlling the consequences of disease, human, societal and economic consequences must be considered. Human consequences include morbidity, mortality and adverse events caused by the prevention methods (e.g., vaccination toxicity). Societal consequences include fear (especially in the context of bioterrorism), stigma and prejudice. Economic consequences include consumer confidence, food safety, agriculture and more.

Depending on the objectives, the types of modeling can differ, the terminologies can differ and the ways of collected data can differ.

**Example: Smallpox vaccine:**

In the United States in 1968, 572 people were confirmed to have serious complications and 9 people to have died as a result of smallpox vaccination. The absolute number of 583 was of concern given that the vaccine was being used to prevent an extremely rare disease in North America. The public health question was a rare event of an imported case [or, today, a terrorist attack], what is the optimum proportion, or coverage, of the population at risk that need to be vaccinated? If the strategy is for the least percentage, models could provide the minimum percentage of the population to be vaccinated. Eventually, the epidemic will be extinguished. That would not be best strategy, because if vaccination is increased, the final size and consequences by the time of extinction will be reduced. Conversely, 100% vaccination is not the best strategy either, because due to the rarity of the disease, the adverse events overtake the benefits. Operations research is needed to provide the optimal percentage to be vaccinated to minimize the overall consequences.

**Example: Basic reproduction number:**

In modeling, the basic reproduction number ($R_0$) allows one to determine the amount of necessary effort to prevent or eliminate an epidemic:

$$R_0 = \text{mean duration of infectious period} \times \text{mean contact number during this period} \times \text{infectivity rate per contact}$$

As an example, consider the question “Can heterosexually transmitted HIV sustain in Europe?” In Europe, the proportion of AIDS cases attributed to heterosexual transmission outside the group of intravenous drug users is very low. Some authors used a rather complicated model, calculated the value for $R_0$ and came to the conclusion that “with present behaviour, the indigenous spread of HIV is not likely to sustain an epidemic in the Norwegian heterosexual population”. However, this conclusion depends on the model assumptions that determine the formula for $R_0$.

**Example: HIV/AIDS:**

In modeling for policy-making for infectious diseases such as HIV/AIDS, the input is confirmed and reported cases of the disease. The statistical model and methods must
correct for data selection biases (reporting delay, under-reporting, etc.) and present trends as functions of time, age and spatial distribution. The outputs are the number of new infections (incidence), the number or percentage of people living with infection (prevalence) and the projection of trends for incidence and prevalence. The outputs must be multiplied by the percentage of people who have access to care and direct and indirect costs to reach the ultimate goal of quantitative statements on needs for treatment/care and economic burden.

Based on data to the end of 1992, the Division modeled the HIV/AIDS trend and determined that the incidence and prevalence were much higher than reported at the time and would continue to climb. This statement was not immediately accepted, particularly because previous studies with limited data had suggested that reporting delays were not very long. In 1995, highly active anti-retroviral therapy was initiated and the model had to be adjusted. Nonetheless, by the end of 1999, it was clear that the Division had been highly accurate in its modeled predictions of the HIV/AIDS trend.

Questions and comments

1. How can the statistical model described be applied to vCJD?

As with the under-reported cases of HIV infection, the observed illness (number of confirmed cases of BSE) can be used to estimate the total burden. The lack of data is certainly a major problem. It might be interesting to model the possibility for horizontal transmission. The number of cases in the United Kingdom dropped dramatically after the feed ban, and there is little evidence of transmission from herd to herd or even within a herd. Modeling might therefore suggest that the disease could not be sustained for very long.

2. According to much of the analysis and modeling described at this meeting, Scrapie in sheep should probably self-extinguish. Nonetheless, it has been extremely recalcitrant to any type of management for centuries. It is suggested that the models described should all be applied to Scrapie in sheep. If the models suggest that Scrapie will die out, then the models would clearly be flawed. Policy-makers should be cautious about placing too much weight on the predictions of models.
Working with Small Samples

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Small samples can present big problems. The relative rarity of vCJD means that statisticians are pushed to the edge in trying to measure the phenomenon. Nonetheless, there are statistical strategies for dealing with small sample sizes, two of which are effect sizes/significance levels and exact permutation inference.

Significance tests are what bring \( p \) values the statistical probability of the likelihood of a phenomenon occurring by chance alone. They are driven by both the size of the effect and the size of the study. In any study of the relationship between two variables, one needs an estimate of the level of significance at which to reject \( H_0 \) (null hypothesis). This is expressed by the \( p \) value. One also needs an estimate of the degree of departure from \( H_0 \), which is expressed by the effect size. Thus, the relationship between the effect size and the significance test can be expressed as follows:

\[
\text{significance} = \frac{\text{size of effect}}{\text{size of study}}
\]

In other words, the \( p \) value is a function of both the magnitude of the effect and the size of the study.

Often, small samples lead to results not reaching conventional significance levels (\( p < 0.05 \)). They can also lead to mistakenly accepting \( H_0 \). A consideration of effect size can lead to insight of a possible relationship that might be significant if more subjects were available. Variant CJD falls into this category, which is why one must go beyond the pure statistical approach and look at more than just the \( p \) value.

Possible outcomes of the relationship between effect sizes and significance levels can be expressed in a simple table:

<table>
<thead>
<tr>
<th>Significance Level</th>
<th>Small Effect</th>
<th>Large Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small</td>
<td>No inferential problem</td>
<td>Mistakenly conclude no relationship</td>
</tr>
<tr>
<td>Large</td>
<td>Mistake statistical significance for practical importance</td>
<td>No inferential problem</td>
</tr>
</tbody>
</table>

Exact permutation inference for categorical and nonparametric data means that exact \( p \) values and confidence intervals can be calculated with small samples based on permutational
distribution (e.g., Fisher’s exact test) of the test statistics. With the computing power of today and the efficient algorithms developed in the 1980s, permutation distributions can be used in more complex situations.

Unconditional sampling distributions

The exact distribution of risk factors depends on the sampling scheme used to generate them. When classifications are categorical, one can have full multinomial sampling, produce multinomial sampling or use Poisson sampling. Under each sampling scheme, there will be unknown quantities or parameters.

With full multinomial sampling, one can sample \( N \) individuals to determine if they have vCJD and a given risk factor. With product multinomial sampling, one takes a number of individuals and classifies them all to either have vCJD or not. Poisson sampling is a variation on the others.

The probability distributions for a given risk factor depend on \( rc \) (where \( r = \) row and \( c = \) column) unknown parameters. Under \( H_0 \), unknown parameters are reduced to \( r + c \) or \( c \). Asymptotic inference relies on estimating these unknown parameters (e.g., maximum likelihood equations). In exact inference, nuisance parameters are eliminated by conditioning on sufficient statistics.

Conditional sampling distribution

Key to exact permutational inference is eliminating the nuisance parameters from the probability distributions. This is done by restricting the sample space to the set of \( r \times c \) contingency tables that have marginal sums.

Nuisance parameters are eliminated by conditioning on the margins of the observed contingency table. Some margins are not fixed for sampling.

Calculating exact \( p \) values for small samples is not a trivial task. Software that assists is StatXact 4 (version 4.01). It can be found at www.software.com.tw/soft/statxac1.htm. Another excellent resource is the Exact-Stats web site, which is hosted by a group of statisticians and where problems and solutions can be posted (e.g., a BSE-related problem was posted September 1999) and searched by topic. The address is www.mailbase.ac.uk/lists/exact-stats.
Panel Discussion

Panelists:
Robert Peterson, Mike Coulthart, Bob Hills, Robert Rohwer, Herbert Budka, Maura Ricketts, Mark Pickett and George Wells

International efforts

Susie ElSaadany is putting together an international advisory committee on risk assessment for rare and emerging diseases. She will be contacting a variety of people, but participants at this meeting were invited to contact Ms. ElSaadany with any ideas on who should be a member of the committee or what expertise should be represented (susie_elsaadany@hc-sc.gc.ca).

It was suggested that another international conference of risk assessors in this area be convened in spring 2003. From an international perspective, there is certainly room at the international level to review the risks related to BSE. Numerous countries and agencies have started assessing the risks from different perspectives. It would be useful to learn more about why they use different methods and whether they thereby get different results. It would be valuable to have different experts before an audience to question and discuss the assessments. Risk assessment is the tool of the wealthy. For global organizations such as the WHO, it can be frustrating to see all the power, intelligence and time going to reduce risk from near zero to very near zero. Risk assessment has a role in semi-legal organizations outside the national authorities, such as Codex and the WTO.

Similarly, an international conference would be extremely useful from a laboratory perspective. Agenda items could include the ways in which biological models, especially in animals, connect with risk assessment needs to be examined, and the effects on risk mitigation of introducing new screening tests for the blood supply. There is a huge gap between risk assessors or modelers and laboratory or data people. It would be useful if models could get beyond recognition that such measures as the feed ban work to issues such as what it would take to make a BSE epidemic self-sustaining.

If an international conference is held, the right mix of people is necessary. In addition to modelers, content people must be invited (e.g., laboratory experts, policy experts, recipients of policy decisions [patients, physicians], data experts, etc.). Physicians and hospitals, for example, need to know how to relate BSE risk to practice (e.g., at what level does it become necessary for hospitals to undergo decontamination procedures for surgical instruments? Are these precautions in balance with the costs?) Communications people should also be invited, because one thing that the world of science does not do well is to communicate with the public about small risk. Science in general needs to be able to communicate better about what it does. (“If you can’t explain something in a way that a reasonably intelligent 14-year-old would understand, you don’t fully understand it yourself.”)

Other potential questions to be considered at an international level are the human risk if BSE has entered sheep (no precautions are in place anywhere) and the human exposure limit line (i.e., possible exposure at which there is no longer a hazard). The possibility of broadening the conference beyond vCJD to other blood-borne pathogens or perhaps xenotransplantation was also raised. It was noted that the objective or deliverable of any such conference would have to be clearly established before planning, perhaps by an international panel.
Nature of modeling

One idea that seemed to be brought forth during the meeting was the idea that if data exists, then a model is not needed, and if data is missing then the model is speculative fiction, so why use it. Nonetheless, a model is useful for answering “what if” questions. Certainly with BSEs and vCJD, it is far from the truth to say that there is no relevant data. In addition, modeling is not done in isolation. Expert opinion and consensus help build and validate the model.

For policy-makers, models must be transparent, reproducible and should apply standard methods such as face validity, content validity, etc. If models generate a result that is counter-intuitive, then the modelers must be able to clearly explain what data and assumptions they used, how and why they came up with the result. Confidence in the results, or at least knowledge of what degree of confidence should be placed in the results, is essential. In addition, the model must be able to answer the specific questions that were raised by the policy-maker. The model should not raise more questions than it answers, although it is useful when a model can point out important areas where there are significant data gaps and are thus worthy of research.

It is important to communicate the results of modeling to decision-makers and the public in a meaningful way. Models are thinking tools C no more, no less.
Closing Remarks

Susie ElSaadany thanked all participants for the contributions to this important meeting. International communication must be kept alive and done frequently. There is a tremendous need to work globally such that blood safety is no longer just the luxury of the rich. It is a global village. Canada cannot protect itself without reaching out to the rest of the world.