

**Review of Scientific Evidence to Inform
Australian Policy on Transmissible Spongiform
Encephalopathies (TSEs)**

2009 Addendum

Version of 20 September 2009

(Minor amendment 9 October 2009)

Prepared by

Prof John Mathews
Consultant
Health Explanations Pty Ltd
19 Earl St
Carlton North 3054
mathewsj@unimelb.edu.au

Scope of this Report

The required scope of the consultancy is described in the Terms of Reference.

This 2009 Addendum emphasises those questions that could not be resolved in earlier reports because of limited information. Otherwise, it is intended to be as self-contained as possible. The Executive Summary with Conclusions is supported by a short Scientific Review, and by risk estimates and essential references dealing with evidence that may have changed since the earlier reviews. It has been impossible to access all potentially relevant references in the time available¹. The earlier reports providing scientific advice to government on TSE policy are available as annexes.

Acknowledgements

Information for this review was provided by the Department of Health and Ageing, the Therapeutic Goods Administration (TGA), Food Standards Australia and New Zealand (FSANZ), and the Department of Agriculture, Forestry and Fisheries (DAFF).

The National Health and Medical Research Council provided access to working papers and reports of the Transmissible Spongiform Encephalopathy Advisory Committee (TSEAC). That Committee provided helpful comments on a draft version of this report.

The University of Melbourne provided access to facilities and approved the secondment of Ms Joanne Chesson to assist the consultant in the acquisition and collation of references, and in the formatting of the report.

The consultant is entirely responsible for the selection of the information for this report, and for the interpretations offered. In doing so, he has drawn upon more than 40 years of experience as an epidemiological researcher; he published on kuru in 1965-76 and again in 2008. As Deputy Chief Medical Officer he advised government on TSE policy from 1999-2004, and he represented the Chief Medical Officer on TSEAC from 2004-2006.

¹ Pubmed alone lists some 13,000 scientific papers with potential relevance to this review.

TERMS OF REFERENCE	4
EXECUTIVE SUMMARY	5
CONCLUSIONS.....	5
New understandings from surveillance and epidemiology	5
New understandings and questions from laboratory science	6
Implications of the science	7
SCIENTIFIC EVIDENCE.....	9
BACKGROUND AND HISTORY	9
Understanding TSEs	9
Understanding prions.....	10
Bovine Spongiform Encephalopathy	11
Variant Creutzfeldt-Jakob Disease (vCJD).....	11
Blood-borne transmission.....	13
Continuing Significance of the Global BSE epidemic.....	13
How does vCJD risk relate to BSE burden?	14
Predicting the final size of the primary vCJD epidemic in the UK.....	14
Predicting the size of the secondary vCJD epidemic in UK	15
SCIENCE AND CONTROL MEASURES	17
How adequate are the control measures in BSE-affected countries?.....	17
New OIE framework for BSE control and trade.....	18
Evolving BSE policies in the UK and other countries.....	19
RISKS FOR AUSTRALIA	20
Risk management to prevent BSE entering Australia.....	20
What is the risk of vCJD from Australian beef products?	20
What is the risk of vCJD from imported beef products?	21
Is there an Australian risk from other animal TSEs?.....	21
Risk of vCJD in Australian residents who were exposed to BSE while resident overseas.....	22
Risk of secondary transmission of vCJD by Australian blood or blood products	22
Risks of secondary vCJD from Australian plasma products.....	23
Risks to the Australian public from therapeutic goods	24
Risk from surgical spread of vCJD and CJD in Australia	25
SUPPORTING INFORMATION & RISK ASSESSMENTS.....	27
TABLE 1. Important TSEs and their characteristics	27
TABLE 2. BSE incidence by country and year	28
TABLE 3. Incidence of vCJD by country	30
TABLE 4. Risk of vCJD in Australia from beef imports	31
TABLE 5. Estimated final size of primary vCJD epidemic in UK.....	32
TABLE 6. Risk of future vCJD cases in Australia	33
Fig. 1. BSE surveillance in UK and rest of EU by year.....	34
Fig. 2. Time course of vCJD deaths in UK epidemic	35
Fig. 3. Bovine Infective Units (ID50) Entering the UK Food Chain by Year	36
SELECTED SCIENTIFIC REFERENCES.....	37
OTHER SOURCES. Hot links to selected sites and source documents.....	43

Terms of Reference

The Consultant must update and re-examine the scientific evidence used to inform Australia's BSE policy particularly in relation to food and the flow on implications to human blood, human blood products and other human therapeutic goods to reflect any advances in scientific knowledge since the last update to the review in 2006.

The Consultant must:

- consider the two scientific reports: *Review of the Scientific Evidence to inform BSE Policy* (April 2005); and the *Addendum and Updated Executive Summary Scientific Risk Assessment* (9 August 2006), and in addition:
- consider any new scientific information that has become available since the reports were developed, in the broad but with a specific focus on the implications that a change to policy that allowed low risk beef and beef products to be imported from countries that are considered BSE 'negligible' or "controlled" risk may have for human blood, human blood products and other human therapeutic goods;
- consider any new scientific evidence in relation to the effectiveness of controls that have been put in place to ensure that cattle tissues that could potentially contain the BSE agent do not enter the food chain from countries that have had BSE infections in indigenous cattle;
- draw on relevant scientific literature concerning the transmission of variant Creutzfeldt-Jakob (vCJD) in particular, and where relevant, of other transmissible spongiform encephalopathies (TSEs), to assess the current level of knowledge relating to the science, epidemiology and technical information of vCJD disease and control mechanisms for preventing vCJD contamination in relation to possible transmission by human blood or human blood products or other human therapeutic goods; and
- provide an updated Addendum, with an executive summary, against the reports that clearly articulates any new evidence, updated conclusions, an assessment of the risks associated with a change in food policy that allowed beef and certain beef products to be imported into Australia from BSE "negligible" or "controlled" risk countries and identifies whether any further measures would need to be taken to protect Australia's food, human blood supply or the safety of other human therapeutic goods.

Executive Summary

CONCLUSIONS

New understandings from surveillance and epidemiology

1. It is now very clear that the epidemic of BSE in cattle, most particularly in the UK, triggered a later epidemic of variant Creutzfeldt-Jakob disease (vCJD) in a very small proportion of the people exposed to BSE-contaminated food².
2. Over the last five years the evidence for more effective control of the global BSE epidemic has strengthened. Passive and active surveillance³, carried out in accordance with OIE guidelines and EC legislation, has shown that numbers of BSE-affected cattle are falling year by year in virtually all affected countries (see Table 2 & Fig.1).
3. The amount of BSE-infected material entering the human food chain in “controlled BSE risk” countries such as the UK is now very small (see Fig.3) because of the decline in BSE, the removal of brain and other specified risk materials (SRMs) from carcasses, and the detection and destruction of infected animals.
4. The epidemic of human vCJD from past consumption of BSE-contaminated food still has to run its full course, in UK and other affected countries (see Table 3 & Fig.2).
5. However, the final size of vCJD epidemic in the UK can now be estimated more precisely; it is likely that the maximum number of cases will be limited to several hundred (Table 5), rather than the many thousands previously feared.
6. The risk of future food-borne transmissions leading to human vCJD is very small, if not negligible, even in the UK (see Table 5), where previously the risk was greatest.
7. The final size of any primary vCJD outbreak in Australia seems likely to be limited to no more than several cases (Table 6). As no case has yet been observed in Australia, and as the overseas epidemic of vCJD is declining, it is possible that Australia will escape without any cases of vCJD.

² It is important to recognise (vCJD), that many primary transmissions of vCJD, which have already happened because of the past consumption of BSE-infected food, have not yet led to disease. This means that **future cases** will arise from **past transmissions** for some years to come. However, because consumption of BSE-infected food has virtually ceased, there are unlikely to be any future **primary** transmissions, even in UK. Future person to person (**secondary**) transmissions can occur via blood, plasma products, or contaminated surgical instruments.

³ Passive surveillance is detection of BSE in cattle that come to attention because they show signs of disease. Active surveillance is detection of BSE through routine testing of otherwise healthy animals.

8. Even if cases of vCJD are detected in Australia from overseas exposure to BSE-contaminated food, the numbers will be small, making it unlikely that there will be any secondary cases in Australia from blood, plasma products or surgical transmission (Table 6).

New understandings and questions from laboratory science

9. Experimental models for prion disease have identified circumstances where infectivity can be “carried” in an animal for long periods, and transmitted to others, without the “carrier” animal ever developing disease within the normal lifespan of the species.
10. Such findings have raised the possibility that the primary epidemic of food-borne transmission in the UK may have infected a large number of as yet undetected “carriers” of vCJD, who might transmit the prion to others, without themselves being affected by disease within the usual incubation period. However, if this were happening and those infected by secondary transmission were at risk of disease with an incubation period comparable to, or shorter than that of the primary vCJD epidemic, we should by now have seen a secondary peak in vCJD beginning to emerge in the UK. As this has not happened, any theoretical risk of disease in “carriers”, or their secondary progeny, could only emerge after a very much longer incubation period, if at all.
11. New and sensitive methods for the detection of vCJD prions in blood may help to answer, in future years, whether the observed clinical cases of vCJD are all that matters in the human epidemic, or whether they are merely the tip of the iceberg, with a larger number of as yet undetected “carriers”.
12. If “carriers” are detected⁴, it would be crucial to see whether those not developing disease are protected by PrP genotype or other genetic factors, and to determine, whether, over longer incubation periods, they will develop vCJD or some other manifestation of prion disease.
13. Animal experiments have shown that in some circumstances, it is possible to partly prevent or delay the onset of prion disease by immunising with the prion protein, or by giving anti-prion antibodies⁵. Although it is theoretically possible that pre-symptomatic carriers of vCJD might benefit from such immunisation strategies, trials will not be justified until the many ethical and scientific problems have been resolved.

⁴ Such work presents many ethical dilemmas. See Tabrizi et al (2003); Bird (2004); Duncan (2005); Shalowitz et al (2009). Earlier surveys using tonsillectomy and appendicectomy specimens were done using permanently de-identified samples. With appropriate ethical safeguards, it might be possible to use a “re-identifiability code”, so that if a person were to subsequently develop vCJD, it would be possible to look back and see whether their blood had previously been tested for prion status. Such a system could also allow for “carrier positive” individuals to opt-in for any treatment that might subsequently become available.

⁵ See Sakaguchi et al (2009).

14. Other therapies to treat or prevent vCJD have been proposed, but none has been shown to be effective⁶.
15. Recent scientific advances also allow for the more effective sterilisation of medical and surgical instruments and devices that need to be re-used after the possibility of contamination with vCJD-infected material.
16. Techniques to monitor the effectiveness of prion clearance after sterilisation procedures have also been greatly improved.

Implications of the science

17. Beef imports from “controlled risk” or “negligible risk” countries, with appropriate certification, would lead to only a negligible⁷ increase in vCJD risk in Australia (Table 4).
18. Any BSE-related risks arising from therapeutic goods and cosmetics are also considered to be negligible. These risks would not be expected to change if beef products were imported from “controlled risk” or “negligible risk” countries.
19. The risks of secondary transmission of vCJD in Australia arising from blood transfusion, use of plasma products, or from surgical and dental procedures are very small or negligible (Table 6).
20. It is possible that a new generation of laboratory assays will soon be able to detect prions with high sensitivity and specificity in blood and other samples. If justified by the likely balances of benefits to costs, these assays could then be applied to detect:
 - a. Any prion contamination of human plasma pools and plasma clotting factors prepared in Australia;
 - b. Any prion contamination of bovine ingredients in Australian vaccines and other therapeutic goods;
 - c. Any prion contamination of Australian blood donations;
 - d. Any prions in blood of Australian deferred donors.
21. If individual blood samples were to be tested for vCJD prions, there would be a need to address complex ethical issues. Testing could proceed with de-identified samples, but with a confidential “re-identifiability code” that would allow for look-back if a tested person subsequently became diseased, and also allow for opt-in by a person testing positive if a new treatment option were to subsequently become available.

⁶ See Geschwind (2009).

⁷ “Negligible risk” does not imply zero risk. It simply implies that the risk in question is very small in comparison with the other risks that people assume in everyday life. An estimate of the absolute risk to Australians from UK beef imports is quantified in Table 4, and found to be 40 million times less than the risk from road accidents.

22. Good public communication would help to:

- Reassure the Australian public about any proposed changes in food imports;
- Reassure the risk groups (eg haemophiliacs and other recipients of plasma products) about the low levels of risk to them, in the light of new assessments such as in Table 6;
- Reassure health professionals and dentists, and patients about the low risks of secondary transmission of vCJD following surgical or medical procedures in Australia, while emphasising the need for continuing “universal precautions”.
- Remind health professionals and the general public, that although the risk is low, it is still possible that a person first infected in the UK will develop vCJD in Australia.

23. In preparation for any such case of vCJD, CJD surveillance in Australia needs to be maintained, with adequate support and access to specialist anatomical pathology services and facilities.

24. The vCJD response plan, previously developed by DOHA, outlines advice to be followed with any suspect case of vCJD; in the meantime, provisions of the plan that are no longer current could be updated, and responsible staff could be re-briefed.

25. Advice about the new procedures for the sterilisation of instruments potentially contaminated with vCJD and CJD prions could be updated, together with advice about the availability of new tests that can assess the completeness of prion inactivation following such sterilisation procedures.

26. NHMRC previously provided advice on TSEs to government through TSEAC. As the science continues to evolve, there may be a continuing need for expert review, perhaps through a reconvened TSEAC, or another expert group.

Scientific Evidence

BACKGROUND AND HISTORY

Understanding TSEs

27. Transmissible spongiform encephalopathies (or TSEs) are degenerative diseases of the brain and nervous system that are “transmissible” from individual to individual; when examined under the microscope, the “encephalopathy”, or disease of the brain, shows “spongiform” changes⁸.
28. The first TSE to be recognised was scrapie, which had been known for several hundred years as a sporadic disease of sheep. As early as 1899, scrapie was shown to be transmissible by injection of brain tissue from affected sheep to otherwise unaffected sheep; disease in recipients developed after a latent period of 6 months or more. Scrapie has also been transmitted to mice and to other experimental animals in the laboratory.
29. The epidemic of kuru, a fatal disease of the nervous system affecting the Fore people in the highlands of Papua and New Guinea, was first reported in 1957⁹. Spongiform changes in human brains from kuru patients, reminiscent of the changes in scrapie brains, led researchers to inject affected human brain tissue into chimpanzees. In 1966, Gajdusek, Alpers and co-workers reported that kuru had developed in a recipient chimpanzee after an incubation period of 20 months.
30. Spongiform changes in human brains were also known to occur in Creutzfeldt-Jacob disease (CJD), a rare degenerative disease causing rapidly progressive dementia in the elderly. By 1967, Gajdusek and colleagues had shown that human CJD was also transmissible to chimpanzees. Kuru and CJD were later transmitted to other primate species.
31. As early as 1961-2, Robert and Shirley Glasse (later Shirley Lindenbaum), anthropologists working with the Fore, suggested that kuru had spread from person to person through the ritual cannibalism of relatives who had died from the disease. Epidemiological analysis supported their conclusions, and deduced that the incubation period of the kuru cases occurring in the early 1960s could be as short as four years, with a mean of perhaps 10-12 years. Cannibalism had been suppressed by government patrols in the 1950s, so that if there were no other mode of transmission, the epidemic was predicted to wane in subsequent decades.
32. Subsequent follow-up of kuru cases by Michael Alpers and others has shown that the epidemic has waned as predicted. No person born since the suppression of

⁸ See for example Chesebro (2003) in the appended list of references consulted. Note that many potentially relevant references could not be cited in this selective review.

⁹ The kuru story is summarised in Collinge et al (2006), Alpers (2008) and Mathews (2008).

cannibalism has been affected by kuru. The last cases seen in the kuru epidemic will have had incubation periods of over 50 years.

33. The idea that kuru had spread by cannibalism was further supported in 1980 when the disease was transmitted to a spider monkey following the oral administration of affected brain tissue.
34. In 1974 it was realised that CJD had been inadvertently transmitted from person to person following the transplantation of a cornea from the cadaver of a person dying from CJD. Such iatrogenic (“doctor-induced”) transmission was subsequently shown to occur following the use of neurosurgical instruments, or grafts of dura mater from human brains, or injections of human pituitary hormones, all apparently contaminated with material from CJD-affected patients¹⁰.

Understanding prions

35. The transmissible agents causing scrapie, kuru and other TSEs were at first thought to be slow viruses, but by the 1980s no such viruses had been found.
36. Instead, Prusiner showed that the disease-causing agent behaved as if it was a prion¹¹, or modified form (PrP^{Sc}) of a normal protein (PrP^{C}) expressed in normal brain and in other tissues. PrP^{Sc} appears to trigger a self-perpetuating disease process by facilitating the conversion of PrP^{C} to more of itself; the lengthy time taken for the accumulation of PrP^{Sc} helps to explain the incubation period of the disease, while the distribution of PrP^{Sc} within the nervous system helps to explain the clinical profile of different TSEs.
37. The pathogenic prion, PrP^{Sc} , tends to aggregate and stick to surfaces. It is also resistant to heat and to most enzymes that break down normal proteins. These properties make it difficult to clean and sterilize instruments or materials contaminated by contact with TSE tissues. In turn, this helps to explain the emergence of CJD transmitted by surgery or other “iatrogenic” (doctor-induced) procedures.
38. CJD and other familial TSEs also occur in individuals with rare inherited mutations in the gene encoding the PrP^{C} protein¹²; such genetically different forms of the protein seem more susceptible to being converted to pathogenic forms, PrP^{Sc} .
39. Table 1 summarises essential information about the more important TSEs.

¹⁰ Will (2003)

¹¹ See Chesebro (2003). The pathogenic prion is different for each disease: we refer to PrP^{Sc} in scrapie, and PrP^{BSE} in BSE. For generic purposes we can refer to PrP^{TSE} . See Aguzzi et al (2007), Manuelidis et al (2009), Wilson & Nixon (2009) for more information on prion biology.

¹² Chesebro (2003).

Bovine Spongiform Encephalopathy

40. The epidemic of bovine spongiform encephalopathy (BSE) in cattle in the United Kingdom (UK), first reported in 1986, was caused by feeding meat and bone meal (MBM) of bovine origin as a food supplement to calves¹³. This causal sequence was equivalent to bovine cannibalism, echoing the mode of spread of kuru amongst the Fore in Papua New Guinea.
41. With the causal connection made, the feeding of MBM to ruminants in the UK was banned in 1988¹⁴. However, because of the long incubation period of BSE, averaging some 5 years, and initially poor compliance with the MBM ban, the annual numbers of animals with clinically apparent BSE continued to rise until the peak year of 1992.
42. By 2009 it is estimated that more than 183,000 cattle had been diagnosed with clinical signs of BSE in the UK (Table 2). Some 3 million cattle incubating BSE could have entered the human food chain over that same period.
43. Because of early concerns about the possible spread of BSE to humans, BSE affected animals were removed from the human food chain in the UK in 1988.
44. In 1989, bovine brain and spinal cord and other tissues with the largest potential loads of infective prions (designated Specified Risk Materials) were banned from the human food chain in the UK to further minimise the risks of transmission to humans from otherwise healthy animals that might nevertheless have been incubating BSE.
45. In 1996, healthy older cattle (> 30 months of age) were banned from the human food chain in the UK. Elsewhere in Europe they were allowed into the food chain if the carcass tested negative for BSE by an approved rapid test. In 2005, the UK aligned its policies with those of the EC, but still banned any animal born prior to 1996 from entering the food chain.
46. Epidemics of BSE in other countries were much smaller than in the UK (see Table 2 and Fig.1), and occurred later because of the later introduction and lesser use of MBM food supplements. Control measures were also delayed relative to those in the UK, but by 2001, there were control measures in place with active and passive surveillance in EC countries.

Variant Creutzfeldt-Jakob Disease (vCJD)

47. The first cases of variant CJD died in the UK in 1995 and were reported in 1996. Patients typically presented with behavioural or psychiatric symptoms, at a much younger age than in classical CJD, and the disease ran a longer clinical course to

¹³ See for example, Smith and Bradley (2003).

¹⁴ Scientifically important aspects of BSE control policy are summarised in Ferguson and Donnelly (2003) and in Comer and Huntly (2003). Recent changes can be accessed at the OIE and EC websites.

death; vCJD, now recognised as the human equivalent of BSE, is attributed to the past consumption of BSE-contaminated food¹⁵.

48. The incidence of vCJD in the UK peaked in 2002; by 2009 there had been a total of 169 deaths (see Table 3 & Figure 2). France was the only other country with a substantial number of cases (25 by 2009), but the French epidemic was delayed, relative to that in the UK, in part because of the later introduction of contaminated MBM for cattle feed in France & also apparently because of human exposure to late shipments of contaminated food products from UK¹⁶.
49. The average age of vCJD patients is some 28 years, with an average incubation period of perhaps 16-17 years¹⁷. These observations imply that the critical exposures are more likely to have occurred in childhood or adolescence. It is not clear whether this is because younger people had greater exposure to BSE-contaminated food or because older children or adolescents were more susceptible to a given dose of contaminated product.
50. One hypothesis is that the risk of vCJD is specifically related to consumption of food (eg sausage) containing “recovered meat” contaminated with BSE material from brain, spinal cord or dorsal root ganglia¹⁸. It was thought that some children and adolescents could have been particularly exposed by eating school-dinners using recovered meat products. However, detailed analysis suggests that adults ate recovered meat products as frequently as children.
51. Thus the age-distribution of initiation of vCJD may depend on a susceptibility to exposure which is maximal in later childhood and adolescence¹⁹. The biological basis for such age-dependence is not understood. One possibility is that the mucosal immune system modulates the gastro-intestinal absorption of PrP^{BSE}, and offers least protection to those aged 8-20 years (the most susceptible group).
52. The proportion of people developing v-CJD after exposure to BSE-contaminated food is very small; despite the majority of UK residents having had potential exposure in the period 1986-96, only 165 UK residents have apparently been affected by dietary exposure. So far, all v-CJD affected persons have been genetically identical (homozygous Met/Met) at codon 129 of the PrP protein gene²⁰.
53. It is also unclear whether there could be a second peak in the epidemic of vCJD developing after longer incubation periods, potentially in persons exposed to lower doses of BSE, or following exposure at an older age, or in those who are heterozygous at codon 129 of the PrP locus, who developed kuru with a longer incubation period. However, even in kuru, with 50 year incubation periods for the

¹⁵ See for example Will (2003).

¹⁶ Chadeau-Hyam et al (2005).

¹⁷ See Valleron et al (2001), Smith et al (2004), Ghani et al (2003), d’Aignaux et al (2001).

¹⁸ See Cooper and Bird (2003).

¹⁹ Cooper & Bird (2003), Valleron et al (2001), Boelle et al (2004).

²⁰ Mead et al (2009). One instance of vCJD prion transmission, without disease, has been reported in an MV heterozygote.

last few patients²¹, there was only ever a single broad peak in the overall epidemic curve.

Blood-borne transmission

54. TSE transmission by blood transfusion was first demonstrated for scrapie in mice and in sheep.
55. The first case of vCJD following blood transfusion was reported in the UK in 2003, seven years after the recipient was transfused with blood from a donor who developed vCJD three years after donating.
56. A total of 4 blood-borne transmissions of vCJD have now been reported²², although in one case the recipient died without developing symptoms, and the diagnosis was based on autopsy detection of vCJD prions in lymphoid tissues. In each case transmission was associated with the transfusion of blood that was not leucocyte-depleted²³. No disease has been reported following the transfusion or injection of plasma products, although prion transmission was detected at autopsy in one haemophilia patient who died of unrelated causes. UK has sourced most processed plasma products from overseas plasma since 1999.

Continuing Significance of the Global BSE epidemic

57. The epidemic of BSE in UK cattle has now waned to a low level (Figure 1), and because of this, and the other control measures, the amount of BSE-contaminated material entering the human food chain in UK is now very small (Fig.3)²⁴. This implies that the potential for future transmissions to humans must be less than 0.1% of what it was during the years of peak risk. Even if the continuing risk were not to diminish much further in future years, we might safely assume that the number of future human transmissions would be very much less than 0.1% of those that have already occurred (eg 0.1% of 200-400 cases of vCJD in UK would correspond to no more than 0.2-0.4 of an extra case from transmissions that could happen in the future. See also Table 5).
58. The BSE epidemics in other countries are orders of magnitude smaller than in the UK, and with the years of peak incidence lagging some five years behind the UK experience in countries such as Ireland, Switzerland, Portugal, Spain and Italy (see Table 2). It is also true that BSE control measures were introduced later in other countries, and with less stringent application in some.

²¹ Collinge et al (2006).

²² Most of transfusion story is reviewed in Coste et al (2009). See also Anon (2007), Ironside et al (2006), Dorsey et al (2009), Gillies et al (2009), Hewitt et al (2006), Lefrere & Hewitt (2009), Turner & Ludlum (2009), Wallis (2009), Farrugia et al (2005), Farrugia (2009), Cervia et al (2006).

²³ St. Romaine et al (2004), Gregori et al (2004).

²⁴ Comer & Huntly (2003), Ferguson & Donnelly (2003); Arnold et al (2008) have provided updated estimates on how BSE infectivity increases over the incubation period.

How does vCJD risk relate to BSE burden?

59. In UK there have been over 183,000 confirmed BSE cases since 1986 (Table 2); in addition, as many as 3 million animals incubating BSE have entered the food chain over the same period. This burden of BSE has so far resulted in 169 (166 primary and three secondary) cases of vCJD in UK (Table 3 & Fig.2), so that the average risk to date is of the order of 1 human case of vCJD for every 1100 confirmed BSE cases, or perhaps 1 human case for every 10-20,000 diseased animals entering the food chain.
60. BSE numbers are very much smaller for other affected countries (Table 2), and interpretation is complicated by the fact that some of their vCJD cases (Table 3) were apparently caused by importation of BSE-contaminated food from the UK. Food importation from UK at an earlier stage of the BSE epidemic helps to explain the relatively large vCJD epidemic in France (25 cases so far)²⁵ relative to the number of confirmed BSE cases (993), a ratio of 1 human case for every 40 BSE cases.
61. Anecdotal reports suggest that in unusual circumstances, vCJD can be transmitted to one or more persons by ingestion of tissues from single animals. For example vCJD was reported in 2007-8 in a mother aged 60+, and her son aged 41 in a family in a Spanish village, where they ate brain from locally killed cattle²⁶. The occurrence of vCJD in the same year in two relatives, one of whom was well outside the usual age-range for vCJD, suggests that both were exposed to a dose of infective agent that was very large, and thus able to break through the “species” and “age” barriers to cause vCJD with relatively constant incubation periods in both persons.
62. At the population level, the human risk of vCJD can be related to the estimated level of BSE infectivity entering the food chain²⁷. Prior to 1996, some 54 million bovine infective doses (ID₅₀) entered the UK food chain, which has been followed by only 165 vCJD cases – so far a ratio of 1 human case for every 300,000 bovine infective doses. Infectivity entering the UK food chain in later years is reduced about a million-fold compared with peak years (Figure 3).

Predicting the final size of the primary vCJD epidemic in the UK

63. 166 primary cases of vCJD have been diagnosed in the UK since 1996, with only 4 cases alive in September 2009 (Table 3 & Fig.2). Newly diagnosed cases have been in decline each year since the peak of 28 cases diagnosed in 2000. Estimating the future behaviour of the vCJD epidemic has not been easy. Early estimates, based on uncertain information about the biology and transmission between species, could not exclude a maximum epidemic size of 30,000 vCJD

²⁵ Chadeau-Hyam et al (2005).

²⁶ http://www.eurosurveillance.org/edition/v13n15/080410_3.asp

²⁷ This is not directly proportional to the number of BSE-affected cattle, as the other measures such as rejection of diseased cattle, SRM removal, and rejection or screening of OTM (aged over thirty months) animals had most effect in reducing infectivity. See Comer and Huntly (2003).

cases. With more information, the best current estimate of the final size of the primary UK epidemic is of a total of 215 cases (including the 166 cases already known) with an upper limit of perhaps 330 cases²⁸.

64. Current projections are nevertheless still based on uncertain knowledge about the number of persons in UK, already infected by PrP^{BSE}, who could develop vCJD in later years. The number potentially incubating vCJD has been estimated by screening for PrP^{BSE} in surgical samples taken from the appendix or tonsil of otherwise healthy people²⁹. The surveys of appendix tissue yielded 3 positives in 11,247 samples, whereas all of 64,000 tonsil samples were negative. As detection of prion in the tonsil is routinely used to confirm the diagnosis of vCJD in suspect cases, the negative tonsil tests suggest that the risk of pre-symptomatic vCJD is less than 59 per million in the exposed age-groups. The estimate from appendicectomy specimens is 60-853 per million persons.
65. The difference between appendix and tonsils could just be due to chance. However, a recent analysis suggests that the estimated risk of pre-symptomatic vCJD based on positive appendix samples is too high, and statistically inconsistent with the recent behaviour of the vCJD epidemic³⁰, suggesting that although some exposed persons could become “carriers” of prions, potentially able to transmit to others, they might never develop clinical disease themselves.
66. There is also uncertainty about the distribution of the incubation period of vCJD, and the extent to which it is influenced by host genotype. So far, all clinical cases of vCJD have been homozygous MM at codon 129 of PrP, suggesting either that MV and VV genotypes are not susceptible, or that they could develop disease after a longer incubation period, as seen in kuru and iatrogenic CJD³¹. However, even if cases develop in MV and VV genotypes after a longer incubation period, it seems unlikely that the final size of the primary epidemic will be more than twice the current size (166 cases).

Predicting the size of the secondary vCJD epidemic in UK

67. The transmission of vCJD by blood transfusion shows that a secondary epidemic (ie involving human-to-human spread) is possible. The introduction of leuco-depletion³² (removal of white cells from blood before transfusion) will have reduced, but not eliminated, the risk of future secondary transmissions.
68. Three secondary cases of vCJD have developed 5, 7 & 8 years after blood transfusion; the fourth transmission was discovered at autopsy in a recipient of vCJD blood, who died from unrelated causes without symptoms of vCJD³³. These incubation periods are considerably shorter than the average of 16-17 years for vCJD following ingestion of contaminated beef products; such shortening is

²⁸ See Ferguson et al (2002), Ghani (2003), Ghani et al (2003), Clarke & Ghani (2005), Cooper & Bird (2003), and the calculations in Table 5.

²⁹ Clewly et al (2009) present new data and review the interpretation of all available data.

³⁰ Clarke & Ghani (2005).

³¹ Collinge et al ((2006), Will et al (2003), Mead et al (2008).

³² St Romaine et al (2004); Gregori et al (2004); Coste et al (2009).

³³ Coste et al (2009).

characteristic of TSEs which overcome the species barrier and spread within the new species³⁴.

69. There is no known case of secondary vCJD resulting from injection or infusion of plasma or plasma products such as clotting factors, although there is a UK autopsy report of vCJD prions in a haemophilia patient who died from unrelated causes and without signs of vCJD after receiving clotting factors prior to 1999 prepared from a blood donation from a person who later died from vCJD³⁵. As a precautionary measure the UK began to source plasma products from overseas sources in 1999. This would have reduced any risk of secondary transmissions from plasma-derived prions.
70. The challenge is to predict the final size of the secondary transfusion epidemic in the UK, and to decide whether secondary transmission can occur from those who are “carriers”, as well as those in the “pre-symptomatic” stages of vCJD. Four transmissions following the use of (non-leucodepleted) blood have been recognised so far in the UK arising from a total of 22 primary cases of vCJD who had donated blood before diagnosis. Of 64 identified recipients, only 26 were still alive in later 2008³⁶. Thus to a first approximation we can say that 22 primary cases of vCJD gave rise to only 4 known secondary transmissions; on this basis the secondary epidemic would die away and could not be self-sustaining.
71. But what about the 26 live recipients who might also be incubating or carrying vCJD, and the 38 deceased recipients? A self-sustaining epidemic of blood-borne transmission would only become possible if a substantial majority of them were carriers, and if they in turn became blood donors. This was always unlikely, as blood recipients come from older age groups than blood donors. The UK ban on transfusion recipients becoming donors, introduced in 2004, also helps to ensure that the blood-borne secondary outbreak will gradually die away. This conclusion is robust to most assumptions about undetected carriers of vCJD in the blood donor pool; it is also supported by detailed modelling³⁷. The likely future testing of UK blood with the Amorfix test³⁸, which is highly sensitive and specific, could soon provide more explicit data about the numbers of UK blood donors and recipients who could be in the pre-clinical or carrier stage of vCJD.
72. The size of the secondary epidemic of vCJD cases in the UK will also depend upon the magnitude of “iatrogenic” spread through the use of grafts or contaminated surgical instruments originating from undetected carriers or those in the pre-symptomatic phases of vCJD³⁹. No graft (other than blood transfusion) has yet been associated with secondary transmission of vCJD. Nevertheless, because of the usual practice of grafting organs from a single donor to multiple recipients,

³⁴ Hill & Collinge (2003).

³⁵ See www.hpa.nhs.uk and Eaton (2009).

³⁶ See also Coste et al (2009). Because many transfusions are given to elderly people with life-threatening illnesses, the mortality after blood transfusion is much greater than in the general population.

³⁷ Clarke et al (2007).

³⁸ See Coste et al (2009) and also

[//www.amorfix.com/press/2009/2009_07_17_uk_tender_announcement.pdf](http://www.amorfix.com/press/2009/2009_07_17_uk_tender_announcement.pdf)

³⁹ See for example Dunstan and Alpers (2005) & Garske et al (2006).

there is a risk of multiple secondary cases if even a single donor is a carrier or in the pre-clinical stage of vCJD.

73. There is no proven case of vCJD having been transmitted via contaminated surgical instruments, although the retrospective records that would be needed to support such a pathway of infection have not been available. Models based on incomplete information suggest that the risk of a self-sustaining vCJD epidemic transmitted via contaminated surgical instruments will be very low unless there is a large pool of undetected UK “carriers”, each with a “permanent” risk of transmitting the infection⁴⁰.
74. Research is in progress to obtain improved data on the re-use of surgical instruments, on the epidemiology of surgical patients, and on more effective processes for sterilization. A policy of universal precautions would require that all operations were performed with single-use instruments, or that all instruments were sterilized in ways that would remove any prion contamination. It is certainly not feasible to ban repeat surgery, or to ban patients from surgery if they have a history of prior blood transfusion.

SCIENCE AND CONTROL MEASURES

How adequate are the control measures in BSE-affected countries?

75. BSE has not been completely excluded from UK and European herds. Each year there are still a small number of affected animals detected by passive and active surveillance (see Table 2 & Fig. 1) that were born after the bans on MBM. The source of infection for these animals is not fully understood.
76. BSE in cattle born after the recycling ban (BAB) may have been caused by contamination of permitted stock-feed with residual MBM on some farms in the years after the ban⁴¹. The other possibility is of vertical transmission of BSE from mother to calf, for which the evidence has been equivocal⁴². However, in view of recent evidence for the transmission of scrapie to lambs via ewes’ milk⁴³, it is timely to reconsider the possibility that BSE can occasionally be transmitted to calves by milk from cows that are infectious without showing signs of clinical disease.
77. The UK food chain has had additional protections in place: the ban on SRMs, the exclusion of carcasses from older animals, and the exclusion of animals that test positive for BSE. UK authorities now believe that BSE has been substantially

⁴⁰ Garske et al (2006), & also Olsen et al (2005), Stevenson et al (2009), Lumley & Head (2008).

⁴¹ Jarrige et al (2007).

⁴² Donnelly (1998)

⁴³ Lacroux et al (2008).

excluded from the human food chain in the UK (see Fig. 3) and from meat products that the UK exports to other countries⁴⁴.

78. Because of the size of the BSE outbreak in the UK, the commitment to its control has been impressive, even though it took some years for all necessary measures to be fully implemented. Other countries, forewarned by the UK experience, have implemented control measures under the aegis of OIE and the EU, and experienced much smaller outbreaks (Table 2 & Fig.1). The UK reported 183,256 cases of BSE up to December 2007 – the next largest epidemic was in Ireland, with 1622 cases.
79. For most developed countries there is now sufficient evidence to conclude that BSE is either absent or well-controlled, according to OIE criteria (see Fig.1). Those developed countries at risk or affected by BSE have ongoing systems for passive surveillance (ie for the diagnosis of BSE in clinically suspect animals) and for active surveillance (eg the systematic testing of apparently healthy bovines above 30 months of age). In such countries, there is negligible or controlled risk that BSE materials could enter the food chain, or potentially contaminate therapeutic goods using raw materials from that country (see “Other Sources” for links to additional surveillance reports from OIE and EU).
80. However, for a number of developing countries, there is insufficient evidence to exclude the presence of BSE, and to be confident that appropriate measures for detection and control are in place.

New OIE framework for BSE control and trade

81. OIE now classifies the BSE risk status of the cattle population of a country on the basis of a risk assessment and other criteria. The cattle population of a country can be classified into three categories: *negligible BSE risk*, *controlled BSE risk* or *undetermined BSE risk*.
82. The *negligible BSE risk* distinction applies to cattle and commodities from countries or zones that pose a negligible risk of transmitting the BSE agent as demonstrated by 1) a risk assessment; 2) the appropriate level of BSE surveillance; 3) one of the following: no BSE cases, only imported BSE cases or indigenous BSE cases born no more recently than 11 years; 4) an existing education and reporting program; and 5) a feed ban that has been in place for at least eight years if an indigenous or imported case or other risk factors exist.
83. The *controlled BSE risk* category describes cattle and commodities from a country or zones that pose a negligible risk of transmitting the BSE agent due to commodity-specific risk mitigation measures. The conditions for this category are similar to the conditions for a negligible BSE risk distinction except that controlled risk countries with indigenous BSE cases must demonstrate an education and reporting program and an effective feed ban. Both negligible risk

⁴⁴ See Comer & Huntly (2003) and Feguson & Donnelly (2003). However, in the early years of the BSE outbreak, contaminated UK beef products exported to France probably infected some of the 25 French people who would later develop vCJD. See Chadeau-Hyam & Alperovitch (2005).

and controlled risk countries must also identify, track and prevent birth cohorts and feed cohorts of the known BSE-infected animal(s) from entering the food chain and export trade.

84. The OIE Terrestrial Animal Health Code recommends imports from controlled BSE risk countries resume if: 1) the country meets the requirements for controlled risk; 2) live cattle selected for export are identified by a permanent identification system; and 3) the cattle selected for export are born after a feed ban was implemented (if the country has indigenous BSE cases).
85. OIE recommends that countries importing products from controlled risk countries require: ante- and post-mortem inspections, that meat come from cattle that were not subject to air-injection stunning, and fresh meat and meat products not contain prohibited tissues or mechanically separated meat from the skull and vertebral column from cattle older than 30 months.
86. The cattle population of a country or zone poses an *undetermined BSE risk* if it cannot be demonstrated that it meets the requirements for *negligible or controlled risk*.
87. OIE criteria for establishing individual country risk classifications include surveillance and testing of livestock herds, protocols followed after positive tests and risk management strategies. For example in May 2007, OIE classified the United States as a *controlled risk* country in regard to BSE. According to the OIE definition, controlled risk means that regulatory controls are effective and that fresh beef and beef products from cattle of all ages can be safely traded

Evolving BSE policies in the UK and other countries

88. In 1994 the EC introduced a general ban on the feeding of mammalian meat and bone meal (MBM) to ruminants. In 2000 the ban was extended to prohibit the feeding of animal protein to ruminants and the feeding of processed animal protein (PAP) to all animals farmed for food production.
89. Current EU policies require rapid BSE testing of all fallen stock age over 24 months, and all BSE suspects (passive surveillance). All animals slaughtered for human consumption over the age of 30 months must also be tested (active surveillance). In the UK, all animals born before 1996 are killed for destruction.
90. The TSE Roadmap, published in 2005 by the EC, canvassed future options for TSE surveillance and control.
 - e. One option was to introduce tolerance levels for certain types of PAP in animal feed. SEAC had reservations about whether permitted PAP could be introduced without the possibility of MBM contaminations, and could not assess the potential risks for human health.
 - f. Another option was to allow fish meal in the diet of young ruminant animals. However, this could be risky in countries where there was a risk

that fish meal could be contaminated with MBM, and it could be difficult to discriminate between PAP of the different types in such countries.

- g. Likewise, it could be difficult to administer an option that allowed the feeding of non-ruminant PAP to non-ruminants in a way that eliminated the possibility of cross-contamination with MBM.

91. SEAC⁴⁵ has recently assessed a proposal to raise the age at which healthy slaughtered cattle should be tested for BSE. The model concluded that even if the age for testing in the healthy slaughter surveillance stream were raised to 60 months, much less than one BSE case would be missed annually in the GB herd. SEAC advised that this would be a negligible increase in risk to humans.

RISKS FOR AUSTRALIA

Risk management to prevent BSE entering Australia

92. In 1996, to minimise the risk of BSE in Australia, the livestock industry introduced a voluntary ban on the feeding of MBM of ruminant origin to Australian cattle. At the same time, Government banned the importation of cattle, beef and beef products from the UK. Quarantine regulations were updated in 1999 to restrict imports from other countries that were known or suspected to be BSE-affected.

93. Australia monitors some 9 million cattle going to slaughter annually for signs of BSE, and has been testing suspect animals since 1997. In 2005, Australia upgraded its BSE surveillance to meet OIE guidelines. As the world-wide epidemic of BSE is now almost over, and as Australia has had no BSE, it is now even more unlikely that a native case of BSE could occur as part of an undetected outbreak following earlier importation of MBM or an asymptomatic infected animal.

94. Rare cases of “atypical BSE”, usually in older bovines, have recently been reported from several countries⁴⁶. It is highly unlikely, but just possible, that the BSE screening program in Australia will detect an isolated case of a BSE or atypical BSE in an older bovine. Without MBM to drive an amplification cycle in Australia, such “spontaneous disease” would present no risk of a TSE outbreak in Australian cattle.

What is the risk of vCJD from Australian beef products?

95. As Australian herds are BSE-free, it is highly unlikely that any animals with asymptomatic disease, whether imported or as part of an undetected local outbreak, could have entered the local food chain. Accordingly, the risk of human disease from such a source is effectively zero. Even if an older animal entering the

⁴⁵ Spongiform Encephalopathy Advisory Committee (UK) - www.seac.gov.uk

⁴⁶ Ferguson-Smith & Richt (2009)

food chain had developed spontaneous but undetected TSE, the chance of even a single human case of vCJD or TSE would likely be small.

What is the risk of vCJD from imported beef products?

96. The current risk for Australia is low, firstly because as a meat-exporting country, imports of meat products have always been low. More importantly, Australia has restricted importation of beef and beef products from BSE-affected countries.
97. Collagen, gelatine, fats and tallows, and milk and dairy products are exempt from import restrictions. Otherwise FSANZ requires certification by a *Competent National Government Authority* in accordance with the earlier Australian risk categorisation of countries for each consignment of beef products for export to Australia. The detailed certification requirements⁴⁷ ensure that the beef product should be derived from BSE-free animals in BSE-free herds in the country of origin, that the materials to be imported should not contain specified risk materials, that MBM bans are enforced, and that surveillance measures in place would have been able to detect BSE, had it occurred.
98. If Australia were to permit the importation of beef products from BSE-affected countries such as the UK, there would be a theoretical but negligible increase in risk of vCJD (see Table 4).

Is there an Australian risk from other animal TSEs?

99. Scrapie does not occur in Australian sheep, and there is no evidence to link scrapie in sheep with any human TSE. Thus any risk to Australians from scrapie must be effectively zero.
100. Because BSE can be transmitted experimentally to many species, there have been concerns that BSE could have entered British sheep flocks and goat herds. However, no naturally infected sheep have been detected in large-scale screening programs, although a BSE-like syndrome has been detected in a goat in France⁴⁸. The risk of BSE in Australian sheep or goats must be remote.
101. There is no evidence of chronic wasting disease (CWD) in Australian deer herds. Even though CWD prions have been detected in the velvet that covers the antlers of infected animals overseas⁴⁹, there is no evidence of transmission to humans in contact with CWD-infected herds. Nevertheless, people are advised not to eat meat from deer-herds where the risk of CWD cannot be excluded. If CWD were detected in Australian animals, or if products from CWD-infected herds were inadvertently imported, the risk of transmission to humans would likely be small, and authorities would respond quickly to the potential threat.
102. BSE is experimentally transmissible to pigs by injection of infected material, albeit with difficulty because of the species barrier. This has led to considerable

⁴⁷ See FSANZ website.

⁴⁸ http://ec.europa.eu/food/food/biosafety/bse/goats_index_en.htm

⁴⁹ Angers et al (2009)

concern about the possibility of TSE transmission to pigs from recycling of MBM and other animal residues as pig-feed; if this were to occur it could set up a new cycle of TSE amplification in pigs, with the consequent risk of a spread to humans. However, no instance of oral transmission of any TSE to pigs has been reported, despite many experimental attempts. Recent experiments show that mice expressing porcine PrP are susceptible to injected bovine BSE, and even more susceptible to BSE after its passage through sheep⁵⁰. Nevertheless, in the absence of evidence for oral transmission to pigs, and in view of the hypothetical nature of the risk of an amplification cycle in pigs, the feeding of ruminant MBM to pigs has not been disallowed in Australia. Any consequential risk of human disease is assumed to be remote.

Risk of vCJD in Australian residents who were exposed to BSE while resident overseas

103. Australian residents who were aged 8-20 years when resident in the UK between 1980 and 1996 would have been at greatest risk from exposure to BSE-contaminated food. The magnitude of this risk can be estimated, very approximately, from the estimated final size of the vCJD epidemic in the UK, and the “transfer factor” between UK and Australia (ie the proportion of the UK residents from that time, including visiting Australians, who are now resident in Australia).
104. Calculations (see Table 6) suggest that Australia might expect between 0.4 and 4 Australian cases of vCJD resulting from any exposures to BSE-infected food that might have already occurred in the UK.
105. No case of vCJD has yet been diagnosed in Australia – this is not surprising, given the low estimates of risk.

Risk of secondary transmission of vCJD by Australian blood or blood products

106. In the absence of any primary cases of vCJD in Australia, the risk of secondary cases must be very low. Recent calculations (Table 6) suggest that Australia might expect no more than 0.1-0.2 persons to be affected by a secondary transmission. In other words, it is likely that we will see no such case.
107. The theoretical risk of secondary transmissions in Australia has been further reduced by Australian donor deferra⁵¹ of all persons receiving blood or blood products in the UK since 1980 and for all persons resident in UK for six months or more over the period 1980-1996. Removal of white cells from blood (leucodepletion), introduced progressively over the period 2003-7 in Australia, would have further diminished the theoretical risk for transfusion recipients⁵².

⁵⁰ Espinosa et al (2009).

⁵¹ Correll et al (2001).

⁵² Coste et al (2009).

108. Highly sensitive tests for the detection of vCJD in blood and other fluids are currently being evaluated overseas⁵³, but none has yet been applied for screening of blood samples to help detect pre-symptomatic or carrier cases of vCJD. The Amorfix test has recently demonstrated 100% specificity when used on 20,000 blood donations in France, and the company has recently signed a contract for testing blood in the UK⁵⁴. The terms of the contract and testing regime are confidential. The ethical framework for such testing will also need careful attention, as in the early days of HIV testing⁵⁵. Even if such testing is seen to be justified for all blood donations in the UK, the case could be weaker in Australia, with fewer positives expected (eg 0.4 to 4 over the life of the vCJD epidemic). However, if the results of the supposed UK survey validate the new screening test, and if the results prove to be informative and are made available to Australian health authorities, there would be a basis for judging the likely cost-effectiveness of blood donor screening for vCJD in Australia.

Risks of secondary vCJD from Australian plasma products

109. Australian plasma products, including clotting factors, are prepared by CSL from pools of Australian plasma. The pooling is significant because it means that even if only a single donor were infected, there is the potential to contaminate all doses prepared from that batch, with the possibility that all recipients of that batch might be secondarily infected. Although secondary transmission by clotting factors has been documented in a single UK case⁵⁶, this was not associated with vCJD disease. From 1999 the UK began to source clotting factors from overseas plasma; recombinant clotting factors were introduced subsequently as clinically appropriate. However, fresh frozen plasma for the UK has still been sourced from UK donations, except for recipients born since 1996.

110. The risk to Australian recipients of plasma products, including clotting factors, is believed to be very small, because of the protection offered by⁵⁷:

- The very low risk of primary vCJD in the Australian donor pool (Table 6);
- The sequestration of Australian plasma by CSL, so that plasma products for use in Australia are prepared from low-risk Australian plasma;
- Plasma processing techniques that are designed to remove most of the vCJD prions that could be theoretically present.
- The increasing use of recombinant clotting factors for Australian patients;
- The regulation by TGA of any plasma products, sourced from overseas, that may be derived from blood donations outside Australia.

⁵³ Coste et al (2009); Edgeworth et al (2009); Fujihara et al (2009) ; Grassi et al (2009).

⁵⁴ http://www.amorfix.com/press/2009/2009_07_17_uk_tender_announcement.pdf

⁵⁵ See footnote 4.

⁵⁶ One recipient has been shown to be prion positive after receiving clotting factors for haemophilia; the person had no signs of vCJD and died of unrelated causes. See Eaton (2009) & www.hpa.nhs.uk El-Shanawanay et al (2009) found no signs of vCJD or prions at autopsy of a person exposed to immunoglobulin prepared from blood of a person who had subsequently died from vCJD.

⁵⁷ Farrugia et al (2005); Farrugia (2009); Burdick et al (2006); Thyer et al (2006A,B); Chtourou et al (2007) ; Flan & Arrabal (2007).

111. In view of the small risk of any vCJD in Australia, and the additional protections offered by donor deferral and by the manufacturing safeguards, the risk of any secondary transmissions from plasma products in Australia appears to be very small or negligible.

Risks to the Australian public from therapeutic goods

112. There is negligible risk to the Australian public from therapeutic goods manufactured from Australian raw materials. Although there are theoretical concerns about the possibility of contamination from a spontaneous case of BSE, or some other TSE, the probability that such an animal could ever contaminate the raw materials for Australian therapeutic goods would be exceedingly small.

113. Therapeutic goods manufactured from overseas raw materials pose a potential risk for the Australian population. These risks are managed by TGA using the EMEA classification of ruminant tissues according to published and documentary evidence of potential TSE risk. Category C tissues (no detectable infectivity reported in the literature) can be self-certified by external sponsors. Therapeutic materials derived from Category B (potentially low infectivity) and Category A (potentially high infectivity)⁵⁸ tissues are fully evaluated by TGA, on the basis of evidence provided by sponsors, and independent enquiries, to ensure that they have been derived from sources that are known to be TSE-free. TGA standards are rigorously applied, and it is widely believed that there is negligible risk of TSE transmission from TGA-approved products.

114. Complementary medicines are also regulated by TGA to ensure that they are prepared from BSE-free ingredients.

115. More recently, regulation of cosmetic ingredients, through NICNAS, has been updated to further protect the Australian population.

116. TGA is alert to new evidence that is potentially relevant to its regulatory approach. For example:

- Detection of infectivity in milk from scrapie-infected sheep;
- Detection of infectivity in fat from CWD-infected deer and fat from scrapie-infected mice⁵⁹;
- Detection of prions in antler velvet and cardiac muscle of CWD-infected deer;
- The possibility that TSEs might become established in pigs, chickens or even fish fed with TSE-contaminated ruminant material, with the risk of subsequent spread to humans;
- Detection of vCJD prions in a haemophilia patient, a previous recipient of clotting factors before 1999, who died from unrelated causes;

⁵⁸ Of course no tissue source that was infective would ever be approved by TGA. The categories simply indicate that there would be a possibility of infectivity *if* the tissue *were* derived from an infected animal, and the obligation on TGA is to ensure that the materials were derived from animals (and herds) that are known to be BSE free.

⁵⁹ See Race et al (2008). Fat has hitherto been regarded as Category C (no known infectivity).

- BSE prions seem much more resistant to inactivation by detergents and heat than prions of mouse or human origin;
- The recent development of sensitive assays (eg by Amorfix) for the detection of prions in blood samples and other biological fluids.

Risk from surgical spread of vCJD and CJD in Australia

117. In view of the few expected cases of vCJD in Australia (0.4-4 over the course of the epidemic), there is a correspondingly low, and almost certainly negligible, risk of secondary spread through the re-use of contaminated surgical instruments after prior use on a person with known or undetected vCJD.
118. The numbers of CJD patients in Australia are greater: some 20 new diagnoses per year⁶⁰. As CJD patients are older and more likely to need surgery in the years immediately prior to their illness becoming clinically apparent, the aggregate risk of secondary surgical transmissions is likely to be greater for CJD than for vCJD. However, vCJD prions have a wider distribution in lymphoid and other tissues as well as brain, whereas CJD prions are more restricted to brain and nervous system. Hence the risk for CJD transmission would be greater following neurosurgical procedures, whereas vCJD transmission could also follow general or abdominal surgery, tonsillectomy, and even dental surgery⁶¹ or endoscopy⁶² on a patient with known or undetected vCJD⁶³.
119. Because PrP^{BSE} prions are resistant to heat and detergents, there is considerable uncertainty about how best to clean and re-sterilise re-usable surgical instruments. The problem is most pressing for expensive instruments that are not robust enough to withstand high temperature autoclaving and treatment with strong alkali.⁶⁴
120. To minimise the risk of secondary vCJD transmission following surgery, the UK mandated the use of disposable (single-use) surgical instruments for tonsillectomy. This decision was revoked after claims that post-operative mortality had increased following the introduction of disposable instruments. Many other instruments, such as laparoscopes and other endoscopes, are too expensive to be designated as “single-use”.
121. New approaches to the cleaning and sterilisation of surgical and medical instruments have added treatment steps using proteolytic enzymes and oxidants able to break down the PrP^{BSE} that sticks to instrument surfaces⁶⁵. However, until recently, it has been too difficult to assay for residual prion or infectivity on surfaces, making it impossible to verify whether all infectivity has been removed.

⁶⁰ Klug et al (2008).

⁶¹ Azarpazhooh & Fillery (2008); Porter (2003).

⁶² Head & Ironside (2007)

⁶³ Olsen et al (2005); Stevenson et al (2009);

⁶⁴ See CJD and vCJD guidelines on DOHA website.

⁶⁵ Fichet et al (2004); Fichet et al (2007) ; Peretz et al (2006) ; Dickinson et al (2009); Edgeworth et al (2009)

122. A new technique allows for the precise measurement of prion infectivity, absorbed to the surface of metal wires, down to very low levels. This assay has been used to verify the effectiveness of the new enzyme/oxidant-based procedures designed to sterilise prions absorbed to metal wires. However, the new infectivity assay cannot itself be applied directly to larger instruments being sterilised.
123. The new assay can also be used to test biological samples for infectivity at low cost, with a turn-around time of three weeks to obtain results⁶⁶.

⁶⁶Edgeworth et al 2009.

SUPPORTING INFORMATION & RISK ASSESSMENTS

TABLE 1. Important TSEs and their characteristics

TSE (host)	Clinical features	Usual transmission	Mean incubation period	Experimental transmission to
Scrapie (sheep)	Behavioural disorder & ataxia	“Spontaneous” – possibly by milk	Usually more than 6 months	Goats, mice and other species
BSE	Behavioural disorder & ataxia	Bovine meat and bone meal to calves	5 years (range 2-10)	Mice, sheep, goats
CWD⁶⁷ (deer & elk)	Behavioural disorder & ataxia	“Spontaneous”	Several years	Ferrets, monkeys, goats
HUMAN				
Kuru	Ataxia & terminal dementia in Fore	Oral (cannibalism)	10-12 yrs (range 4-40)	Primates & others
vCJD (‘human BSE’)	Behavioural disorder & dementia in younger persons	Oral (BSE contaminated food)	16-17 years (range 4-30?)	Humanised mice and other species ⁶⁸
Sporadic CJD	Dementia in an older person	“Spontaneous”	?	Primates and other species
Iatrogenic CJD	Progressive dementia (usually in adults)	Grafts of cornea or dura mater or hormones or instruments contaminated with CJD material	Range 1.5 - 30 years	Primates and other species
Familial CJD	Progressive dementia	Associated with inherited mutations in PrP genes ⁶⁹	?Lifetime	Primates and other species

⁶⁸ Inadvertent secondary transmission to humans by blood transfusion, with a mean incubation period of perhaps 7-8 years.

⁶⁹ Other mutations in PrP genes cause other familial neurological disorders such as GSS or FFI.

TABLE 2. BSE incidence by country and year

Country/Year	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
Austria	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	2	2	1	0	
Belgium	0	0	0	0	0	0	0	0	1	6	3	9	46	38	15	11	2	2	0	0	
Canada	0	0	0	0	1(b)	0	0	0	0	0	0	0	0	0	2(a)	1	1	5	3	4	1(c)
Czech Republic	0	0	0	0	0	0	0	0	0	0	0	0	2	2	4	7	8	3	2	0	
Denmark	0	0	0	1(b)	0	0	0	0	0	0	0	1	6	3	2	1	1	0	0	0	
Finland	0	0	0	0	0	0	0	0	0	0	0	0	1(a)	0	0	0	0	0	0	0	
France	0	0	5	0	1	4	3	12	6	18	31(a)	161(d)	274(e)	239(f)	137(g)	54(h)	31	8	9	8	
Germany	0	0	0	1(b)	0	3(b)	0	0	2(b)	0	0	7	125	106	54	65	32	16	4	2	
Greece	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	
Ireland	15(a)	14(a)	17(a)	18(a)	16	19(a)	16(a)	73	80	83	91	149(d)	246(e)	333(f)	183(g)	126(h)	69(i)	41(j)	25(k)	23(l)	5(c)
Israel	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	
Italy	0	0	0	0	0	2(b)	0	0	0	0	0	0	48	38(a)	29	7	8	7	2	1	
Japan	0	0	0	0	0	0	0	0	0	0	0	0	3(e)	2	4(g)	5	7	10	3	1	
Liechtenstein	0	0	0	0	0	0	0	0	0	2(a)	0	0	0	0	0	0	0	0	0	0	
Luxembourg	0	0	0	0	0	0	0	0	1	0	0	0	0	1	0	0	1	0	0	0	0(c)
Netherlands	0	0	0	0	0	0	0	0	2	2	2	2	20	24	19	6	3	2	2	1	
Poland	0	0	0	0	0	0	0	0	0	0	0	0	0	4(f)	5	11	19	10	9	5	4(c)
Portugal	0	1(b)	1(b)	1(b)	3(b)	12	15	31	30	127	159	149(a)	110	86	133	92(a)	46	33	14	18	
Slovakia	0	0	0	0	0	0	0	0	0	0	0	0	5	6	2	7	3	0	1	0	
Slovenia	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	2(a)	1	1	1	0	
Spain	0	0	0	0	0	0	0	0	0	0	0	2	82	127	167	137	98	68	36	25	
Sweden	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	
Switzerland	0	2	8	15	29	64	68	45	38	14	50	33(d)	42	24	21(g)	3	3(i)	5	0	0	
United Kingdom	see particular table																				
United States of America	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	

Number of cases of bovine spongiform encephalopathy (BSE) reported in the United Kingdom ⁽¹⁾

	Alderney	Great Britain	Guernsey ⁽³⁾	Isle of Man ⁽²⁾	Jersey	Northern Ireland	Total United Kingdom
1987 and before ⁽⁴⁾	0	442	4	0	0	0	446
1988 ⁽⁴⁾	0	2 469	34	6	1	4	2 514
1989	0	7 137	52	6	4	29	7 228
1990	0	14 181	83	22	8	113	14 407
1991	0	25 032	75	67	15	170	25 359
1992	0	36 682	92	109	23	374	37 280
1993	0	34 370	115	111	35	459	35 090
1994	2	23 945	69	55	22	345	24 438
1995	0	14 302	44	33	10	173	14 562
1996	0	8 016	36	11	12	74	8 149
1997	0	4 312	44	9	5	23	4 393
1998	0	3 179	25	5	8	18	3 235
1999	0	2 274	11	3	6	7	2 301
2000	0	1 355	13	0	0	75	1 443
2001	0	1,113	2	0	0	87	1,202
2002	0	1,044	1	0	1	98	1,144
2003	0	549	0	0	0	62	611
2004	0	309	0	0	0	34	343
2005	0	203	0	0	0	22	225
2006	0	104	0	0	0	10	114
2007	0	53	0	0	0	14	67
2008	0	33	0	0	0	4	37
2009 ⁽⁵⁾	0	4	0	0	0	2	6

From the OIE.

Number of reported cases of bovine spongiform encephalopathy (BSE) in farmed cattle worldwide http://www.oie.int/Eng/info/en_esbmonde.htm

Number of cases of bovine spongiform encephalopathy (BSE) reported in the United Kingdom http://www.oie.int/eng/info/en_esbru.htm

TABLE 3. Incidence of vCJD by country**VARIANT CREUTZFELDT-JAKOB DISEASE****CURRENT DATA (SEPTEMBER 2009)**

COUNTRY	TOTAL NUMBER OF PRIMARY CASES (NUMBER ALIVE)	TOTAL NUMBER OF SECONDARY CASES: BLOOD TRANSFUSION (NUMBER ALIVE)	CUMULATIVE RESIDENCE IN UK > 6 MONTHS DURING PERIOD 1980-1996
UK	166 (4)	3 (0)	169
France	25 (1)	-	1
Republic of Ireland	4 (0)	-	2
Italy	1 (0)	-	0
USA	3 [†] (0)	-	2
Canada	1 (0)	-	1
Saudi Arabia	1 (1)	-	0
Japan	1* (0)	-	0
Netherlands	3 (0)	-	0
Portugal	2 (0)	-	0
Spain	5 (0)	-	0

[†] the third US patient with vCJD was born and raised in Saudi Arabia and has lived permanently in the United States since late 2005. According to the US case-report, the patient was most likely infected as a child when living in Saudi Arabia.

*the case from Japan had resided in the UK for 24 days in the period 1980-1996.

From the CJD Surveillance Unit – University of Edinburgh. <http://www.cjd.ed.ac.uk>

TABLE 4. Risk of vCJD in Australia from beef imports

Population at risk	Future Annual Exposure (bovine ID ₅₀)	New vCJD transmissions each year	Chance of a single vCJD case in next 50 years
UK	< 100 ID ₅₀	0.0006	0.03
Australia	< 7 ID ₅₀	0.000042	0.002

To assess the potential risk to Australian consumers, we base our assumptions and parameters on those used in recent assessments of risk to the UK food supply. We note that from some 54 million bovine ID₅₀ that entered the UK food supply up to 1996, there are unlikely to be more than 330 cases of human vCJD over the full course of the epidemic. This corresponds to some six human cases per million bovine ID₅₀. We also note that with UK controls in place, there would be no more than 100 bovine ID₅₀ entering the human food chain in the UK each year, and probably much less⁷⁰. Thus the expected risk to UK residents *from new transmissions* will be no more than 0.0006 each year, or at most a 3 in a hundred chance of a single case in the next two generations⁷¹.

To assess the potential Australian risk from any future importation of beef products from the UK and other “controlled risk” countries, we assume that:

- the quality control on exports would be at least as good as the beef products for home consumption;
- Australia would import no more than 10% of its annual supply of beef products from a “controlled” risk country such as UK;
- per capita Australian consumption of beef products could be up to twice as high as in the UK.

On this basis, the aggregate risk to Australian residents from consuming UK beef would be up to 7% of the aggregate risk to the UK population. In other words, there would be no more than a *2 in 1000 chance of a single new vCJD transmission in Australia over the next two generations* – and the risk could be much smaller than that because of the progressive decline in BSE incidence in UK herds. This risk estimate is not zero, but it is small enough to justify the term “negligible”. The risk that each Australian has of dying from a road accident over the next two generations is perhaps 40 million times greater than the theoretical risk of them dying of vCJD transmitted by imported beef products.

Importation of beef products from other “controlled risk” countries would likely add an even more negligible risk to the Australian population.

Conclusion: Despite a theoretical increase in risk from any future importation of beef products from “BSE controlled risk” countries, the absolute risk to the Australian population is likely to be negligible.

⁷⁰ Comer & Huntly (2003) estimated that the annual aggregate burden to the UK population was much closer to 1 ID₅₀, whereas Ferguson & Donnelly (2003) had annual estimates in the range 100 ID₅₀, to allow for proposed changes to the OTM rule and other uncertainties.

⁷¹ The underlying assumption is that the risk is linearly proportional to the likely dose of infectious agent. However, there are clues suggesting that there may be a threshold dose needed to overcome the species barrier; if so, the risk may be even lower than that suggested by the linear assumption.

TABLE 5. Estimated final size of primary vCJD epidemic in UK

To estimate the final size of the vCJD epidemic we need to add the currently known numbers of primary (putatively food-borne) vCJD (166 cases) to our best estimate of the numbers of people, still incubating vCJD, who will develop clinical disease in future years.

This Table summarises various ways to estimate the number of future cases

Observations used	Assumptions	Best estimate or Conclusion	Confidence interval
Epidemic curve of 166 vCJD diagnoses from 1995-2009 (primary cases)	<ol style="list-style-type: none"> 1. Incubation period averages 16-17 years 2. Persons aged 8-20 at greatest risk of infection 	50 future clinical cases	10-165 future cases
Detection of 3 prion-affected appendices in 10,278 samples from 1961-85 birth cohort	Detection of prions indicates that such “carriers” might transmit to others by blood donation without necessarily becoming diseased themselves ⁷²	4000 “carriers”	1000- 16000 “carriers”
Detection of no prion-affected tonsils in 12,753 samples from 1961-85 birth cohort	As above	No “carriers”	0-6000 “carriers”
Four instances of secondary transmission following blood transfusion after incubation periods of 5-8 years. No unexplained recent increase in vCJD cases	<ol style="list-style-type: none"> 1. Transmission by blood is possible 2. Shorter incubation period is characteristic of within-species transmission. 	If there are large numbers of carriers, few will cause disease, at least with expected incubation periods	

Conclusion: The final size of the primary epidemic of vCJD in the UK is most likely to be about 216 cases (166 currently known and 50 future cases developing over the next generation). The potential upper limit of 330 cases, based on observations up to 2003, may even be too high⁷³.

What is the significance of “carriers”? The detection of prions in 3 of 10,278 appendectomy specimens from the at-risk birth cohorts suggests that a large number of persons could be prion carriers in the UK. The negative result from tonsillectomy specimens does not rule this out, although it reduces the best estimate of carrier numbers in the UK to perhaps 2000. However, if as many carriers as this were at risk of developing vCJD with the usual incubation period, the epidemic curve of clinical cases would not have declined – in fact it would have kept on going up from 2002. This forces us to conclude that “carriers”, as detected in the appendectomy survey, are not at risk of disease (except possibly with very long incubation periods), or that the estimate of carrier frequency is far too high, presumably because of some unknown bias (see below).

⁷² It is also implicitly assumed that appendices carrying prions are no more likely to be surgically removed than other appendices. This would not be true – for example – if prion accumulation in the appendix increased the risk of appendicitis and consequential surgery.

⁷³ Clarke & Ghani (2005).

TABLE 6. Risk of future vCJD cases in Australia

Observations	Assumptions made	Best estimate of future numbers	Confidence intervals
Primary transmissions			
No cases of vCJD yet diagnosed in Australia	Any outbreak should be more than half over	No cases	0-6 cases in Australia 0-1.5 cases in donors
169 vCJD cases in UK & no more than 165 expected in future	Transfer factor 0.2-1%	1.5 cases (0.4 in a donor)	0.4-4 cases in Australia 0.1-1 cases in donors
Secondary transmissions			
4 cases of secondary transmission in UK	Both above	0.0-0.14 secondary transmissions in Australia	There could be none

Hitherto, there have been no cases of vCJD detected in Australia. If we assume that any cases in Australia, from primary infection in UK, would be following the same time-course as in UK, we would expect any Australian outbreak to be half over by 2009. On the basis, having seen no cases to date, it can be inferred that the final size of any Australian outbreak is very unlikely to be more than 6 cases.

This estimate agrees quite well with the alternative estimate (0.4-4 cases) derived from the size of the primary epidemic in the UK (liberal estimates of 200-400 cases of vCJD up to 2080) and the “transfer factor” of 0.2-1% from UK to Australia.

Of the vCJD cases that could occur in Australia, only a minority would be in blood donors.

To estimate the maximum credible risk from secondary transmission in Australia from blood or plasma, we take the maximum credible size of the (future) primary epidemic in Australia (6 cases) and pro-rata by the proportion of secondary to primary cases already seen in UK. The maximum credible number is $6 \times 4 / 166 = 0.14$ of a case.

Attempts to estimate the risks of secondary transmission of vCJD by surgical or dental procedures have been hampered, even in the UK, by lack of data. However, any risks must be small, even in the UK, because of the lack of a second peak in the vCJD epidemic. It is very unlikely, even in the UK, that any surgical transmission could result in a self-sustaining secondary epidemic. In Australia, with no primary vCJD cases yet seen, the risks must be very much smaller.

Conclusions: The maximum credible number of future Australian cases of vCJD resulting from BSE exposures in the UK that have already happened is 6, but it is quite possible that the number will be zero. The risk for vCJD developing in any Australian blood donor is proportionally less. It is likely that the number of secondary transmissions in Australia from blood, plasma products, and surgical interventions will be zero.

Fig. 1. BSE surveillance in UK and rest of EU by year

Chart B4: Evolution of BSE cases detected by passive surveillance and active monitoring in the UK

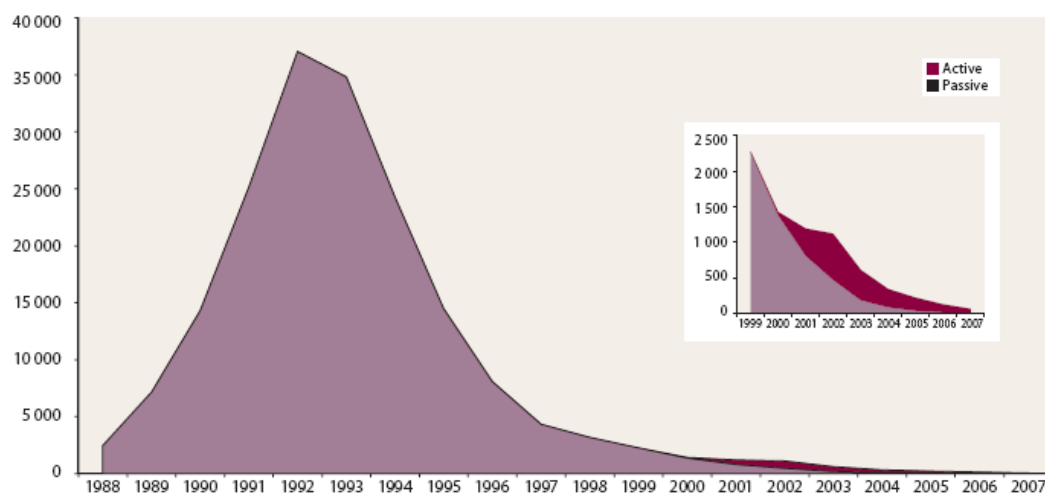
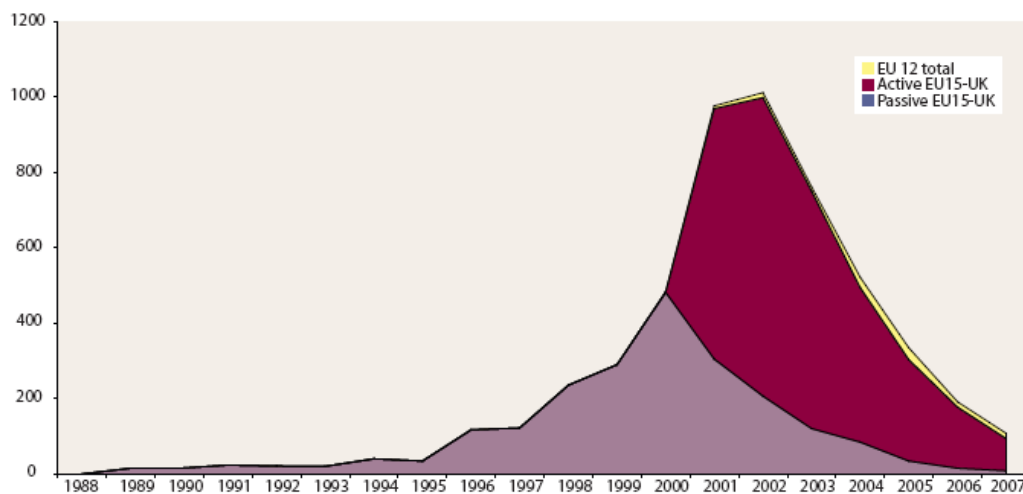
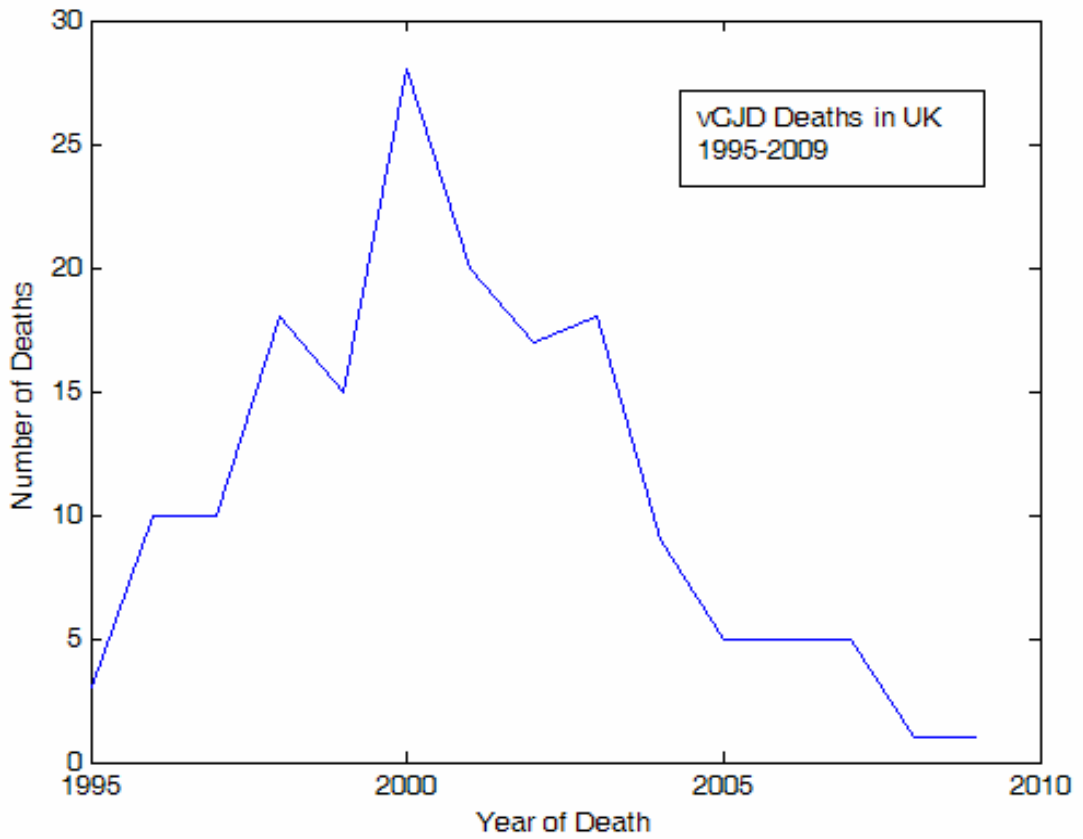


Chart B5: Evolution of BSE cases detected by passive surveillance and active monitoring in the rest of the EU



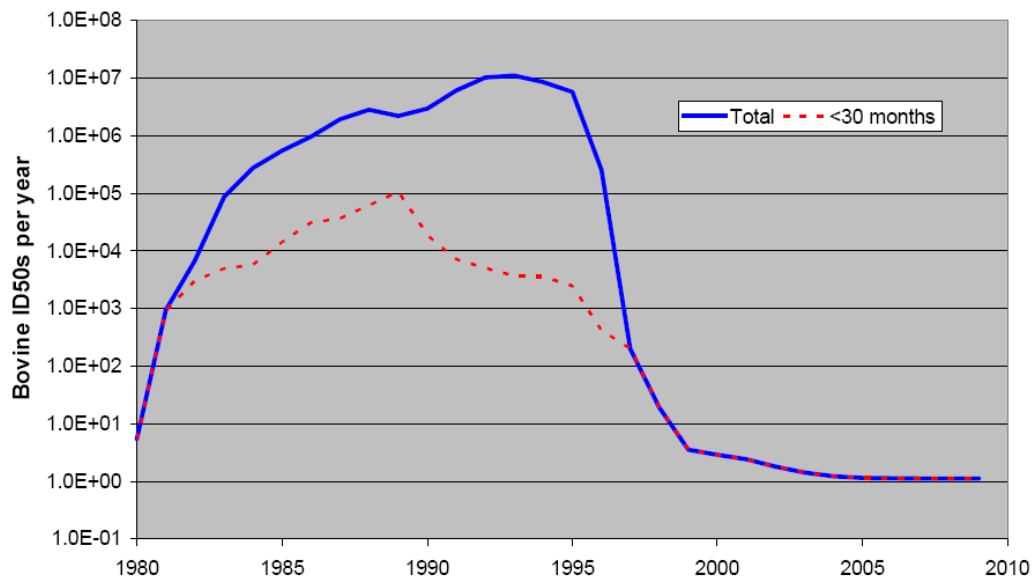
From the “*Report on the monitoring and testing of ruminants for the presence of TSE in the EU in 2007*”. See <http://ec.europa.eu>

Fig. 2 Time course of vCJD deaths in UK epidemic



From the National CJD Disease Surveillance Unit at the University of Edinburgh, The reporting is ostensibly complete to September 2009.

Fig. 3. Bovine Infective Units (ID50) Entering the UK Food Chain by Year



Note the logarithmic scale of doses, so that the amount of infective material entering the food chain in 1993 is about 10 million times greater than in 2006. The dotted red line shows the contribution from younger animals (less than 30 months at slaughter), and the gap between that line and the top blue line shows the contribution from older animals. As older animals were removed from the food chain by 1997, the lines converge in later years. From Comer and Huntly (2003).

SELECTED SCIENTIFIC REFERENCES

- Aguzzi, A., Heikenwalder, M. & Polymenidou, M. Insights into prion strains and neurotoxicity. *Nat Rev Mol Cell Biol* **8**, 552-61 (2007).
- Alpers M.P. The epidemiology of kuru: monitoring the epidemic from its peak to its end. *Proc Roy Soc B* **363**, 3707-13 (2008).
- Angers RC, Seward TS, Napier D, Green M, Hoover E, Spraker T, O'Rourke K, Balachandran A, Telling GC. Chronic wasting disease prions in elk antler velvet. *Emerg Infect Dis* **15** 696-703 (2009).
- Anon. Fourth case of transfusion-associated vCJD infection in the United Kingdom. *Euro Surveill* **12**, E070118 4 (2007).
- Appleby, B.S. et al. Characteristics of established and proposed sporadic Creutzfeldt-Jakob disease variants. *Arch Neurol* **66**, 208-15 (2009).
- Arnold, M.E., Hawkins, S.A., Green, R., Dexter, I. & Wells, G.A. Pathogenesis of experimental bovine spongiform encephalopathy (BSE): estimation of tissue infectivity according to incubation period. *Vet Res* **40**, 8 (2009).
- Azarpazhooh, A. & Fillery, E.D. Prion disease: the implications for dentistry. *J Endod* **34**, 1158-66 (2008).
- Balen, A.H. & Lumholtz, I.B. Consensus statement on the bio-safety of urinary-derived gonadotrophins with respect to Creutzfeldt-Jakob disease. *Hum Reprod* **20**, 2994-9 (2005).
- Bessen, R.A., Martinka, S., Kelly, J. & Gonzalez, D. Role of the lymphoreticular system in prion neuroinvasion from the oral and nasal mucosa. *J Virol* **83**, 6435-45 (2009).
- Bird, S.M. Attributable testing for abnormal prion protein, database linkage, and blood-borne vCJD risks. *Lancet* **364**, 1362-4 (2004).
- Bird, S.M., Merrall, E.L., Ward, H.J. & Will, R.G. Survival and re-operation rates after neurosurgical procedures in Scotland: implications for targeted surveillance of sub-clinical variant Creutzfeldt-Jakob disease. *Neuroepidemiology* **33**, 1-11 (2009).
- Bishop, M.T. et al. Predicting susceptibility and incubation time of human-to-human transmission of vCJD. *Lancet Neurol* **5**, 393-8 (2006).
- Boelle, P.Y., Cesbron, J.Y. & Valleron, A.J. Epidemiological evidence of higher susceptibility to vCJD in the young. *BMC Infect Dis* **4**, 26 (2004).
- Brandel, J.P. et al. Variant Creutzfeldt-Jakob disease in France and the United Kingdom: Evidence for the same agent strain. *Ann Neurol* **65**, 249-56 (2009).
- Burdick MD, Pifat DY, Petteway SR Jr, Cai K. Clearance of prions during plasma protein manufacture. *Transfus Med Rev* **20** 57-62 (2006).
- Cervia, J.S. et al. An overview of prion biology and the role of blood filtration in reducing the risk of transfusion-transmitted variant Creutzfeldt-Jakob disease. *Transfus Med Rev* **20**, 190-206 (2006).
- Chadeau-Hyam M, Alperovitch A. Risk of variant Creutzfeldt-Jakob disease in France. *Int J Epidemiol* **34**,46-52 (2005).
- Chang, B. et al. Surround optical fiber immunoassay (SOFIA): an ultra-sensitive assay for prion protein detection. *J Virol Methods* **159**, 15-22 (2009).
- Chesebro, B. Introduction to the transmissible spongiform encephalopathies or prion diseases. *Br Med Bull* **66**, 1-20 (2003).

- Chtourou S, Porte P, Nogr  M, Bihoreau N, Cheesman E, Samor B, Sauger A, Raut S, Mazurier C. A solvent/detergent-treated and 15-nm filtered factor VIII: a new safety standard for plasma-derived coagulation factor concentrates. *Vox Sang* **92** 327-37(2007).
- Clarke, P. & Ghani, A.C. Projections of the future course of the primary vCJD epidemic in the UK: inclusion of subclinical infection and the possibility of wider genetic susceptibility. *J R Soc Interface* **2**, 19-31 (2005).
- Clarke, P., Will, R.G. & Ghani, A.C. Is there the potential for an epidemic of variant Creutzfeldt-Jakob disease via blood transfusion in the UK? *J R Soc Interface* **4**, 675-84 (2007).
- Clewley, J.P. et al. Prevalence of disease related prion protein in anonymous tonsil specimens in Britain: cross sectional opportunistic survey. *BMJ* **338**, b1442 (2009).
- Collinge J, Whitfield J, McKintosh E, Beck J, Mead S, Thomas DJ, Alpers MP. Kuru in the 21st century--an acquired human prion disease with very long incubation periods. *Lancet* **367**,2068-74 (2006).
- Comer P.J. Huntly P.J. Exposure of the human population to BSE infectivity over the course of the BSE epidemic in great Britain and the impact of changes to the Over Thirty Month Rule. DNV Consulting. (2003).
- Cooper JD, Bird SM. Predicting incidence of variant Creutzfeldt-Jakob disease from UK dietary exposure to bovine spongiform encephalopathy for the 1940 to 1969 and post-1969 birth cohorts. *Int J Epidemiol* **32**,784-91 2003).
- Correll PK, Law MG, Seed CR, Gust A, Buring M, Dax EM, Keller AJ, Kaldor JM. Variant Creutzfeldt-Jakob disease in Australian blood donors: estimation of risk and the impact of deferral strategies. *Vox Sang* **81** 6-11 (2001).
- Coste, J., Prowse, C., Eglin, R. & Fang, C. A report on transmissible spongiform encephalopathies and transfusion safety. *Vox Sang* **96**, 284-91 (2009).
- Cousens, S. et al. The geographical distribution of variant Creutzfeldt-Jakob disease cases in the UK: what can we learn from it? *Stat Methods Med Res* **12**, 235-46 (2003).
- d'Aignaux, J.N.H., Cousens, S.N. & Smith, P.G. Predictability of the UK Variant Creutzfeldt-Jakob Disease Epidemic. *Science* **294**, 1729-1731 (2001).
- de Vos, C.J. & Heres, L. The BSE risk of processing meat and bone meal in nonruminant feed: a quantitative assessment for the Netherlands. *Risk Anal* **29**, 541-57 (2009).
- Dickinson, J. et al. Decontamination of prion protein (BSE301V) using a genetically engineered protease. *J Hosp Infect* **72**, 65-70 (2009).
- Donnelly, C.A. Maternal transmission of BSE: interpretation of the data on the offspring of BSE-affected pedigree suckler cows. *Vet Rec* **142**, 579-80 (1998).
- Dorsey, K. et al. Lack of evidence of transfusion transmission of Creutzfeldt-Jakob disease in a US surveillance study. *Transfusion* **49**, 977-84 (2009).
- Duncan, R.E. et al. Ethical considerations in presymptomatic testing for variant CJD. *J Med Ethics* **31**, 625-30 (2005).
- Dunstan, R.A. & Alpers, M.P. Variant Creutzfeldt-Jakob disease: implications for the health care system. *Aust N Z J Public Health* **29**, 308-12 (2005).
- Eaton, L. Haemophilia patient had variant CJD agent in spleen. *BMJ* **338**, b705 (2009).
- Edgeworth, J.A., Jackson, G.S., Clarke, A.R., Weissmann, C. & Collinge, J. Highly sensitive, quantitative cell-based assay for prions adsorbed to solid surfaces. *Proc Natl Acad Sci U S A* **106**, 3479-83 (2009).

- El-Shanawany, T., Jolles, S., Unsworth, D.J. & Williams, P. A recipient of immunoglobulin from a donor who developed vCJD. *Vox Sang* **96**, 270 (2009).
- Espinosa, J.-C. et al. Transgenic Mice Expressing Porcine Prion Protein Resistant to Classical Scrapie but Susceptible to Sheep Bovine Spongiform Encephalopathy and Atypical Scrapie. *Emerging Infectious Diseases* **15**, 1214-1221 (2009).
- Farrugia, A. Globalisation and blood safety. *Blood Rev* **23**, 123-8 (2009).
- Farrugia, A., Ironside, J.W. & Giangrande, P. Variant Creutzfeldt-Jakob disease transmission by plasma products: assessing and communicating risk in an era of scientific uncertainty. *Vox Sang* **89**, 186-92 (2005).
- Ferguson, N.M. & Donnelly, C.A. Assessment of the risk posed by bovine spongiform encephalopathy in cattle in Great Britain and the impact of potential changes to current control measures. *Proc Biol Sci* **270**, 1579-84 (2003).
- Ferguson, N.M., Ghani, A.C., Donnelly, C.A., Hagens, T.J. & Anderson, R.M. Estimating the human health risk from possible BSE infection of the British sheep flock. *Nature* **415**, 420-4 (2002).
- Ferguson-Smith M.A. , Richt J.A. Rare BSE mutation raises concern over risks to public health. *Nature* **457** 1079 (2009)
- Fichet G et al Novel methods for disinfection of prion-contaminated medical devices. *Lancet* **364**, 521-6 (2004).
- Fichet G, Antloga K, Comoy E, Deslys JP, McDonnell G. Prion inactivation using a new gaseous hydrogen peroxide sterilisation process. *J Hosp Infect* **67** 278-86 (2007).
- Flan, B. & Arrabal, S. Manufacture of plasma-derived products in France and measures to prevent the risk of vCJD transmission: precautionary measures and efficacy of manufacturing processes in prion removal. *Transfus Clin Biol* **14**, 51-62 (2007).
- Fujihara, A. et al. Hyperefficient PrP Sc amplification of mouse-adapted BSE and scrapie strain by protein misfolding cyclic amplification technique. *FEBS J* **276**, 2841-8 (2009).
- Garske, T., Ward, H.J., Clarke, P., Will, R.G. & Ghani, A.C. Factors determining the potential for onward transmission of variant Creutzfeldt-Jakob disease via surgical instruments. *J R Soc Interface* **3**, 757-66 (2006).
- Geschwind, M.D. Clinical trials for prion disease: difficult challenges, but hope for the future. *Lancet Neurol* **8**, 304-6 (2009).
- Ghani, A.C. Commentary: Predicting the unpredictable: the future incidence of variant Creutzfeldt-Jakob disease. *Int J Epidemiol* **32**, 792-3 (2003).
- Ghani, A.C., Ferguson, N.M., Donnelly, C.A. & Anderson, R.M. Factors determining the pattern of the variant Creutzfeldt-Jakob disease (vCJD) epidemic in the UK. *Proc Biol Sci* **270**, 689-98 (2003).
- Gillies, M. et al. A retrospective case note review of deceased recipients of vCJD-implicated blood transfusions. *Vox Sang* (2009).
- Grassi, J., Maillet, S., Simon, S. & Morel, N. Progress and limits of TSE diagnostic tools. *Vet Res* **39**, 33 (2008).
- Gregori, L., et al Effectiveness of leucoreduction for the removal infectivity of TSEs from blood. *Lancet* **364** 529-31 (2004)

- Grist, E.P. An evaluation of United Kingdom environmental bovine spongiform encephalopathy risk assessment. *Integr Environ Assess Manag* **1**, 152-9 (2005).
- Hamaguchi, T. et al. Medical procedures and risk for sporadic Creutzfeldt-Jakob disease, Japan, 1999-2008. *Emerg Infect Dis* **15**, 265-71 (2009).
- Head, M.W. & Ironside, J.W. vCJD and the gut: implications for endoscopy. *Gut* **56**, 9-11 (2007).
- Hewitt, P.E., Llewelyn, C.A., Mackenzie, J. & Will, R.G. Creutzfeldt-Jakob disease and blood transfusion: results of the UK Transfusion Medicine Epidemiological Review study. *Vox Sang* **91**, 221-30 (2006).
- Hill, A.F. & Collinge, J. Subclinical prion infection in humans and animals. *Br Med Bull* **66**, 161-70 (2003).
- Hilton, D.A. Pathogenesis and prevalence of variant Creutzfeldt-Jakob disease. *J Pathol* **208**, 134-41 (2006).
- Hoyos Flight, M. Prions: Getting a whiff of prion function. *Nat Rev Neurosci* **10**, 82-82 (2009).
- Ironside, J.W. Variant Creutzfeldt-Jakob disease: risk of transmission by blood transfusion and blood therapies. *Haemophilia* **12 Suppl 1**, 8-15; discussion 26-8 (2006).
- Jarrige N, Ducrot C, Cazeau G, Morignat E, La Bonnardière C, Calavas D. Case-control study on feed risk factors for BSE cases born after the feed ban in France. *Vet Res* **38** 505-16 (2007).
- Jayawardana, B.C., Shimada, K.-i., Fukushima, M. & Sekikawa, M. Study on presence/absence of central nervous tissues as BSE specified risk material in processed and raw meat products in Japan. *Food Control* **20**, 187-190 (2009).
- Klug, G.M. et al. Surveillance of Creutzfeldt-Jakob disease in Australia: 2008. *Commun Dis Intell* **32**, 232-6 (2008).
- Lacroux C., et al Prions in milk from ewes incubating natural scrapie. *PLoS Pathog* **4**, e1000238. Epub (2008).
- Lee, S.T. & Roh, J.K. Innocent white blood cells in sporadic Creutzfeldt-Jakob disease? *Lab Invest* **89**, 612-3 (2009).
- Lefrere, J.J. & Hewitt, P. From mad cows to sensible blood transfusion: the risk of prion transmission by labile blood components in the United Kingdom and in France. *Transfusion* **49**, 797-812 (2009).
- Lloyd, S.E. et al. HECTD2 is associated with susceptibility to mouse and human prion disease. *PLoS Genet* **5**, e1000383 (2009).
- Lumley, J.S. & Serious Hazards of Transfusion, C. The impact of Creutzfeldt-Jakob disease on surgical practice. *Ann R Coll Surg Engl* **90**, 91-4 (2008).
- Manuelidis, L., Liu, Y. & Mullins, B. Strain-specific viral properties of variant Creutzfeldt-Jakob disease (vCJD) are encoded by the agent and not by host prion protein. *J Cell Biochem* **106**, 220-31 (2009).
- Mathews, J.D. The changing face of kuru, a personal perspective. *Proc Roy Soc B* **363**, 3779-84 (2008).
- Mead, S. et al. Genetic risk factors for variant Creutzfeldt-Jakob disease: a genome-wide association study. *Lancet Neurol* **8**, 57-66 (2009).
- Murray, K. et al. Is there evidence of vertical transmission of variant CJD? *J Neurol Neurosurg Psychiatry*, jnnp.2009.172148 (2009).
- Olsen, S.B., Sheikh, A., Peck, D. & Darzi, A. Variant Creutzfeldt-Jakob disease: a cause for concern. Review of the evidence for risk of transmission through abdominal lymphoreticular tissue surgery. *Surg Endosc* **19**, 747-50 (2005).

- Peretz D, et al Supattapone S, Giles K, Vergara J, Freyman Y, Lessard P, Safar JG, Inactivation of prions by acidic sodium dodecyl sulfate. *J Virol* **80** 322-31 (2006)
- Pocchiari, M. Prevalence of variant CJD in the UK. *BMJ* **338**, b435 (2009).
- Porter, S.R. Prion disease: possible implications for oral health care. *J Am Dent Assoc* **134**, 1486-91 (2003).
- Quadrio, I. et al. Rapid diagnosis of human prion disease using streptomycin with tonsil and brain tissues. *Lab Invest* **89**, 406-13 (2009).
- Race B, Meade-White K, Race R, Chesebro B. Prion infectivity in fat of deer with chronic wasting disease. *J Virol* **83** 9608-10 (2009).
- Ruegger, J. et al. A case-control study of sporadic Creutzfeldt-Jakob disease in Switzerland: analysis of potential risk factors with regard to an increased CJD incidence in the years 2001-2004. *BMC Public Health* **9**, 18 (2009).
- Sakaguchi, S., Ishibashi, D. & Matsuda, H. Antibody-based immunotherapeutic attempts in experimental animal models of prion diseases. *Expert Opin Ther Pat* **19**, 907-17 (2009).
- Salman, M.D. Chronic wasting disease in deer and elk: scientific facts and findings. *J Vet Med Sci* **65**, 761-8 (2003).
- Shalowitz, D.I., Barnosky, A. & Smith, L.B. Ethical analysis of communicating the risk of iatrogenic Creutzfeldt-Jakob disease. *Infect Control Hosp Epidemiol* **30**, 805-6 (2009).
- Smith, P.G. The epidemics of bovine spongiform encephalopathy and variant Creutzfeldt-Jakob disease: current status and future prospects. *Bull World Health Organ* **81**, 123-30 (2003).
- Smith, P.G. & Bradley, R. Bovine spongiform encephalopathy (BSE) and its epidemiology. *Br Med Bull* **66**, 185-98 (2003).
- Smith, P.G., Cousens, S.N., d' Huillard Aignaux, J.N., Ward, H.J. & Will, R.G. The epidemiology of variant Creutzfeldt-Jakob disease. *Curr Top Microbiol Immunol* **284**, 161-91 (2004).
- St Romain, C., Hazlehurst, G. & Jewell, A.P. Leucodepletion for transmissible spongiform encephalopathies. *Br J Biomed Sci* **61**, 48-54 (2004).
- Stevenson, M.D., Oakley, J.E., Chick, S.E. & Chalkidou, K. The cost-effectiveness of surgical instrument management policies to reduce the risk of vCJD transmission to humans. *Journal of the Operational Research Society* **60**, 506-518 (2009).
- Sugiura, K., Kikuchi, E. & Onodera, T. Updated prediction for the BSE epidemic in dairy cattle in Japan. *Prev Vet Med* **89**, 272-6 (2009).
- Tabrizi, S.J., Elliott, C.L. & Weissmann, C. Ethical issues in human prion diseases. *Br Med Bull* **66**, 305-16 (2003).
- Thyer J, Unal A, Hartel G, Middleton D, Bingham J, Braun M, Uren E, Maher D. Investigation of prion removal/inactivation from chromatographic gel. *Vox Sang* **91** 301-8 (2006).
- Thyer J, Unal A, Thomas P, Eaton B, Bhashyam R, Ortenburg J, Uren E, Middleton D, Selleck P, Maher D. Prion-removal capacity of chromatographic and ethanol precipitation steps used in the production of albumin and immunoglobulins. *Vox Sang* **91** 292-300 (2006).
- Turner, M.L. & Ludlam, C.A. An update on the assessment and management of the risk of transmission of variant Creutzfeldt-Jakob disease by blood and plasma products. *Br J Haematol* **144**, 14-23 (2009).

- Valleron, A.J., Boelle, P.Y., Will, R. & Cesbron, J.Y. Estimation of epidemic size and incubation time based on age characteristics of vCJD in the United Kingdom. *Science* **294**, 1726-8 (2001).
- Wallis, J.P. vCJD and blood transfusion. *Br J Haematol* **145**, 669-70 (2009).
- Ward, H.J. et al. Risk factors for variant Creutzfeldt-Jakob disease: a case-control study. *Ann Neurol* **59**, 111-20 (2006).
- Will R.G., Acquired prion disease: iatrogenic CJD, variant CJD, kuru. *Br Med Bull* **66**, 255-265 (2003).
- Will, R. Variant Creutzfeldt-Jakob disease. *Folia Neuropathol* **42 Suppl A**, 77-83 (2004).
- Wilson, D.A. & Nixon, R.A. Sniffing out a function for prion proteins. *Nat Neurosci* **12**, 7-8 (2009).

OTHER SOURCES. Hot links to selected sites and source documents

Number of reported cases of bovine spongiform encephalopathy (BSE) in farmed cattle worldwide http://www.oie.int/Eng/info/en_esbmonde.htm

Number of cases of bovine spongiform encephalopathy (BSE) reported in the United Kingdom http://www.oie.int/eng/info/en_esbru.htm

VARIANT CREUTZFELDT-JAKOB DISEASE - WORLD WIDE NUMBERS

<http://www.cjd.ed.ac.uk/vcjdworld.htm>

CJD STATISTICS – UK REFERRALS AND DEATHS

<http://www.cjd.ed.ac.uk/figures.htm>

Bovine Spongiform Encephalopathy Status of OIE Members

http://www.oie.int/eng/Status/BSE/en_BSE_free.htm

UK Enquiry – the Nature and Causes of BSE

www.bseinquiry.gov.uk/report/volume2/chaptea6.htm

SPONGIFORM ENCEPHALOPATHY ADVISORY COMMITTEE

http://www.seac.gov.uk/summaries/seac97_summary.pdf

Department of Health (UK)

www.dh.gov.uk/en/index.htm

http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_103330.pdf

http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/document/digitalasset/dh_4136945.pdf

http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/document/digitalasset/dh_4136946.pdf

Defra (Department for Environment Food and Rural Affairs)

www.defra.gov.uk

Food Standards Agency

www.food.gov.uk

[BSE Controls Review](#)

Health Protection Agency

www.hpa.org.uk

European Food Safety Authority (EFSA)

www.efsa.europa.eu

Variant CJD Response Plan

[http://www.healthemergency.gov.au/internet/main/publishing.nsf/Content/A90C01F5D7BEFD27CA256F190004794A/\\$File/control](http://www.healthemergency.gov.au/internet/main/publishing.nsf/Content/A90C01F5D7BEFD27CA256F190004794A/$File/control)

CJD Resource Centre

www.nibsc.ac.uk/cjd/World.html#Europe

EU Commission BSE webpages

http://ec.europa.eu/food/index_en.htm

Food and Agriculture Organisation of the United Nations

www.fao.org/ag/againfo/home/en/index.htm

UK CJD Surveillance Unit

www.cjd.ed.ac.uk/

World Organisation for Animal Health (OIE)

www.oie.int/eng/en_index.htm

New Therapies Scrutiny Group

www.mrc.ac.uk/utilities/search/MRC001958

Wildlife Information Network

<http://www.wildlifeinformation.org/>

Further information on CJD

www.cjdalliance.net

NATIONAL BLOOD AUTHORITY

<http://www.nba.gov.au/pubs/factsheets-blood-sector.html>

Australian Red Cross Blood Transfusion Service

<http://www.transfusion.com.au/search-result.aspx?search=vCJD>

AMORFIX

http://www.amorfix.com/press/2009/2009_07_17_uk_tender_announcement.pdf

Australian information about vCJD for the general public.

[http://www.health.gov.au/internet/main/publishing.nsf/Content/15441E24D46B4BFC CA256F1900047A76/\\$File/public.pdf](http://www.health.gov.au/internet/main/publishing.nsf/Content/15441E24D46B4BFC CA256F1900047A76/$File/public.pdf)

CJD Foundation

www.cjdfoundation.org

FSANZ

www.foodstandards.gov.au

DAFF vaccines

http://www.daff.gov.au/__data/assets/pdf_file/0018/11862/2004-10a.pdf